**School of Public Health**

# Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes

**Sally Ann Vindedzis**

**This thesis is presented for the Degree of**
**Doctor of Philosophy**
**of**
**Curtin University**

**April 2014**

**Declaration**

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: S. V ..... 

Date: 16/3/2014.

## ABSTRACT

Hypoglycaemia in diabetes-related states is caused by relative insulin excess and can cause tremor, hunger, sweating, behavioural changes, confusion, fitting and coma. The initial treatment of hypoglycaemia is dietary with recommendations for this based on expert opinion or older laboratory-based studies using intravenous insulin or older pre-analog insulins. Hypoglycaemia in diabetes-related states is well researched but has tended to focus on mechanisms and prevention, hypoglycaemia-associated autonomic failure and long-term consequences of hypoglycaemia. There are few studies in the area of diet and treatment of hypoglycaemia.

The series of published papers presented in this thesis therefore investigates dietary practices in the treatment of hypoglycaemia in adults with diabetes and diabetes-related states along a continuum, from those with increased diabetes risk; to diabetes in free-living individuals and then to those dependent on others for their care, inpatients with diabetes on nasogastric feeding.

The first two papers aimed to identify, in free-living individuals in two different states of glucose dysmetabolism, effective dietary treatments of hypoglycaemia or relative hypoglycaemia. The first paper presents a case study of a woman with normal glucose tolerance and elevated 1-h postload glucose. It examines the relationship between loss of first phase insulin, 1-h postprandial hyperglycaemia with subsequent rapid drop in blood glucose resulting in relative hypoglycaemia, carbohydrate intake, GI and weight gain, and assesses the effect of a low carbohydrate diet and early intervention with short-acting preprandial insulin on glycaemia over 2 h, comparing this to treatment with sitagliptin, or no treatment. Results showed a significant difference between the 1-h postload rise for low carbohydrate and insulin-treated meals compared with no treatment or sitagliptin. On a regime of either low carbohydrate meals or preprandial insulin, glycaemic variability, symptoms of relative hypoglycaemia and consequent postprandial hunger and weight decreased. It has been suggested that recognition and management of those with normal glucose tolerance and 1-h glucose $\geq$ 8.6mmol/L may reduce incidence of diabetes and vascular events. This represents the first published case of successful management. The second paper investigated dietary treatment of hypoglycaemia in insulin-treated diabetes, aiming to determine if there was a significant difference in the need for repeat treatment of hypoglycaemia following

initial treatment with 15 or 20 g of fast-acting carbohydrate with wait-time to repeat treatment either 5 or 10 min. Results showed that 20 g of fast-acting carbohydrate resolved hypoglycaemia within 10 min in 89.3% of free-living individuals on current insulin regimes compared with 63.2% for 15 g. Decreasing the wait-time to retreatment to 5 min increased repeat treatments. Hyperglycaemia at 30 min post hypoglycaemia was not significant. An initial treatment of 20 g carbohydrate with a 10 min wait-time to repeat treatment was thus judged optimal.

The next two papers aimed to assess self-reported current practices in dietary treatment of hypoglycaemia in adults with insulin-treated diabetes. Paper 3 investigates self-reported patterns of food selection for self-treatment of hypoglycaemia and compares this with recommendations, duration of action of carbohydrate, and self-reported efficacy of treatment. Results showed that 78% of responders reported initial treatment with recommended foods, but only 40.8% of these were quick-acting carbohydrate, with 46.4% using quantities exceeding Australian recommendations but within European recommendations. Although non-adherence is not a reason to review recommendations, in view of the results of paper 2, the relatively low evidence level on which recommendations are based and the variation in world recommendations, this study supports increasing Australian recommendations. Only 55.8% of responders reported ingesting follow-up food, possibly increasing risk of repeat hypoglycaemic episodes. Therefore in the fourth paper repeat hypoglycaemia within 2 h of a primary hypoglycaemic event was investigated to identify any association between omission of followup longer-acting carbohydrate after an initial hypoglycaemic event and increased frequency of repeat hypoglycaemia. Hierarchical logistic regression showed omission of follow-up food was not a significant predictor of increased likelihood of repeat hypoglycaemia irrespective of method of insulin administration. This study supports judicious, rather than routine use of follow-up longer-acting carbohydrate post primary hypoglycaemic event.

The fifth paper aimed to assess knowledge of alcohol-induced hypoglycaemia by people with type 1 diabetes and compare this to easily available internet-based information. Results showed that 6 national Diabetes Associations provided general information on alcohol and hypoglycaemia, eating with, and snacking after alcohol and sustained hypoglycaemic effect, but the specified possible duration of hypoglycaemia varied from unspecified to 16 - 24 h, and only 2 guidelines provided

information on reduction of long-acting insulin. Most people with type 1 diabetes (88.2%) identified the hypoglycaemic effect of alcohol, but only 32.4% postulated duration of 4+ h post-consumption for this. The main deficits identified were lack of knowledge of duration of alcohol-induced hypoglycaemia and the lack of provided information on reduction of long-acting insulin, an important strategy to minimize hypoglycaemic risk associated with significant alcohol consumption.

The next two papers aimed to assess treatment and frequency of hypoglycaemia in inpatients in the general ward on total nasogastric feeding. Paper 6 describes a retrospective review to determine factors associated with hypoglycaemia. Results show frequency of hypoglycaemia as 10.9% patient-days with ≥1 hypoglycaemic episode with no association with feed type. There was an association between sulphonylurea treatment and extended hypoglycaemia. Kaplan-Meier survival curves showed a significantly longer time to a subsequent hypoglycaemic episode in patients whose treatment was reduced in response to hypoglycaemia compared to those whose treatment remained unchanged. Frequency of hypoglycaemia could not be compared with other studies due to variation in reporting methods. Consequent to this Paper 7 was a systematic review of the literature that aimed to answer the questions: What are the existing summary statistics of frequency of hypoglycaemia in insulin-treated adults on established nasogastric feeding in the general ward? To what extent does lack of homogeneity in defining, identifying and reporting hypoglycaemia affect these statistics? Only 9 studies were judged suitable according to inclusion/exclusion criteria and all had the assessment of efficacy of insulin/feed regimens as their primary objective. Studies exhibited major heterogeneity; with definitions of hypoglycaemia varying and five different methods of reporting frequency of hypoglycaemia utilized, precluding pooled analysis. A descriptive synthesis of results was generated. The major conclusions were that reporting methods incorporating patients numbers and duration of feeding and multilevel documentation of hypoglycaemia are crucial to allow interstudy comparisons.

The overall aim of this thesis, presented as seven papers has been to increase knowledge in the under-researched area of dietary practices in the treatment of hypoglycaemia. The study findings have allowed recommendations to be made on amendments to the Australian guidelines for treatment of hypoglycaemia in the area of optimal quantity of treating carbohydrate, wait-time to retreatment and appropriate food selection. They have delineated dietary practices in treatment of hypoglycaemia

and their relationship to blood glucose levels, duration of action of carbohydrate and repeat episodes of hypoglycaemia, and also highlighted deficits in knowledge and available information regarding alcohol-induced sustained hypoglycaemia. In the area of hypoglycaemia and nasogastric feeding, they have highlighted factors affecting duration and frequency of hypoglycaemia and identified the need for specific changes in reporting methods and documentation of hypoglycaemia. Findings from all studies will hopefully benefit those who experience hypoglycaemia as a reality in their everyday lives.

**ACKNOWLEDGEMENTS**

To the following people, my sincere and heartfelt thanks:

My supervisor, Associate Professor Jill Sherriff for her support, expertise, knowledge, endless patience, flexibility, thoughtfulness and composure. I would not have persevered without her encouragement. Thank you for everything Jill, you have been tremendous.

My co-supervisor Associate Professor Satvinder Dhaliwal for his statistical expertise and sense of humour.

My 'onsite' associate supervisor Dr Kim Stanton for his knowledge and expertise in the field of diabetes and for giving me someone to argue with.

To John and Susanah for their faith in me, ongoing encouragement, company, humour and housework.

To Eunice Firman, Joyce Gwynne, Bee Choo Lim, Beryl Marsh, Julie Pearse, Anne Perry, Kim Stanton, Angela Sun and A. G. Tan for their practical contribution and/or support in these projects.

And finally, to the patients attending the Diabetic Clinic, who willingly gave time and information. I hope these study results will benefit you.

**DEDICATION**

This is dedicated to my mother, who taught me the value of education. Her own thesis, started in her seventies, was terminated by dementia. This one is for you mum.

## LIST OF INCLUDED PUBLICATIONS

**Vindedzis SA**, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Low carbohydrate meals or a small dose of insulin normalises one-hour blood glucose in a woman with normal glucose tolerance and elevated one-hour postload glucose: a case report. The British Journal of Diabetes & Vascular Disease. 2013;13(2):103-5.

**Vindedzis S**, Marsh B, Sherriff J, Dhaliwal S, Stanton K. Dietary treatment of hypoglycaemia: should the Australian recommendation be increased? Internal Medicine Journal. 2012;42(7):830-3.

**Vindedzis SA**, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Food selection for treatment of hypoglycaemia in insulin-treated diabetes: what happens in real life? Practical Diabetes. 2012;29(7):271-4.

**Vindedzis S**, Marsh B, Sherriff J, Dhaliwal S, Stanton K. Omitting Follow-up Food After Initial Hypoglycaemic Treatment Does not Increase the Likelihood of Repeat Hypoglycaemia. Diabetes Therapy. 2013;4(1):67-75.

**Vindedzis SA**, Marsh B, Sherriff JL, Stanton KG. Alcohol and type 1 diabetes: Patient knowledge of alcohol-induced sustained hypoglycaemia. Diabetes Res Clin Pract. 2013 Nov;102(2):e19-20. doi: 10.1016/j.diabres.2013.08.010. Epub 2013 Sep 26.

**Vindedzis SA**, Marsh B, Sherriff JL, Stanton KG. Hypoglycaemia in inpatients with diabetes on nasogastric feeding. Practical Diabetes. 2014; 31(1):29-31. DOI:10.1002/pdi.1824.

**Vindedzis SA**, Sherriff JL, Stanton KG. Hypoglycemia in Insulin-Treated Adults on Established Nasogastric Feeding in the General Ward: A Systematic Review. Diabetes Educ. 2014. DOI: 10.1177/0145721714523510

I warrant that I have obtained, where necessary, permission from the copyright owners to use any third party copyright material reproduced in the thesis (e.g., questionnaires), or to use any of my own published work (e.g., journal articles) in which the copyright is held by another party (e.g., publisher).
Copies of the permission statements are included in Appendix 2.

## LIST OF CONFERENCE PRESENTATIONS

**Increasing the Australian recommendations for treating hypoglycaemia from 15g to 20g of carbohydrate proved more effective for free-living individuals with insulin-treated diabetes**

**S. Vindedzis***[1], B. Marsh[1], J. Sherriff[2], S. Dhaliwal[2], K. Stanton[1], A. Sun[1], A Perry[1], B. Lim[1].

Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, WA, 6001[1]

School of Public Health, Curtin University, Bentley, WA, 6102[2]

Poster presentation, Australian Diabetes Society- Australian Diabetes Educators Association ASM, Perth, Australia, 31 August - 2 September 2011. Poster number 298.

**Hypoglycemia In Inpatients With Diabetes On Nasogastric Feeding**

**S. Vindedzis***[1], B. Marsh[1], J. Sherriff[2], S. Dhaliwal[2], K. Stanton[1].

Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, WA, 6001[1]

School of Public Health, Curtin University, Bentley, WA, 6102[2]

Poster presentation, Australian Diabetes Society- Australian Diabetes Educators Association ASM, Gold Coast, Australia, 29- 31 August 2012. Poster number 315.

**Alcohol and hypoglycaemia in type 1 diabetes**

**Sally Vindedzis** [1] Beryl Marsh [1] Jill Sherriff [2] Kim Stanton [1]

Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, WA, 6001[1]

School of Public Health, Curtin Health Innovation Research Institute Curtin University, Bentley, WA, 6102[2]

Poster presentation, Australian Diabetes Society- Australian Diabetes Educators Association ASM, Sydney, Australia, 28- 30 August 2013. Poster number 357.

## STATEMENT OF AUTHOR CONTRIBUTION

The nature and extent of the intellectual input by the candidate and co-authors has been validated by all authors, and can be found in Appendix 1.

**TABLE OF CONTENTS**

## LIST OF TABLES



## LIST OF FIGURES

**ABBREVIATIONS**

ADA - American Diabetes Association

ADS - Australian Diabetes Society

ADEA - Australian Diabetes Educators Association

AIHW- Australian Institute of Health and Welfare

AMA - American Medical Association

AusDiab Study - The Australian Diabetes, Obesity and Lifestyle Study

BGL - Blood glucose level

BMI - Body Mass Index

CGM - Continuous glucose monitoring

CSII - Continuous subcutaneous insulin infusion.

CVD - Coronary vascular disease

DAFNE - Dose adjustment for normal eating

DCCT - Diabetes Control and Complications Trial

DSF - Diabetes specific-feed

EASD - European Association for the Study of Diabetes

GABA - Gamma-aminobutyric acid

HDL – High density lipoprotein

HbA1c - HaemoglobinA1c

HAAF - Hypoglycaemia-associated autonomic failure

IDF - International Diabetes Federation

IFCC – International Federation of Clinical Chemists

IFG - Impaired fasting glucose

IGT - Impaired glucose tolerance

IV - Intravenous

Ln – Natural log

MDI – Multiple daily insulin injections

NGT - Normal oral glucose tolerance test

NHMRC - National Health and Medical Research Council

OGTT - Oral glucose tolerance test

ORIGIN study - Outcome Reduction with Initial Glargine Intervention study

PDS - Posttraumatic stress disorder

SMBG - Self-monitoring of blood glucose

UKPDS - UK Prospective Diabetes Study

WHO - World Health Organisation

# CHAPTER 1 INTRODUCTION AND THESIS OVERVIEW

*The work of science is to substitute facts for appearances, and demonstrations for impressions.*
John Ruskin (1819 - 1900)

## 1.1 Introduction

This thesis presents a series of published papers investigating dietary practices in the treatment of hypoglycaemia in adults with diabetes and diabetes-related states. It examines this issue along a continuum, from those who, though classified normal under present classification systems, exhibit measurable impaired glucose handling and quantified increased diabetes risk; moving past formal prediabetes to diabetes in free-living individuals and then to those highly dependent on others for their care, inpatients with diabetes on nasogastric feeding.

The overall aim of this thesis, presented in seven papers, is to quantitatively investigate dietary practices associated with the treatment of hypoglycaemia, as far as practicable, from the perspective of those experiencing it. Therefore, with the exception of paper 7, a systematic review, all projects are practically based and all projects (including the systematic review) were designed to obtain measurable results that would benefit and to be seen to be of benefit to and by, those experiencing hypoglycaemia.

This chapter gives the overall background and significance of the studies, although these are covered in more detail in the studies themselves and, where considered necessary, in prefaces to studies. Limitations of the studies are, in the main, dealt with in the individual studies and also in the concluding chapter. Publication of the research in peer reviewed journals has enhanced the process by providing the opportunity to review, discuss and apply research findings and has allowed these findings to contribute more directly and immediately to the previously existing knowledge in the area of research.

## 1.2 General background and significance

Hypoglycaemia is a state which can impose great discomfit on those experiencing it. Its symptomology can include tremor, hunger, sweating, behavioural changes, confusion, fitting and coma (Donnelly et al., 2005; Stefanova, Cox, & Hill, 2013). In

diabetes and diabetes-related states it is caused by relative insulin excess and in diabetes it is an iatrogenic phenomena (Cryer, Stephen N. Davis, & Shamoon, 2003). The initial, and hopefully only, necessary treatment is dietary. The current basis for recommendations for dietary treatment are based on expert opinion (American Diabetes Association, 2014b) or studies carried out before 1995 under laboratory conditions and using hospital-based medication regimes (intravenous insulin) or now defunct insulins and delivery systems (Brodows, Williams, & Amatruda, 1984; Slama et al., 1990; Wiethop & Cryer, 1993). Insulins and delivery systems have changed significantly since 1995, the most notable change being the introduction of analog insulin in 1998, affecting both patterns of insulin action and hypoglycaemic risk (Hirsch, 2005). There is, however, a dearth of studies investigating dietary treatment of hypoglycaemia on present regimes.

Similarly self-treatment for hypoglycaemia in the free-living person is carried out in widely diverse situations; while driving, at work, in bed in the middle of the night, while surfing, in the supermarket while wheeling a baby and holding a toddler by the hand, in short, wherever hypoglycaemia occurs. Conditions may well not be ideal for a well-reasoned treatment of hypoglycaemia, and indeed, stressful situations have been nominated as causative for severe hypoglycaemia in 6 - 25% of events (Kedia, 2011). In addition, hypoglycaemia itself does not necessarily foster clear thinking (Choudhary & Amiel, 2011). Under real-life conditions, what do people with diabetes use to self-treat their hypoglycaemia? With information on this, we, as health promoters can, to some extent, 'walk in their shoes' and collaborate on food treatments that are, hopefully, realistic within the constraints of daily life, and also effective. There is however a dearth of information in this area, especially in the Australian situation.

Cryer *et al*, in the American Diabetes Association's technical review of hypoglycaemia, assert, unscientifically but evocatively, that those with type 1 diabetes will suffer thousands of episodes of hypoglycaemia and an episode of severe hypoglycaemia approximately annually (Cryer, Davis, & Shamoon, 2003). Many of these people have, understandably, a significant fear of hypoglycaemia (Wild et al., 2007) and there is evidence that hypoglycaemia is feared by those who experience it, more than the long-term complications of diabetes (which include blindness and kidney failure) (American Diabetes Association, 2005). General ratings of health-related quality of life are significantly reduced by those experiencing hypoglycaemic

symptoms, and the reduction is proportional to the severity of those symptoms (Alvarez-Guisasola, Yin, Nocea, Qiu, & Mavros, 2010). From the researcher's personal perspective, having interviewed many thousands of people who have experienced and are still experiencing hypoglycaemia, what has come across is how difficult hypoglycaemia and its treatment are perceived to be, by many who experience it. What the researcher has heard countless times is also reflected in the literature in studies that include interviews with people experiencing hypoglycaemia:

- I am terrified of hypoglycaemia, I run my blood sugars high to avoid it, even though I know it may do me harm later on (Barnett et al., 2010).
- When I get hypo, I panic, grab food and just keep eating until I feel better (Lawton et al., 2013).
- When I've had a hypo my blood sugars go sky high, I don't know how much is ok to eat (Lawton et al., 2013).
- When I get hypo my wife has to remind me not to eat too many glucose tablets, otherwise I find I eat them like candy (Mike, 2012). (1 glucose tablet = 5 g glucose)
- I use my hypos as an excuse to eat chocolate (Sumner, Baber, & Williams, 2000).
- I'm on insulin. Sometimes I start feeling funny, all shaky and sweaty. I don't know what to do so I have a sleep (Elliott, Abdulhadi, Al-Maniri, Al-Shafaee, & Wahlstrom, 2013).

When, as with inpatients on total nasogastric feeding, the person experiencing hypoglycaemia is dependent on others to not only treat their hypoglycaemia but also to identify it, the problems of treatment are compounded. Investigating and quantifying methods of identification, reporting methods and frequency of hypoglycaemic events is an essential first step in its remedy, and again, there is a dearth of information in this area.

So what do people with diabetes who suffer hypoglycaemia want?

1. They want to be freed from walking a line between, on one hand, hypoglycaemia and acute complications, and on the other, ongoing hyperglycaemia with its consequent increased risk of long-term complications of diabetes (Rubin & Peyrot, 2001; Shiu & Wong, 2002).

2. As this is not possible (with current treatment methods for diabetes) they want to self-treat their hypoglycaemia with something that is easily available and resolves their hypoglycaemia as quickly as possible without contributing to subsequent increased blood glucose levels (Nair, Levine, Lohfeld, & Gerstein, 2007; Shiu & Wong, 2002).

As far as possible, within the current scientific framework, the wishes expressed in point 2 have been crystallized into the overall research objectives delineated in the next section.

### 1.3 Research problems and objectives

The main aim of these seven studies was to investigate dietary practices in the treatment of hypoglycaemia with a view to ascertaining and quantifying current practices and, where warranted, making recommendations for more effective treatment. The general research objectives below summarise and unify the overall aims of the investigation. Specific practical research objectives are delineated in individual papers.

Overall objectives aimed:

1. To practically establish and verify, in free-living individuals, in various states of glucose dysmetabolism and on current medication regimes, effective dietary treatments of hypoglycaemia or relative hypoglycaemia.
2. To assess self-reported current practices in dietary treatment of hypoglycaemia and their perceived effectiveness by those with insulin-treated diabetes with respect to resolution of initial hypoglycaemia, prevention of repeat hypoglycaemia and generation of subsequent hyperglycaemia. To compare this to verified scientific standards (Glycaemic Index) and currently-used laboratory-generated recommendations for dietary treatment of hypoglycaemia.
3. To assess individual knowledge of self-treatment of hypoglycaemia in a situation of high risk for sustained hypoglycaemia (alcohol ingestion) and compare this to easily available internet-based information.
4. To assess frequency and treatment of hypoglycaemia in inpatients on nasogastric feeding who are dependent on carers for identification and treatment of hypoglycaemia and therefore at putative high risk from that hypoglycaemia.

### 1.4 Outline of papers included in this thesis

Although a variety of research methods were used, the papers included in this thesis form a progression, starting with relative hypoglycaemia in a state of greatly increased diabetes risk (elevated 1-h post-load glucose), leading into primary hypoglycaemia in free-living people with diabetes (quantities of carbohydrate and patterns of food selection for hypoglycaemic treatment), progressing to secondary or repeat hypoglycaemia in free-living people with diabetes (dietary practices and efficacy of treatment), to the more specialized situations of alcohol-induced sustained hypoglycaemia in diabetes and hypoglycaemia in people with diabetes on nasogastric feeding in the general ward.

The first paper (paper 1) is a case report of a woman with increased diabetes risk but within the accepted present parameters of normal glucose metabolism as measured by series of oral glucose tolerance tests and haemoglobin A1c; that is normal glucose tolerance and elevated 1-h post-load glucose. It examines the relationship between loss of first phase insulin, postprandial hyperglycaemia, relative hypoglycaemia, carbohydrate intake and glycaemic index, and assesses the effect of low carbohydrate diets and early intervention with short-acting preprandial insulin.

The second paper in this thesis (paper 2) looks at treatment of hypoglycaemia in overt diabetes and is a comparative study of the relationship between quantity of carbohydrate and efficacy of treatment of hypoglycaemia in insulin-treated diabetes. The participants in this study were 92 free-living adults on current insulin regimens attending scheduled diabetes clinic appointments and found to have hypoglycaemia on routine testing. The study aimed to determine comparative efficacy of different quantities of carbohydrate and wait-times to retreatment of primary hypoglycaemia. The effect of this on subsequent hyperglycaemia was also assessed.

The third paper (paper 3) investigates self-reported qualitative and quantitative patterns of food selection for self-treatment of hypoglycaemia in 119 free-living people with insulin-treated diabetes as compared with international and national guidelines, rate of absorption of carbohydrate, self-reported efficacy of treatment and subsequent hypoglycaemia.

In the fourth paper (paper 4) repeat hypoglycaemia within 2 h of a primary hypoglycaemic event is investigated in greater depth, with a questionnaire being developed, validated and administered to 169 free-living insulin-treated individuals

with a view to delineating the association (or lack of) between omission or under-treatment with carbohydrate after an initial hypoglycaemic event and repeat hypoglycaemia. A secondary aim was to investigate the association between repeat hypoglycaemia and presence or absence of symptoms and duration of action of carbohydrate.

The fifth paper (paper 5) looks at the more specialized issue of sustained hypoglycaemia post-alcohol consumption. Although the mechanism of this is well known, knowledge by those with type 1 diabetes of the key aspects of alcohol-induced sustained hypoglycaemia in the presence of insulin is not well researched, nor is the content of freely available information on this topic. Participants were 50 people with type 1 diabetes. Available information and participant knowledge were assessed according to 6 key criteria.

The last two papers investigate the specialized and under-researched area of hypoglycaemia in inpatients with diabetes on nasogastric feeding in the general ward. Paper 6 describes a retrospective review of 50 inpatients treated with insulin and insulin secretagogues on $\geq$ 3d nasogastric feeding to determine factors influencing hypoglycaemia and uses survival analysis for time to event analysis to clarify the issue of the effect of medication change on subsequent hypoglycaemic events. Paper 7 is a systematic review of the literature carried out in accordance with PRISMA and QUOROM statement guidelines and aimed to answer the questions: 1. What are the existing summary statistics of frequency of hypoglycaemia in insulin-treated adults on established nasogastric feeding in the general ward? 2. To what extent does lack of homogeneity in defining, identifying and reporting hypoglycaemia affect these statistics?

The final chapter of this thesis provides a summary of research findings and examines their contribution to existing knowledge in the area being researched. It looks at the overall limitations of the study. It makes recommendations for action on the findings and also directions for further research. Much of this has been covered in the published journal articles, however this chapter brings together the research findings with respect to the overall study objectives.

# CHAPTER 2 LITERATURE REVIEW

**Literature review ceased 15/2/2014**

**Preamble:** This literature review is structured to firstly review glucose dysmetabolism (prediabetes and diabetes) and subsequently hypoglycaemia. This is intended to elucidate the background within which hypoglycaemia is examined in this thesis.

## 2.1 Diabetes and diabetes risk

Diabetes is a group of diseases exhibiting hyperglycaemia resulting from impaired insulin secretion and/or action. Prediabetes signals an increased risk of diabetes. Prediabetes and diabetes are both diagnosed on abnormal fasting, or 2-h blood glucose levels (BGL) on an oral glucose tolerance test (OGTT) (American Diabetes Association, 2013c), although following the World Health Organisation (WHO) recommendation in 2011, elevated haemoglobin A1c (HbA1c) can also be used for diagnosis (d'Emden et al., 2012). One-hour BGL is routinely measured at OGTT but not assessed for diagnosis of prediabetes or diabetes (American Diabetes Association, 2013c). Where fasting and 2-h levels are within the normal range, prediabetes and diabetes are excluded and the OGTT is classified as normal (NGT).

### *2.1.1 Prediabetes*

**Definition**

Prediabetes is defined by one or more of the following: impaired fasting glucose (IFG) diagnosed by increased fasting glucose (≥ 6.1 and < 7 mmol/L) and/or impaired glucose tolerance (IGT), defined by fasting glucose < 6.1mmol/L and 2-hour OGTT levels (≥ 7.8 and < 11.0 mmol/L), respectively, and/or HbA1c of 5.7 - 6.4% (American Diabetes Association, 2013b). In 2003, the expert committee report of the American Diabetes Association (ADA) reduced the normal blood glucose cut-off to < 5.6 mmol/L and thus the IFG cut-off above this figure (American Diabetes Association, 2014a), however the Australian Diabetes Society do not concur with this and retain the original definition (Twigg, Kamp, Davis, Neylon, & Flack, 2007).

**Prevalence**

The prevalence of prediabetes varies widely between ethnic groups. Approximately 16.4% of Australian adults have been identified with prediabetes (Twigg, Kamp, Davis, Neylon, & Flack, 2007) compared to 4.7% in Bangladesh, 4.6% in India, 19.5% in Nepal (Jayawardena et al., 2012) and 66.3% in a developing population in South China (Zhang et al., 2012). In the majority of populations, IGT is more prevalent than IFG. Considerably fewer have IFG and less again both combined (Unwin, Shaw, Zimmet, & Alberti, 2002b).

Overweight and obesity increase the prevalence of prediabetes, with a recent UK study showing a rate of IGT of 18.1% among overweight and obese young adults (Wilmot et al., 2013). Prediabetes is also more common in those aged ≥ 40 years, with IFG more prevalent in men than women, although the reason for this is not known (Cowie et al., 2009).

**Mechanism**

Insulin resistance and β-cell dysfunction are present in both IFG and IGT (Bergman, 2013; Tabak, Herder, Rathmann, Brunner, & Kivimaki, 2012) however those with isolated IFG show greater hepatic insulin resistance including increased endogenous glucose production. They have a decrease in first phase insulin response (0 - 10 min post-consumption) and reduced response over the first 30 min with later phase insulin response (60 - 120 min) being normal. By contrast isolated IGT is characterized by greater muscle insulin resistance with subsequent hyperinsulinemia and both abnormal early and late phase insulin secretion on OGTT (Nathan et al., 2007; Tabak et al., 2012).

Prediabetes is often accompanied by obesity, hypertension, dyslipidemia and increased subclinical inflammation (Abdul-Ghani & DeFronzo, 2009; Colak et al., 2013). Adipocyte insulin resistance is present in both individuals with IFG and IGT (Abdul-Ghani & DeFronzo, 2009) and lipid accumulation in the liver appears to be an important factor in obesity-related insulin resistance (Haus et al., 2010). Body fat distribution is an additional factor affecting insulin resistance with adipose tissue within the abdominal region increasing insulin resistance (Bergman, 2013).

**Risk of diabetes**

Prediabetes confers a high risk of diabetes, with those exhibiting both IFG and IGT being at especially high risk (Bergman, 2013). Diabetes risk has been shown to progressively increase with increasing fasting BGL within the normal range (Park et

al., 2006; Tirosh et al., 2005). It has been estimated that per year, 4 - 6% of those with IGT, 6 - 9% with IFG and 15 - 19% of those with both, progress to diabetes, with 60 - 70% eventually being diagnosed with diabetes (Tabak et al., 2012). Similar proportions (5 - 10%) will revert to normoglycaemia (Gerstein et al., 2007; Tabak et al., 2012) and this is associated with a 56% reduced risk of future diabetes (Bergman, 2013). In those who develop diabetes, abnormal glucose values are sometimes observed up to 13 y before overt diabetes (Tabak et al., 2012) and this accelerates markedly 2 - 6 y preceding diagnosis of diabetes (Ferrannini et al., 2004; Mason, Hanson, & Knowler, 2007). It was demonstrated in the Insulin Resistance Atherosclerosis Study that insulin resistance, β-cell dysfunction and visceral adipose tissue were independent predictors of incidence of type 2 diabetes. Visceral adipose tissue was a stronger predictor in women than men (Hanley et al., 2009).

**Vascular risk**

Prediabetes is associated with increased incidence of vascular disease (Tabak et al., 2012). Increased risk has been variously assessed as 10% (IGT) and 40% (IFG) compared to those with normal glucose regulation (Levitzky et al., 2008) and relative risk from 0.83 - 1.34 (IGT) and 0.65 - 2.50 (IFG) (Ford, Zhao, & Li, 2010). It has not been determined if this increased risk is dependent on development of diabetes (Tabak et al., 2012) but in many studies, it remains significant even after controlling for other known risk factors, suggesting that hyperglycaemia is the determining factor (Milman & Crandall, 2011). The San Antonio Heart Study demonstrated that atherogenesis in the prediabetic state was significantly greater in insulin-resistant subjects compared to relatively insulin-sensitive subjects (Haffner, Mykkanen, Festa, Burke, & Stern, 2000) and the ADA Consensus Statement affirms that prediabetes modestly increases the hazard ratio for cardiovascular disease (~1.1 - 1.4) and that IGT is a slightly stronger risk predictor than IFG (Nathan et al., 2007). To the contrary, a community-based cohort study involving 2157 individuals with prediabetes showed that prediabetes is not an independent risk factor for cardiovascular events in older adults (Deedwania et al., 2013).

**Microvascular risk**

Typically, the cut-off glucose value defining diabetes versus prediabetes also defines the level at which diabetic microvascular complications begin to occur, but in reality diabetic retinopathy, nephropathy, and neuropathy do occur at lower levels among individuals with prediabetes (Milman & Crandall, 2011) and prediabetes can increase

risk of microvascular complications and microalbuminuria (Bahar, Makhlough, Yousefi, Kashi, & Abediankenari, 2013; Tabak et al., 2012).

**Intervention**

Some risk factors associated with prediabetes are potentially reversible. The Diabetes Prevention Program Research Group targeted excessive fasting and post-prandial BSL, excess body weight, and lack of physical activity in a trial involving 3234 adults with prediabetes. Follow-up was 2.8 y and interventions were lifestyle changes or pharmacological intervention with metformin, an oral hypoglycaemic agent. Lifestyle changes reduced diabetes incidence by 58% (95% CI 48 - 66%) and metformin by 31% (95% CI 17 - 43%), compared to placebo (Knowler et al., 2002). Similarly a meta-analysis of 10 randomised trials showed risk ratio for interventions versus control of 0.83 (95% CI 0.80 - 0.86) with lifestyle changes being more effective than pharmacotherapy (0.52, 0.46 - 0.58 versus 0.70, 0.58 - 0.85, $P < 0.05$) (Hopper, Billah, Skiba, & Krum, 2011). The ADA Consensus statement quotes figures of 25 - 60% prevention of diabetes in those with IFG and IGT with lifestyle changes and pharmacological intervention, with lifestyle changes by far the most effective (Nathan et al., 2007). This meta-analysis also addressed the effect of these interventions on vascular events and all-cause mortality and found no significant difference in risk of all-cause mortality and cardiovascular infarction and death between those with intervention and controls. There was borderline reduction for strokes (0.76, 0.58 - 0.99) with intervention versus control (Hopper et al., 2011).

### *2.1.2 Elevated one-hour postload glucose*

One-hour BGL is routinely measured at OGTT but is not a criterion for diagnosis of prediabetes or diabetes (American Diabetes Association, 2013c). Where fasting and 2-h BGL levels are within the normal range a NGT is recorded, irrespective of the level at 1 h. It has, however, been shown that individuals with a normal NGT but elevated postload 1-h BGL have a greatly increased risk of diabetes (Abdul-Ghani, Abdul-Ghani, Ali, & DeFronzo, 2008; Cubeddu & Hoffmann, 2010).

**Definition**

Yen *et al* used the terminology ‘1-h glucose spikers’, which they defined as individuals having a normal OGTT (WHO/IDF, 2006) (fasting glucose < 5.5 mmol/L and 2-hour glucose < 7.8 mmol/L) but a 1-h glucose >11.0 mmol/L (Yen,

Williams, & Twigg, 2008). Meisinger *et al* used different definitional terminology, 'elevated1-h postload glucose' but the same glucose cut-off point, on the grounds that as there was no standard criterion for defining asymptomatic hyperglycemia for a 75-g challenge at 1 h, they would use a cut-off value of 11.1 mmol/L (the 2-h cut-off point for diagnosis of diabetes), to define elevated postload plasma glucose (Meisinger, Wölke, Brasche, Strube, & Heinrich, 2006). Harada *et al* defined elevated 1-h postload plasma glucose with a cut-off at 10 mmol/L (Harada et al., 2008) citing a higher risk of developing diabetes for those with a 1-h blood glucose above this cut-off than those with a lower level (Kuzuya et al., 2002). Most other studies use the terminology 'elevated 1-h postload glucose' but use a lower cut-off point of 8.6 mmol/L (Abdul-Ghani et al., 2008; Bianchi et al., 2013; Cubeddu & Hoffmann, 2010; Kim et al., 2013; Succurro et al., 2009; Taheri, Iraj, Amini, Amini, & Aminorroaya, 2010) identifying ≥ 8.6 mmol/L as a cut-off marking increased cardiovascular and diabetes risk (Abdul-Ghani et al., 2008; Cubeddu & Hoffmann, 2010; Succurro et al., 2009).

**Prevalence**

Unlike prediabetes, there are no population-based epidemiological studies assessing prevalence of NGT with elevated 1-h BGL in the general population. Several studies have assessed prevalence in selected populations. An Australian study involving 11,925 subjects referred for OGTT aged 47 ± 16 y, using > 11 mmol/L as the cut-off, estimated that approximately 5.8% of that population were 1-h spikers (Yen et al., 2008). A Japanese study in a similar population (those referred for OGTT) showed a much higher prevalence (37.2%), possibly because they used a lower cut-off point of > 10 mmol/L (Harada et al., 2008). The GENFIEV study followed 926 Italian subjects in a cardiovascular risk study and reported 39% had NGT with 1-h postload glucose > 8.6 mmol/L (Bianchi et al., 2013) whereas in a study of 490 unselected Latino-Hispanics 8.3% exhibited NGT with 1-h postload glucose > 8.6 mmol/L (Cubeddu & Hoffmann, 2010).

**Mechanism**

<u>Normal pancreatic beta cell insulin secretion phases</u>

The effect of blood glucose levels on insulin secretion varies, so that a given glucose concentration does not give rise to a specific rate of insulin secretion. Insulin secretion appears to be modified by time-specific mechanisms. It is commonly accepted that there are 2 phases, with the first phase being a surge of insulin in

response to a fast change in blood glucose levels. This lasts about 10 min. The second phase is a sustained insulin release over a more prolonged interval. The mechanism is postulated to be a glucose sensing mechanism via the key enzyme glucokinase (Vagn Korsgaard & Colding-Jorgensen, 2006). First phase insulin is released in the first 5 - 10 min after the β-cell is exposed to a significant increase in glucose (Caumo & Luzi, 2004). It anticipates and minimizes the postprandial insulin rise (Hong et al., 2008). Both animal and human studies have shown that the mechanism is mainly mediated at the level of the liver, allowing immediate inhibition of glucose production by the liver thus restraining the rise over and after the meal (Del Prato & Tiengo, 2001), although recent research has shown a role for salivary amylase (Mandel & Breslin, 2012). Second phase insulin is released as blood glucose levels increase, and is a more sustained release, which is geared to the glycaemic load of the meal (Vagn Korsgaard & Colding-Jorgensen, 2006).

Modification of beta cell insulin secretion phases in elevated post-load glucose

Those with NGT and elevated 1-h post-load glucose have lost part, or all of their first phase insulin release (Harada et al., 2008). When first phase insulin release is lost, glucose rises rapidly after a meal which stimulates the second phase insulin release to be greater and more prolonged (Caumo & Luzi, 2004; Temelkova-Kurktschiev et al., 2000). In an older study, when first phase insulin release in people with type 2 diabetes was simulated by giving a small dose of insulin pre-meal, peak BGL was decreased and, in addition, free fatty acid levels fell at a faster rate after the meal (Bruce, Chisholm, Storlien, & Kraegen, 1988).

**Risk of prediabetes and diabetes**

All studies show increased risk of progression to prediabetes and diabetes in those with NGT and elevated 1-h postload glucose levels. An Australian study of 11,925 subjects referred for an initial OGTT conducted follow-up OGTTs at 2.8 y for 883 of the subjects and showed 35.5% conversion to IGT in those with NGT and elevated 1-h glucose as compared to 9.8% conversion rate in the population with true NGT (Yen et al., 2008). They also generated the ratio of glucose to the natural log (ln) of insulin and showed that in those with true NGT this ratio had a concave downward slope from 0 - 2 h while those with elevated 1-h postload glucose had an upward sloped curve similar to that of combined IFG and IGT, consistent with insulin deficiency with a glucose challenge. A positive glucose:ln insulin ratio differential from 0 - 1 h in elevated 1-h postload glucose, increased sensitivity in those with elevated 1-h

postload glucose who progressed to IGT, to 45.8% (Yen et al., 2008). In a study in obese Hispanic youth, a 1-h BGL ≥ 8.6 mmol/L was shown to be an independent predictor of β-cell deterioration with a 2.5 times greater likelihood of developing prediabetes during follow-up, independent of body composition (Kim et al., 2013). Cubeddu and Hoffman also identified a similar increased risk in an unselected population of 490 Latino-Hispanics (Cubeddu & Hoffmann, 2010). Unwin commented that although IGT is strongly predictive of diabetes, 40% of those diagnosed with diabetes have a NGT at baseline (Unwin et al., 2002b). It has not yet been established how many of these individuals have elevated 1-h postload glucose.

**Vascular risk and all-cause mortality**

The CATAMERIS study followed 400 individuals with NGT and elevated 1h postload glucose (> 8.6 mmol/L) and showed they had an atherogenic profile similar to those with IGT (Succurro et al., 2009). The GENFIEV study also demonstrated similar increased cardiovascular risk in those with NGT and increased 1-h postload glucose (Bianchi et al., 2013). The Erfurt Male Cohort Study followed 1160 non-diabetic men over 30 y and showed 1 h postload hyperglycemia (BGL ≥ 11.1 mmol/L) was a long-term predictor for all-cause mortality (log-rank test, $p < 0.0001$) (Meisinger et al., 2006).

### 2.1.3 *Diabetes*

**Definition**

Diabetes is differentiated from prediabetes as being a state with a significantly increased risk of microvascular damage (retinopathy, nephropathy and neuropathy) which is associated with significant morbidity and reduced life expectancy (World Health Organisation/International Diabetes Federation, 2006.). The most recent classification was carried out by the expert committee of the ADA and utilized the association between fasting plasma glucose and diagnosed retinopathy as the cornerstone in identifying glucose cut-off levels. Based on this, and data from three epidemiological studies, the committee assessed retinopathy against measured fasting plasma glucose, 2-h glucose on OGTT and HbA1c and identified cut-off levels of: fasting plasma glucose ≥ 7.0 mmol/L; 2-h glucose on OGTT ≥ 11.1 mmol/L; and HbA1c ≥ 6.5% as levels above which a marked increase in retinopathy was observed (American Diabetes Association, 2014a).

**Prevalence**

Diabetes is a significant worldwide health problem, with the Atlas of the IDF reporting 382 million people with diabetes in 2013, with a projected rise to 592 million by 2035. The IDF reports that Australia has 1,648,860 diagnosed cases of diabetes (20 - 79 y) with a national prevalence of 9.99% (International Diabetes Federation, 2013). The Australian Government Institute of Health and Welfare reports that from 1989 - 90 to 2011 - 2012, the age-standardised prevalence of diabetes more than doubled, from 1.5% to 4.2%, however, it remained stable between 2007 - 2008 (4.1%) and 2011 - 12 (4.2%). This is based on self-reported data from the National Health Survey (Australian Institute of Health and Welfare, 2013). A systematic review of 24 studies investigating diabetes prevalence and determinants in indigenous Australian populations reported a rate of diabetes varying from 3.5% to 33.1% (Minges et al., 2011).

**Classification of diabetes**

Based on etiology and pathogenesis, the vast majority of cases of diabetes fall into the following two broad categories (American Diabetes Association, 2014a):

Type 1 diabetes: Those with type 1 diabetes have an absolute deficiency of insulin secretion resulting from autoimmune destruction of the β-cells of the pancreas and those at increased risk of developing this type of diabetes are often identifiable by genetic markers. The expression of type 1 diabetes is therefore related to genetic susceptibility and environmental factors that are still not well understood (American Diabetes Association, 2014a). Autoimmune destruction of pancreatic β-cells over time eventually result in a complete lack of endogenous insulin which is associated with secondary abnormalities in glucagon, and, as the disease progresses defects in counterregulatory responses develop (McCall & Farhy, 2013).

According to the National Health Survey (2011-2012), in Australia in 2011 - 2012 approximately 119,000 people (or 11.9% of those with diabetes) had diagnosed type 1 diabetes; approximately 53% males and 47% female. Type 1 diabetes can be diagnosed at any age. A Swedish study which assessed all new cases of type 1 diabetes diagnosed during a 3 y period by antibody testing, reported an incidence of type 1diabetes which was highest at ages 0 - 9 y and then again at ages 50 - 80 y. Almost 60% of new type 1 cases were diagnosed in people over age 40 y (Thunander et al., 2008). In Australia the level of detail on prevalence of type 1 diabetes obtained from the National Health Survey is limited due to the low incidence of type 1

diabetes but the evidence is that for people aged 45 y or more, 0.6% have type 1 diabetes, compared with 0.3% among those aged less than 45 y. (Australian Institute of Health and Welfare, 2013). Australia has the highest estimated incidence rate of type 1 diabetes in the Pacific region in children, with 22.3 cases per 100,000 children (International Diabetes Federation, 2013). The 2011 NHMRC National Evidence-Based Clinical Care Guidelines in Type 1 Diabetes assert grade A evidence that at present there are no recommended interventions to delay or prevent the onset of type 1 diabetes (Craig et al., 2011).

Type 2 diabetes: The mechanism of type 2 diabetes varies from insulin resistance, with relative rather than absolute insulin deficiency, to a defect in insulin secretion with associated insulin resistance. Type 2 diabetes is progressive over time with β-cell function declining, making control of BGL progressively more difficult over time (Corathers, Peavie, & Salehi, 2013). Obesity is associated with insulin resistance. Adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones and proinflammatory cytokines which potentiates the development of insulin resistance (Kahn, Hull, & Utzschneider, 2006) and both overall and abdominal adiposity strongly predict risk of type 2 diabetes (Wang, Rimm, Stampfer, Willett, & Hu, 2005). However, the evidence shows there are many different causes of type 2 diabetes with many specific aetiologies not thoroughly elucidated, but, unlike type 1 diabetes, autoimmune destruction of β-cells does not occur (American Diabetes Association, 2014a).

Type 2 diabetes has a much higher prevalence than type 1. In Australia in 2011 - 2012, 848,000 people (or 84.9% of those with diagnosed diabetes) had type 2 diabetes. In 2007 - 2008, approximately 3.8% of Australians had been diagnosed with type 2 diabetes. Slightly more males than females had type 2 diabetes (4.3% and 3.3% respectively). Prevalence increased with increasing age, from 0.1% of those aged 0 - 34 y to 14.7% of age 65 - 69 y, then decreasing to 12.4% of those ≥ 80 y (Australian Institute of Health and Welfare, 2013).

**Treatment of diabetes**

In the absence of some form of endocrine pancreas transplant, diabetes at present has no cure and treatment of both types of diabetes has the aim of controlling glycaemia with positive adjunct effects on complications of diabetes.

Type 1 diabetes: As type 1 diabetes is characterised by insulin deficiency, the standard treatment at present, is insulin replacement with dietary modification

designed to balance the pattern of insulin action. The main goal of treatment is physiological replication of normal insulin secretion (McCall & Farhy, 2013).

Conventional insulin regimes incorporate both basal and premeal preparations. Previously, absorption of regular human insulin was slow, with metabolic effect up to 60 min after injection, tending to give postprandial hyperglycaemia and possible later hypoglycaemia. Basal insulin action was not consistent, but peaked and exhibited variable absorption affecting glycaemic control (Swinnen, Hoekstra, & DeVries, 2009). Research is ongoing in both identifying insulins and insulin regimes which more closely approximate the true physiological situation and also investigating more effective routes of insulin delivery (McCall & Farhy, 2013). Insulin analogs with modified amino acid sequences have been developed allowing faster insulin absorption, action and enhanced dissipation (Hirsch, 2005). The decreased variability and more physiological action of analog insulins allowed improved glycaemic control with lower risk of hypoglycaemia (Hermansen et al., 2004) and the 2011 NHMRC National Evidence-Based Clinical Care Guidelines in Type 1 Diabetes assigns grade 3 evidence to the use of human insulin and insulin analogues (Craig et al., 2011).

Technological advances in the area of insulin delivery include insulin pens, insulin pumps and the ultimate ongoing development of artificial pancreas closed-loop technology. Insulin pumps or continuous subcutaneous insulin infusion (CSII) allow a more physiological delivery of insulin with, in many cases, reduction in glycaemic excursions and improved quality of life (Cummins et al., 2010; McCall & Farhy, 2013). Pancreatic transplantation, which was first carried out 25 y ago, is the only existing therapy allowing normal glucose control without exogenous insulin, however it carries with it the risks associated with immuno-suppression and rejection. Although 32,000 procedures have been carried out worldwide, it is proportionally a little-used therapy at present (Iacovidou & Hakim, 2013).

Type 2 diabetes: Diet and exercise are the cornerstones of treatment of type 2 diabetes (Avery, Flynn, van Wersch, Sniehotta, & Trenell, 2012; Vetter, Amaro, & Volger, 2014). Weight loss reduces insulin resistance and therefore improves glycaemic control, with even 5 - 10% loss of body weight being significant. Surgical intervention such as lapbanding is increasingly being used (Inzucchi et al., 2012). Maintaining glycaemic control over time becomes progressively more difficult as a result of declining β-cell function and additional therapy is required to maintain

control (Corathers et al., 2013). As type 2 diabetes is not associated with absolute insulin deficiency, oral therapy, in addition to diet and exercise, is normally the next stage of treatment. The situation with respect to treatment of type 2 diabetes is complex and there are an increasing number of therapies available (Inzucchi et al., 2012). Metformin, a biguanide, is the usual first-line medication recommended. It acts to reduces hepatic glucose output, has some action to improve β-cell function, and does not cause hypoglycaemia, however it is a gastric irritant and is not always tolerated (Inzucchi et al., 2012; Lu, Zang, & Li, 2013). Combination therapy, adding in one or two oral or non-insulin injectible agents may be a next step (Inzucchi et al., 2012). Oral agents are sulphonylureas and meglitinides which stimulate insulin secretion but also potentiate weight gain and hypoglycaemia; thiazolidinediones, that facilitate insulin action, potentiate weight gain but not hypoglycaemia, dipeptidyl peptidase-4 inhibitors that increase insulin secretion proportionate to BGL, have some effect improving β-cell function and are not associated with hypoglycaemia, and alpha-glucosidase inhibitors that delay digestion and absorption of intestinal carbohydrate, are not associated with hypoglycaemia but frequently cause flatulence (Consoli & Di Fulvio, 2013; Inzucchi et al., 2012; Lu et al., 2013; Plosker, 2014).

A recently developed group of medications are the sodium-glucose linked transporter 2 (SGLT2) inhibitors (SGLT-2). These agents inhibit renal glucose reabsorption resulting in glucosuria and therefore a reduction of blood glucose. They lower both fasting and postprandial blood glucose levels, aid weight loss and do not cause hypoglycaemia (Angelopoulos & Doupis, 2014).

Non-insulin injectible agents are glucagon-like peptide-1 receptor agonists which potentiate insulin action proportional to BGL, increase satiety and potentiate weight loss with negligible hypoglycaemia (Inzucchi et al., 2012; McCormack, 2014). Due to progressive destruction of β-cells, insulin therapy is often required over time in many with type 2 diabetes, although there is disagreement on when this should be commenced (Swinnen et al., 2009). Insulin therapy potentiates weight gain and is associated with hypoglycaemia but has a positive effect on β-cell function (Rotella, Pala, & Mannucci, 2013; Swinnen et al., 2009). All medications have variable effects on other complications of diabetes, however this is considered outside the scope of this review.

**Methods of assessing diabetes control**

The main methods for assessment of diabetes control are monitoring of blood or interstitial glucose, and measurement of HbA1c (American Diabetes Association, 2014b).

Capillary blood glucose level: BGL is an assessment of diabetes control in the short term. Laboratory assessment of BGL is by venous plasma levels. Measurement of BGL by free-living people and at point of care is normally by glucose meter, which measures capillary blood and provides an almost immediate result (Tonyushkina & Nichols, 2009).WHO publishes capillary blood equivalence values for venous plasma values for glucose, but questions have been raised as to the reliability of these. There is evidence that venous results may be higher than capillary in fasting and random blood samples but lower in post-prandial samples, with a maximum of 10% error, depending on the level of glucose measured (Colagiuri et al., 2003). **T**he International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Scientific Division Working Group on Selective Electrodes and Point-of-Care Testing have recommended that a factor of 1.11 should be used in converting a capillary blood glucose value to plasma glucose. The recommendation from the ADA is that blood glucose meters must agree with laboratory results to within ± 15%, and that this be reduced to ±5% in future (Tirimacco et al., 2013). The International Standards Organisation is thus revising its criteria that currently state that 95% of the individual glucose results should fall within ± 0.83mmol/L of the results of the manufacturer's measurement procedure at glucose levels <4.2mmol/L and within ±20% at glucose levels ≥4.2mmol/L (Kristensen & Sandberg, 2010).

The performance of blood glucose meters is important, and the level of performance will be dependent on their intended clinical use. Test principals of blood glucose meters are either electrochemical sensor, electrochemical coulometric, optical photometric or amperometric. Sample blood volume needed for testing varies from 0.3 - 4 μL. The range of blood glucose they can accurately test varies from 0.6 - 33.3 mmol/L with 1.1 - 33.3 mmol/L being the most common range. The time it takes to complete the test varies from 4 - 26 sec with 5 and 6 sec being the most common test times (Tirimacco et al., 2013).

The ADA recommends people on multiple daily insulin injections (MDI) or CSII do preprandial and occasional postprandial self-monitoring of blood glucose (SMBG), also before exercise and driving, post hypoglycaemia and for problem-solving

lifestyle changes (American Diabetes Association, 2014b). SMBG in type 2 diabetes is less defined, with a fasting and major postprandial measurement often recommended. The NHMRC clinical guidelines recommend preprandial blood glucose targets of 3.9 - 6.7 mmol/L, postprandial 5 - 10 mmol/L and at 3am (measured weekly) > 3.6 mmol/L, although they stress there are individual differences (Craig et al., 2011).

There is conflicting evidence as to whether SMBG benefits glycaemic control in those with type 2 diabetes (Davis, Bruce, & Davis, 2006; McAndrew, Schneider, Burns, & Leventhal, 2007), however there is also evidence that increased frequency of SMBG among new users was associated with improved glycaemic control regardless of diabetes treatment (Karter et al., 2006) with efficacy > 1 y decreasing, especially in those with type 2 diabetes (Boren & Clarke, 2010). SMBG is the cornerstone of diagnosis and management of hypoglycaemia.

Interstitial blood glucose: The ADA Guidelines For Clinical Practice assert that continuous glucose monitoring of interstitial glucose levels (CGM) can be beneficial to glycaemic control in adults ≥ 25 y on intensive insulin regimens, although, at present CGM is not common practice (American Diabetes Association, 2014b). An advantage of CGM is that it can provide semi-continuous information and identify changes in glucose levels that may have been missed by SBGM. There are two systems of CGM : retrospective and real-time (Langendam et al., 2012). Real-time CGM correlates well with plasma glucose, however calibration with SMBG is required and SMBG is still necessary for making acute decisions (American Diabetes Association, 2014b). Average error for CGM is approximately 15%, with increased error at times of rapid change of glucose levels and with hypoglycaemia. This is related to the transference of glucose from the capillary to interstitial fluid by simple diffusion, with the lag during times of rapid change of glucose probably due to the magnitude of concentration of glucose (Cengiz & Tamborlane, 2009).

Langendam *et al* have shown that sensor-augmented insulin pumps improved glycaemic control in new pump users (Langendam et al., 2012). A Chinese study of the accuracy of a sensor-augmented pump involved 48 patients with type 1 or 2 diabetes, with comparison of 1,317 paired blood-sensor values and reported 88.3% accuracy but concluded that although there was high accuracy in monitoring real-time continuous changes and predicting blood glucose trends, it lacked accuracy with respect to diagnosis of hypoglycaemia and that clinical symptoms should be taken

into account for this (J. Zhou et al., 2012). A recent short-term study comparing newer generation sensors showed improved accuracy and consistency with respect to hypoglycaemia, with the variation coefficient being 7% versus 11%, but the conclusion was that although CGS can provide an alert for hypoglycaemia, or developing hypoglycaemia, at present it lacks the point accuracy of current blood glucose monitors for diagnoses and management of hypoglycaemia (Christiansen et al., 2013).

HaemoglobinA1c: Measurement of HbA1c is a longer term measure of glycaemic control (American Diabetes Association, 2014b). HbA1c consists of a number of stable haemoglobin components which are generated non-enzymatically from haemoglobin and glucose. The rate of formation of HbA1c is directly proportional to the concentration of glucose in the blood. Erythrocytes are permeable to glucose, therefore erythrocyte level of HbA1c is an indicator of the glucose level over the previous 120 days, which is the average lifespan of an erythrocyte (Goldstein et al., 2004). Varied analytic aspects are used for measurement of HbA1c. High-performance liquid chromatography is used to measure the difference in charge between HbA1c and other haemoglobin fractions, and affinity chromatography and immunochemical methods measure the difference in molecular structure. Affinity chromatography is considered to have the least problems with interference and abnormal haemoglobin variants. This has resulted in different results in different laboratories generating the need for standardization (Weykamp, John, & Mosca, 2009). The International Federation of Clinical Chemistry (IFCC) Working Group on Standardisation of HbA1c has been establishing International Reference Methods for HbA1c (Goodall, 2005). The 2007 Consensus Statement On The Worldwide Standardisation Of The Hba1c Measurement by the ADA, European Association for the Study of Diabetes (EASD), IFCC and Laboratory Medicine, and the IDF has recommended that results from this new reference method be compared with results from current methodologies. The IFCC recommends that test results be provided in scientifically correct S1 units, mmol/mol, so an HbA1c value of 5% would become approximately 33 mmol/mol (American Diabetes Association, International Federation of Clinical Chemistry and Laboratory Medicine, & and the International Diabetes Federation, 2007). A more recent consensus statement (2010) by the ADA, the EASD, the IDF, the IFCC and Laboratory Medicine and the International Society for Paediatric and Adolescent Diabetes concurred that the IFCC reference system for

HbA1c should be the standard measurement, and that HbA1c results be reported worldwide in SI units (mmol/mol) and derived National Glycohemoglobin Standardization Program units (%), using an IFCC-National Glycohemoglobin Standardization Program master equation (Hanas & John, 2010).

Mathematical modelling and in vivo studies have shown that a large change in mean blood glucose is accompanied by a large change in HbA1c within a matter of 1.2 weeks, however large variations in blood glucose levels will show an unrepresentative HbA1c and therefore frequent hypoglycaemia skews HbA1c (Goodall, 2005). The ADA recommends that HbA1c be measured twice a year in those with good glycaemic control, and every three months in those with fluctuating control (American Diabetes Association, 2014b). As stated previously, HbA1c is strongly predictive for diabetes complications, however it does not have a role in diagnosing or managing hypoglycaemia.

**Complications of diabetes**

In 2010, nearly 7,750 Australians died from diabetes and diabetes- related causes, 5.4% of all deaths in Australia (Australian Institute of Health and Welfare, 2012). Long-term complications of diabetes are the major cause of morbidity and mortality in those with diabetes and are the result of ongoing damage to small and large blood vessels and nerves throughout the body. These complications include retinopathy, potentially leading to blindness; nephropathy potentially leading to chronic renal failure; peripheral neuropathy, which can lead to foot ulcers and amputations, and autonomic neuropathy which can cause gastrointestinal symptoms and sexual dysfunction. Those with diabetes have increased incidence of cardiovascular and cerebrovascular disease, hypertension and abnormal lipid metabolism (American Diabetes Association, 2013b). Diabetes is an independent risk factor for cardiovascular disease (CVD), which is the major cause of morbidity and mortality for people with diabetes (American Diabetes Association, 2013b). In Australia, in 2007 - 2008, based on self-reported data from the National Health Survey, 58% of people with diabetes had cardiovascular disease (Australian Institute of Health and Welfare, 2013).

The causes of the complications of diabetes are the subject of ongoing research. Whole body glucose metabolism uses a variety of metabolic pathways, therefore chronic hyperglycaemia can induce diverse cellular changes. Genes also play a role in processes leading to complications of diabetes, as does duration of diabetes, and

there is evidence too that increased oxidative stress has a role in the pathogenesis of these complications (Sheetz & King, 2002). Prevention or minimization of complications of diabetes mainly involves strategies to optimize glycaemic control, blood pressure and lipid levels (American Diabetes Association, 2014a) with the 2011 NHMRC National Evidence-Based Clinical Care Guidelines in Type 1 Diabetes assigning grade B evidence to the implementation of intensive glycaemic control to reduce the risk of onset or progression of diabetes complications (Craig et al., 2011). The first (glycaemic control) impinges directly on the topic of hypoglycaemia and will be examined in more detail.

Because complications of diabetes are occur in both type 1 and type 2 diabetes, which have hyperglycaemia as their common feature, it was historically suspected that hyperglycaemia played a major role in the pathogenesis of those complications (DCCT Research Group, 1990). The Diabetes Control and Complications Trial (DCCT) carried out between 1982-1993, was set up to test this hypothesis and to determine whether diabetes complications in those with type 1 diabetes could be prevented or delayed. It was a controlled clinical trial with 1,441 subjects with type 1 diabetes, which compared intensive therapy, aimed at achieving BGL as close to the normal range as possible, with conventional therapy aimed at safe asymptomatic diabetes control. The results showed that those on intensive therapy had a median HbA1c of 7%, compared to 9% in the conventional group and had a reduction of a 35-76% in the early stage microvascular disease. A follow-up observational study, The Epidemiology of Diabetes Interventions and Complications Study, investigated the effects on the more advanced stages of diabetes complications, including CVD and found similar results. The major adverse effect of intensive therapy was an increased risk of severe hypoglycaemia (Nathan, 2014).

A similar study was carried out in those with type 2 diabetes, The UK Prospective Diabetes Study (UKPDS). In the study, 3,867 newly diagnosed patients with type 2 diabetes were randomly assigned to intensive treatment with a sulphonylurea or insulin, or conventional treatment with diet. In the conventional group, medication was added only if there were symptoms of hyperglycaemia or BGL $\geq$ 15 mmol/L. Over 10 years, HbA1c was 7.0% in the intensive group compared with 7.9% in the conventional group and the risks of microvascular complications were reduced 25% in the intensive group compared to the conventional group. Rates of hypoglycaemia per year were 0.7% with conventional treatment and 1.0 - 1.8% with intensive

treatment, depending on the treatment agent used (Genuth, 2008; UKPDS Group, 1998).

## 2.2 Hypoglycaemia

### Introduction

Hypoglycaemia is a blood glucose level below the normal range which may be asymptomatic or have associated adrenergic or neuroglycopenic symptoms. It is not possible to identify a single plasma glucose level that defines hypoglycaemia, therefore it is recommended that, in the absence of diabetes, under clinical conditions of investigation, it is confirmed by documentation of Whipple's triad which consists of: symptoms and signs consistent with hypoglycaemia, a low plasma glucose level and resolution of those symptoms or signs after the plasma glucose concentration is raised (Cryer et al., 2009; Guettier & Gorden, 2006).

### 2.2.1 *Physiology and symptoms*

### Normal physiology

In the healthy individual, hypoglycaemia of magnitude sufficient to impair cognition is prevented by counterregulation (Amiel, 2009). The central nervous system processes and coordinates the response to an acute drop in BGL, which triggers a sequence of counterregulatory responses involving hormones, the autonomic nervous system and the level of glucose itself. This involves a decrease in insulin secretion followed by a rise in systemic glucagon, a rise in adrenaline, growth hormone, and cortisol. There is increasing evidence that β-cell insulin secretion inhibits glucagon secretion and a decrease in insulin secretion potentiates an increase in glucagon secretion during hypoglycaemia. Increased glycogenolysis is potentiated by the decrease in insulin secretion, the rise in systemic glucagon and the rise in epinephrine. Decreased glucose uptake by insulin-dependent tissue is potentiated by the drop in insulin secretion and increased epinephrine. Increased epinephrine also potentiates increased gluconeogenesis and decreased insulin secretion. Overall, these counterregulatory responses limit glucose use by peripheral tissues and increase endogenous glucose production with a resulting rise in glucose. Subjectively, the individual becomes aware of the symptoms and signs of hypoglycaemia, and generally responds to these by seeking food. These very effective mechanisms ensure

that clinical hypoglycaemia is rare in the healthy individual (Cryer, 2011; Guettier & Gorden, 2006; McCrimmon, 2009).

Oxidation of glucose provides more than 90% of the energy needed for the brain. The brain is unable to synthesize glucose and has glucose stores sufficient for only a few minutes. Therefore it is almost totally dependent on a continuous supply of glucose from the bloodstream (Bolli & Fanelli, 1999). Glucose sensors, neurons shown to be regulated by glucose, have been found in a number of brain areas (McCrimmon, 2009). In an in vivo study using fura-2 calcium imaging to assess neuronal response to glucose levels Zhou *et al* have identified the medial amygdalar nucleus area of the brain as one of the glucose-sensing regions. They also suggested that urocortin 3 receptor may provide feedback to inhibit counterregulatory responses (Zhou et al., 2010). Paranjape *et al* have shown, in animal studies, that in addition to insulin acting locally in regulating secretion of glucagon from the pancreas, the ventromedial hypothalamus may be a mediating agent in both euglycaemia and hypoglycaemia (Paranjape et al., 2010) and McCrimmon *et al* have identified AMP-activated protein kinase in the ventromedial hypothalamus as playing a key role in detecting hypoglycaemia and initiating counterregulatory responses to raise glucose levels (McCrimmon et al., 2008). Tong *et al*, in similar animal studies have shown that release of glutamate from the ventromedial hypothalamus is also a key factor in counterregulatory mechanisms (Tong et al., 2007), with Zhu *et al* similarly suggesting that during hypoglycaemia a decreased glucose within the ventromedial hypothalamus rapidly inactivates gamma-aminobutyric acid activated (GABAergic) neurons, which decreases inhibitory GABAergic tone, which potentiates glucose counterregulation (Zhu et al., 2010).

There are several origins of typical symptoms experienced with hypoglycaemia. Firstly, an acute fall in blood glucose level is associated with increased autonomic nervous system activity which gives adrenergic and cholinergic symptoms such as anxiety, tremulousness, palpitation, sweating, nausea and hunger. When hypoglycaemia was induced experimentally by an insulin infusion of different concentrations, feelings of hunger were significantly less intense with a high concentration insulin infusion than during moderate insulin infusion with the investigators concluding that peripheral insulin levels seemed to be associated with the intensity of feelings of hunger (Hermanns et al., 2008). Secondly, brain glucose deprivation compromises the functioning of the central nervous system giving

neuroglycopenic symptoms such as confusion, sensation of warmth, weakness or fatigue, severe cognitive failure, seizure and coma (Cryer, 1999; Guettier & Gorden, 2006).

Adrenergic symptoms of hypoglycaemia following consumption of a meal with a large glycaemic load have been reported to be present in some normals who do not exhibit the complete Whipple's triad and this has been termed idiopathic reactive hypoglycaemia (Sorensen & Johansen, 2010). In a review of this condition, Scheen et al assert that a diagnosis of hypoglycaemia is rarely confirmed (Scheen & Lefebvre, 2004), whereas Sorensen et al in a study of 362 healthy subjects with normal glucose metabolism identified 12.4% as having idiopathic reactive hypoglycaemia based on documented 1-h- or 2-h postprandial glucose levels $< 3.9$ mmol/L (Sorensen & Johansen, 2010). As the Endocrine Society Clinical Practice Guidelines recommend evaluation and management of hypoglycaemia only in patients in whom Whipple's triad is documented (Cryer et al., 2009), the level of glycaemia defining hypoglycaemia is pivotal to this diagnosis, and this is discussed in section 2.2.2.

**Diabetes**

General: Because normal counterregulatory responses to falling plasma glucose levels are so effective, hypoglycaemia is rare in the general population, however this is not the case in diabetes when insulin or insulin secretagogues are used to lower blood glucose levels (Cryer et al., 2009). In diabetes, hypoglycaemia results from an absolute or relative insulin excess and is a byproduct of treatment with exogenous insulin and/or oral hypoglycaemic agents and also compromised glucose counterregulation in type 1 and advanced type 2 diabetes. (American Diabetes Association, 2005; Cryer et al., 2003). Physiological responses are compromised with the loss of the normal decrease in insulin and increase in glucagon and epinephrine in response to falling blood glucose levels. The loss of the glucagon and insulin responses are due to progressive failure of the beta-cells. This develops early in type 1 diabetes but later in those with type 2 diabetes (Cryer, 2011). In type 1 diabetes, insulin is delivered exogenously and therefore insulin levels cannot decrease in response to falling glucose levels, as would happen in the normal situation, and the combination of this fact with compromised glucagon and

epinephrine responses contributes to defective glucose counterregulation (American Diabetes Association, 2005).

Hypoglycaemic unawareness: The main factor determining how the brain responds to hypoglycaemia seems to be previous exposure to a specific level of blood glucose (Amiel, 2009; McCrimmon, 2009). So in diabetes, where control has been tight and blood glucose levels have been maintained at the low end of the normal range, the counterregulatory response is only activated at a level of blood glucose well below normal physiological levels and thus the person with diabetes has unawareness of their hypoglycaemia (Amiel, 2009). The resulting neurogenic responses to lower plasma glucose levels and a shift in the glycaemic threshold for the sympathoadrenal system, which includes epinephrine, means antecedent hypoglycaemia potentiates further hypoglycaemia and further impairment of glucose counterregulation termed hypoglycaemia-associated autonomic failure in diabetes (HAAF) (Cryer, 2013). A recent study has investigated the effects of antecedent hypoglycaemia using a sensor augmented insulin pump which allows insulin suspension at a designated level, the threshold suspend (TS) feature. Hypoglycaemia was induced by exercise, and subjects were randomly assigned to one of two groups, with group one having TS in Period 1 and control in Period 2 and group 2 the reverse. Hypoglycaemia was 63.7 min shorter when TS preceded control, indicating that the TS feature's ability to mitigate hypoglycaemia was decreased by an episode or episodes of prolonged antecedent hypoglycaemia (Garg et al., 2014).

When hypoglycaemia is prolonged, the brain in unable to maintain glucose levels, and as the level of cerebral glucose falls, there are changes in EEG, increased oxidative stress, and death of neurons (Jensen, Bogh, & Lykkesfeldt, 2014).

Compromised counterregulatory responses are attributed partly to failure of β-cells resulting in a failure of the normal mechanism whereby β-cell insulin secretion inhibits glucagon secretion and a decrease in insulin secretion potentiates an increase in glucagon secretion during hypoglycaemia. Loss of both insulin and glucagon responses develop early in type 1 diabetes but only in advanced type 2 diabetes (Cryer, 2011) and the pathophysiology of HAAF explains why the incidence of hypoglycaemia increases as absolute endogenous insulin secretion decreases (Cryer, 2013). In type 1 diabetes, insulin is delivered exogenously and therefore insulin levels cannot decrease in response to falling glucose levels, as would happen in the normal situation, and the combination of this fact with compromised glucagon and

epinephrine responses contributes to defective glucose counterregulation. This results in the clinical syndrome of hypoglycaemia unawareness, that is a loss of the warning symptoms that previously alerted the person with diabetes to recognize the onset of hypoglycaemia and take action to raise blood glucose levels (American Diabetes Association, 2005). A study of 518 people with type 1 diabetes over a 2-year period showed that 19.5% had impaired awareness of hypoglycaemia. Compared to those with normal awareness they were significantly older, had longer duration of diabetes, and had a six-fold higher frequency of severe hypoglycaemia in the previous year (Geddes, Schopman, Zammitt, & Frier, 2008). Avoidance of hypoglycaemia for 2 - 3 weeks restores hypoglycaemic awareness in most affected people (Cryer, 2013; de Galan, Schouwenberg, Tack, & Smits, 2006; Vignesh & Mohan, 2004).

### 2.2.2 *What level defines hypoglycaemia?*

The ADA Working Group on hypoglycaemia defined hypoglycaemia in diabetes as being: episodes of abnormally low blood glucose that expose the individual to potential harm (American Diabetes Association, 2005). This must include episodes of hypoglycaemia without symptoms, as these will predispose the individual to further hypoglycaemic episodes. It is not possible to state a level of blood glucose that uniquely defines hypoglycaemia, because the level of glucose where symptoms occur is variable, as are other manifestations of hypoglycaemia (Cryer, 2010). The ADA Working Group on defining and reporting hypoglycaemia in diabetes recommended that people with diabetes should be aware of the possibility of developing hypoglycaemia at a SBGM level of BGL $\leq$ 3.9 mmol/L. The rationale given for this was that 3.9 mmol/L is the level at which a hormonal glucose counterregulatory response is triggered in those without diabetes and therefore a BGL lower than this would be physiologically identified as antecedent hypoglycaemia, with consequent reduction of counterregulatory hormone response to a subsequent episode of hypoglycaemia (Seaquist et al., 2013). This has often been extrapolated in patient education material to the slogan '4's the floor', with the implication that 4 mmol/L defines the specific onset of hypoglycaemia requiring treatment (Diabetes Co UK, 2013; Medical Update Co. UK, 2013), rather than a level which alerts the person with diabetes of the need for self-awareness of the putative risk of hypoglycaemia (Clarke & Foster, 2012). Cryer asserts that the working group recommendation is not for mandatory treatment of a BGL $\leq$ 3.9

mmol/l but it does mean considering a variety of actions (including self-treatment) such as repeating the BGL measurement, avoiding exercise, avoiding driving and adjustments to treatment regimens (Cryer, 2009). Frier, although agreeing with much of the ADA Working Group's other conclusions on hypoglycaemia, has a major disagreement with the ≤ 3.9 mmol/L cut-off, asserting that this level would be observed by many clinicians in fasting adults without diabetes. He also comments on what he terms 'biochemical hypoglycaemia', a BGL below the normal level with no symptoms of hypoglycaemia, commenting on the difficulty of ascertaining at what level this commenced. He argues that the studies on which the ADA recommendation was based used the 'unphysiological' glucose clamp technique, not comparable with the normal situation. He posits that in those without diabetes and those with type 1 diabetes who retain normal hypoglycaemic awareness and maintain reasonable diabetes control, symptoms of hypoglycaemia and cognitive dysfunction commence only when BGL approaches 3.2 mmol/L and thus suggests an arbitrary cut-off of 3.5 mmol/L (Frier, 2009). Amiel *et al* also disagree with a cut-off of ≤ 3.9 mmol/L as overestimating frequency of hypoglycaemia. They point out that many surgeons and forensic pathologists use glucose cut-off levels < 2.2 mmol/L, to avoid defining healthy people as hypoglycaemic. They support the recommendation by the European Medicines Agency, an EU regulatory agency for the evaluation of medicinal products, that < 3.0 mmol/L be the cut-off when assessing the hypoglycaemic risk of different medications, asserting it is the level defining impaired cognitive function and is a level of clinical significance. In addition, avoidance of BGL < 3.0 mmol/L has been shown to restore hypoglycaemic awareness (Amiel, Dixon, Mann, & Jameson, 2008).

Swinnen *et al*, using data from two trials examining insulin glargine use in 12,837 people with type 2 diabetes, quantified the effect of an alteration of cut-off point for the definition of hypoglycaemia. They reported that a change in cut-off from < 3.1 to < 3.9 mmol/L more than doubled the recorded frequency of hypoglycaemia and the proportion of participants with asymptomatic hypoglycaemia increased from 30.7% to 61.7% at < 3.9 mmol/L compared to < 3.1 mmol/L. They concluded that the cut-off should be lower than the < 3.9 mmol/L recommended by the ADA (Swinnen, Mullins, Miller, Hoekstra, & Holleman, 2009). Contrary to this, Cryer has heatedly defended the level of 3.9 mmol/L as the only safe definitional level for

hypoglycaemia, on the grounds that the issue is not documenting frequency of clinical hypoglycaemia but rather preventing clinical hypoglycaemia (Cryer, 2009).

At present, therefore, there is no consensus on the blood glucose level defining hypoglycaemia, and no prospect of agreement. Until these divisions are resolved, a comprehensive benchmarking process that would allow institutions to compare inpatient diabetes control to accepted guidelines cannot be developed (Cook, Wellik, Kongable, & Shu, 2012) and, from a research perspective, mitigates against valid interstudy comparisons quantifying hypoglycaemia.

### 2.2.3 *Classification of hypoglycaemia*

The ADA Working Group on hypoglycaemia has suggested classification of hypoglycaemia in diabetes in adults. The suggested categories are as follows:

Severe hypoglycaemia: defined by the working group as a hypoglycaemic event where the assistance of another person is needed to actively administer treatment. In the absence of a documented BGL, neurological recovery following normalization of BGL is considered confirmation of the cause being a low BGL (Seaquist et al., 2013). No level of BGL was assigned by the working group but they cited two studies which used definitional levels for severe hypoglycaemia of < 2.8 mmol/L and < 2.2 mmol/L respectively (Krinsley & Grover, 2007; Turchin et al., 2009).

Documented symptomatic hypoglycaemia: defined by the working group as a hypoglycaemic event with typical hypoglycaemic symptoms and a measured BGL < 3.9 mmol/L.

Asymptomatic hypoglycaemia: defined by the working group as a hypoglycaemic event without typical hypoglycaemic symptoms and a measured BGL < 3.9 mmol/L.

Probable symptomatic hypoglycaemia: defined by the working group as a hypoglycaemic event with typical hypoglycaemic symptoms but no measured BGL < 3.9 mmol/L (Seaquist et al., 2013).

Pseudo-hypoglycaemia or relative hypoglycaemia (American Diabetes Association, 2005; Seaquist et al., 2013): defined by the working group as an event with typical hypoglycaemic symptoms with a measured BGL > 3.9 mmol/L. This reflects the fact that those with persistently high BGL levels can experience hypoglycaemic symptoms at > 3.9 mmol/L as BGL declines toward that level (American Diabetes Association, 2005). This event is associated with the release of counterregulatory hormones and is most likely to happen when treatment is revised and glycaemic

control improves. It usually takes 2 - 4 weeks for the brain to readjust to the relatively reduced glucose levels (Briscoe & Davis, 2006). This is because the main determinant of the glucose levels at which the brain responds actively to hypoglycaemia appears to be recent antecedent glucose levels, thus those accustomed to chronic high glucose levels may trigger symptomatic stress responses as the blood glucose falls, even though it is still within the normal range. This can make improvement in glycaemic control difficult (Amiel, 2009; McCrimmon, 2009). The latter four classifications are obviously dependent on definitional level of hypoglycaemia (see section 2.2.2).

The ADA Working Group investigating Defining and Reporting Hypoglycaemia in Diabetes has suggested a further classification as follows:

Nocturnal hypoglycaemia - hypoglycaemia in type 1 diabetes occurs most frequently during sleep and can range in severity from asymptomatic mild hypoglycaemia to severe, potentially fatal hypoglycaemia. Even asymptomatic nocturnal hypoglycaemia exacerbates defective glucose counterregulation thus increasing hypoglycaemic risk. The working party therefore recommends that hypoglycaemic events be defined as daytime or nocturnal events (American Diabetes Association, 2005). Night-time is the longest post-absorptive state with people with diabetes having variable insulin needs throughout the night, with less need for insulin between 0 h and 3h and increased needs between 4h and 7h, mainly due to decreased hepatic insulin sensitivity (Bolli, 2001). Wentholdt et al in a study of 57 people with type 1 diabetes using a glucose sensor showed 33% incidence between 22h and 7h with bedtime glucose being the strongest predictor. There was no difference between those treated with CSII or MDI (Wentholt et al., 2007).

### 2.2.4 *Self-treatment of hypoglycaemia*

Many reviews of hypoglycaemia do not discuss, or merely touch on, the topic of self-treatment of hypoglycaemia; often simply recommending that people with diabetes carry or ingest readily accessible carbohydrate (American Diabetes Association, 2005; Amiel et al., 2008; Amiel, 2009; Seaquist et al., 2013). There is a lack of consensus from sources giving more detailed recommendations, and rationales for these recommendations are often poor (American Diabetes Association, 2008, 2014b; Asian-Pacific Type 2 Diabetes Policy Group, 2002; Bantle et al., 2008; Boyle

& Zrebiec, 2007; Briscoe & Davis, 2006; Cryer et al., 2003; Diabetes Australia, 2009; Diabetes Education Study Group of the European Association for the Study of Diabetes, 1998; Diabetes New Zealand, 2008; Diabetes UK, 2011). There would seem to be a need to provide additional/alternative guidelines. For more discussion on this, see section 4.1.1. Similarly, there is little published information on whether people with diabetes follow these guidelines, what they actually ingest to self-treat their hypoglycaemia, and the efficacy of this self-treatment. Studies available are often dated and report responses to now-outdated insulin regimes and pre-analog insulins (Brodows et al., 1984; Cryer, Fisher, & Shamoon, 1994; Gaston, 1992; Gunning & Garber, 1978). Recent studies are few and some investigate specialized populations. Lawton *et al* investigated self-treatment practices over 1 y among 30 adults with type 1 diabetes who had attended a Dose Adjustment for Normal Eating (DAFNE) course. The study design of individual in depth interviews did not allow for quantification of results. Investigators concluded that people with established type 1 diabetes may have difficulty with recommendations for fixed amounts of carbohydrate and flexible advice may be beneficial (Lawton et al., 2013) and the NHMRC clinical guidelines support use of this program for increased flexibilty in dovetailing insulin and food (Craig et al., 2011). Sommerfield *et al*, in a survey of 101 insulin-treated individuals, compared their self-treatment of hypoglycaemia to Diabetes UK Treatment Guidelines For Hypoglycaemia (Diabetes UK, 2011) which recommends initial treatment with 10 - 15 g of 'refined' carbohydrate and follow-up with 'unrefined' carbohydrate. They reported that the guidelines were followed by 39.6% of participants, with 47.5% undertreating and 12.9% overtreating their hypoglycaemia (Sommerfield et al., 2003). Sumner *et al* surveyed 125 individuals with type 1 diabetes attending routine clinic appointments, reporting that only 24% correctly treated hypoglycaemia with short and long acting carbohydrate, with 6% making inappropriate food choices. Actual foods used for self-treatment of hypoglycaemia were not specified, but sources of information regarding self-treatment were, with more than 50% of participants nominating hospital clinics and GP practices as information providers and approximately 4% reporting having been given no information (Sumner et al., 2000). Elliott *et al*, in a survey of 309 people with type 2 diabetes attending primary health care centres in Oman reported that 27% of those surveyed were unable to recognize hypoglycaemia and 26% were unable to respond to it, with 4% giving 'actively dangerous' responses to hypoglycaemia, such

as increasing dosages of oral hypoglycaemic agents and insulin, or going to sleep. Again, no specific food choices or quantities were reported (Elliott et al., 2013). When hypoglycaemic unawareness or undertreatment of severe hypoglycaemia allow progression of hypoglycaemia to the point where the sufferer becomes unable to self-treat, glucagon, provided as an emergency kit, can be given by injection in a non-medical setting by someone other than the sufferer. Glucagon is a major counter-regulatory hormone that acts to maintain glucose production by glycogenolysis and gluconeogenesis in the liver (Kedia, 2011). It is ineffective in later sustained alcohol-induced hypoglycaemia as in this situation the liver is depleted of glycogen and gluconeogenesis is inhibited by alcohol (Carroll, Burge, & Schade, 2003; Siler, Neese, Christiansen, & Hellerstein, 1998).

### 2.2.5 *Prevalence of hypoglycaemia*

**Elevated one-hour postload glucose**

Neither hypoglycaemia nor relative hypoglycaemia have been documented in the literature in those with NGT and elevated 1-h postload glucose.

**Prediabetes**

Hypoglycaemia in prediabetes is not documented, except under conditions of trauma or experimental trials. The presence of hypoglycaemia is documented with the stressor of burns (prevalence not quantified) (Somerset, Coffey, Jones, & Murphy, 2014) and cardiac surgery (2 asymptomatic hypoglycaemic events in 43 patients) (Hagelberg, Ivert, Efendic, Ohrvik, & Anderson, 2008). It is also documented in some research trials of early treatment of those at risk of diabetes. Hypoglycaemia was documented to have occurred with insulin glargine treatment in prediabetes, in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) study (Hanefeld & Bramlage, 2013; Rusavy, Lacigova, & Kvapil, 2013) with hypoglycaemia and severe hypoglycaemia recorded in 6% and 7.6% respectively of those with prediabetes over median 6.2 y (Mellbin et al., 2013), and in a similar study where 5/18 subjects receiving glargine experienced 16 mild symptomatic hypoglycaemic events (Marbury et al., 2008). Finally, Saloranta *et al* in a study investigating the use of nateglinide in prediabetes, reported hypoglycaemic events in 26.7% subjects receiving nateglinide and 2.3% receiving placebo (Saloranta et al., 2002).

**Diabetes**

There are increasing numbers of studies quantifying hypoglycaemia in diabetes. Interstudy comparison of rates of hypoglycaemia are difficult due to variation in reporting methods; for more discussion of this see section 8.3 (paper 7).

Type 1 diabetes: Cryer *et al* in the ADA's technical review of hypoglycaemia in 2003 estimated rates of symptomatic hypoglycaemia in type 1 diabetes as an average 2/wk and severe hypoglycaemia approximately 1/y, and reported rates of severe hypoglycaemia during aggressive insulin therapy of 62 - 170 episodes per 100 patient-years (Cryer et al., 2003). Donnelly *et al* in 2005, in a population-based study of 267 adults in Scotland over 1 month documented rates of hypoglycaemia of 42.89 mild and 1.15 severe events per patient per year in 94 people with type 1 diabetes. Episodes of hypoglycaemia were prospectively self-documented and cross-checked with blood glucose records. They found that the predictors of hypoglycaemia in these people with type 1 diabetes were a history of previous hypoglycaemia and co-prescribing of any oral drug. The UK Hypoglycaemia Study Group, in an observational study of 107 type 1 subjects over 9 - 12 m in 6 UK secondary care diabetes centres in 2007 documented mean rates of 35.5 and 29.0 mild and 1.1 and 3.2 severe self-reported hypoglycaemic episodes per subject-year (< 5 y and > 15 y duration of diabetes respectively). A longer diabetes duration was associated with loss of endogenous insulin secretion, increased counterregulatory failure and thus increased hypoglycaemia (UK Hypoglycaemia Study Group, 2007). Finally McCoy *et al* in 2013, in a postal survey of 92 adults with type 1 diabetes reported that 28.3% had self-reported at least one episode of severe hypoglycaemia within the last 6 m (McCoy et al., 2013). All reports show substantial rates of hypoglycaemia amongst those with type 1 diabetes, and where assessed against duration of diabetes, show, not surprisingly, increased rates with increasing duration of diabetes coincident with increasing counterregulatory impairment and thus hypoglycaemic unawareness.

Type 2 Diabetes: The ADA 2003 technical review merely asserts that rates of hypoglycaemia in type 2 diabetes are substantially less than in type 1 diabetes, and gives figures for severe hypoglycaemia during aggressive insulin therapy in type 2 diabetes of 3 - 73 episodes per 100 patient-years (Cryer et al., 2003). Donnelly *et al* report rates of hypoglycaemia in insulin-treated type 2 diabetes of 16.37 events per patient per year with 5 of these being severe hypoglycaemic events, that is 0.35 severe episodes per patient per year. Predictors of hypoglycaemia in these people

with type 2 diabetes were a history of previous hypoglycaemia and duration of insulin treatment (Donnelly et al., 2005). The UK Hypoglycaemia Study Group showed self-reported rates of mild hypoglycaemia of 1.92, 4.08, 10.2, and severe hypoglycaemia of 0.1, 0.1, 0.7 episodes per person year for type 2 diabetes on OHA, insulin treatment < 2 y duration and insulin treatment > 5 y duration, respectively. In this study rates of hypoglycaemia in type 2 diabetes was equivalent in OHA and early insulin use and considerably less than in type 1 diabetes (UK Hypoglycaemia Study Group, 2007). In type 2 diabetes, longer duration of diabetes is associated with increasing age and increased loss of endogenous insulin secretion giving a higher propensity for hypoglycaemia, and in addition, there is evidence that symptoms of hypoglycaemia may become less and cognitive dysfunction more with increasing age (Amiel et al., 2008). Finally McCoy *et al,* in a postal survey of 326 adults with type 2 diabetes, reported that 16.9% reported at least one episode of severe hypoglycaemia within the last 6 m (McCoy et al., 2013).

As with those with type 1 diabetes, interstudy comparisons are difficult due to different study groupings and reporting methods, however all studies show rates of hypoglycaemia in early type 2 diabetes which are substantially lower than amongst those with type 1 diabetes but rising rates with longer duration. This is not unexpected as the mechanism of type 2 diabetes varies, but includes insulin resistance and relative insulin deficiency with progressive loss of β-cell function over time. Therefore those with early type 2 diabetes are less likely to be on, or on smaller doses of, insulin or potent OHA which make hypoglycaemia less likely (Amiel et al., 2008; Corathers et al., 2013).

### 2.2.6 *Risk of hypoglycaemia*

**Treatments - types, regimes and delivery methods**

The DCCT and UKPDS showed that intensive insulin regimes, while reducing diabetes complications, markedly increased rates of hypoglycaemia, with the DCCT showing a threefold increased risk of hypoglycaemia with intensive treatment and the UKPDS showing rates of major hypoglycaemic episodes per year as 0.7% with conventional treatment and 1.0 - 1.8% with intensive treatment, depending on treatment given (Nathan, 2014; UKPDS Group, 1998). Ongoing developments in both treatments types and regimes and insulin delivery methods since these two trials

have aimed to maintain and improve treatment quality and minimize hypoglycaemic risk.

Development of treatments and regimes with lower hypoglycaemic risk: Schopman *et al* in a systematic review of hypoglycaemia in patients with type 2 diabetes treated with sulfonylureas extracted data from 22 papers and reported that hypoglycaemia was experienced by 5.9 - 10.1% of sulphonylurea-treated people and severe hypoglycaemia by 0.8%. Hypoglycaemia and severe hypoglycaemia occurred less with newer shorter acting sulphonylurea agents (Schopman et al., 2014). Similarly, analog insulins, which both dissociate more quickly and exhibit less variability and more physiological action profiles, have been shown to decrease hypoglycaemia (Heller, 2002; S. R. Heller, Amiel, & Mansell, 1999; Hermansen et al., 2004). Changing insulin regimes from premixed insulins twice daily to basal-bolus, or MDI regimes theoretically decrease hypoglycaemic risk by eliminating premeal medium acting insulins and increasing flexibility, allowing a more physiological pattern of insulin action and thus less hypoglycaemia. Some evidence suggests that premixed insulin analogues are cost effective and associated with only minor hypoglycaemic risk for the treatment of type 2 diabetes (Garber, Ligthelm, Christiansen, & Liebl, 2007) and those with newly diagnosed type 1 diabetes (Idris, Pillai, Fernando, Thomson, & Tate, 2013) (that is, those with some endogenous insulin production), however other studies strongly indicate that premixed insulin regimes increase hypoglycaemic risk (Riddle, Rosenstock, Vlajnic, & Gao, 2013). Testa *et al* showed equal rates of symptomatic hypoglycaemia in both type 1 and type 2 diabetes using premixed insulin compared to a basal-bolus regime; however glycaemic control was reduced on the premixed regime (Testa et al., 2012).

Changes in insulin delivery methods to minimize hypoglycaemia: CSII or insulin pumps give greater flexibility of insulin delivery and as they utilize only short-acting insulin, allow interruption of insulin delivery when BGL falls excessively, more closely mimicking the physiological situation. Theoretically this should aid minimization of hypoglycaemic risk, however, in reality, there is mixed evidence regarding the effect of CSII versus MDI on rates of hypoglycaemia A systematic review by Yeh *et al* of 33 randomized controlled trials showed both have similar rates of hypoglycaemia (Yeh et al., 2012). Contrary to this, another systematic review of 76 studies making similar comparisons, reported that CSII benefitted glycaemic control by less variability in BGL and lower rates of hypoglycaemia

(Cummins et al., 2010). Papargyri *et al* in a 7 y follow-up of 112 people with type 1 diabetes on CSII showed that hypoglycaemia decreased over time with use of CSII which improved glycaemic control compared to MDI treatment. However it was necessary to implement specific patient training and fine adjustment of insulin infusion doses to minimize hypoglycaemia (Papargyri et al., 2013) All evidence shows that the relatively newly developed sensor-augmented insulin pumps decrease risk of hypoglycaemia (Bergenstal et al., 2013; Yeh et al., 2012). A study by Ly *et al* followed 95 people with type 1 diabetes randomized to a conventional or sensor-augmented pump over 6 months. After 6 months the adjusted incidence rate per 100 patient-months was 34.2 and 9.5 for the pump-only and sensor-augmented pump groups respectively (Ly et al., 2013).

Hypoglycaemia in diabetes is a result of absolute or relative insulin excess caused by insulin or insulin secretagogues (Cryer, 2011). Matching medication and lifestyle is an imperfect science, however, as can be seen above, improvements in treatments and delivery methods are slowly decreasing hypoglycaemic risk.

**Exercise and hypoglycaemic risk**

Exercise is generally recommended for individuals with type 1 diabetes as it improves physical fitness, reduces cardiovascular risk and improves well-being (Chimen et al., 2012), however as it increases glucose utilization, it also increases the risk of hypoglycaemia, especially when exercise is prolonged (Seaquist et al., 2013). Exercise-induced hypoglycaemia in type 1 diabetes is a result of the inability to endogenously decrease exogenously delivered insulin in response to exercise, as would happen in the healthy individual. The result of this is a relative insulin excess and a reduction in blood glucose levels. Exercise may also increase absorption of insulin from the administration site (Guelfi, Jones, & Fournier, 2007). Exercise-induced hypoglycaemic risk in those with type 1 diabetes can be sustained, as glucose uptake by muscle continues to be increased post-exercise, and this glucose is utilized to rebuild muscle and glycogen stores. Hypoglycaemic risk has been reported to persist for up to 31 hours post-exercise (Guelfi, Jones, et al., 2007).

Antecedent episodes of exercise can blunt counterregulatory responses during subsequent hypoglycaemia (Briscoe, Tate, & Davis, 2007). Galessetti *et al*, studied 22 individuals with type 1 diabetes during 90 m of cycling exercise after two 2-h periods of previous day euglycaemia or hypoglycaemia. After day 1 euglycaemia, participants demonstrated normal counterregulatory responses to exercise, but after

previous day hypoglycaemia, reduction of glucagon, catecholamine, cortisol and endogenous glucose production was observed (Galassetti et al., 2006).

Hypoglycaemic risk varies with the duration and intensity of exercise and it is recognised that moderate and high-intensity exercise have differing effects on blood glucose levels (Guelfi, Jones, et al., 2007). In moderate-intensity exercise the muscles increase uptake of glucose and hepatic glucose production increases to compensate for this, but this increase is inhibited by the failure to reduce circulating insulin levels with resulting increased hypoglycaemic risk. In contrast, short bursts of high-intensity exercise are fuelled by creatine phosphate and anaerobic glycolysis, resulting in a rise in blood glucose levels rather than hypoglycaemia (Guelfi, Jones, et al., 2007; Guelfi, Ratnam, Smythe, Jones, & Fournier, 2007). Iscoe *et al*, compared the effect of continuous moderate-intensity exercise with continuous moderate-intensity alternating with intermittent high-intensity exercise on blood glucose levels in trained athletes with type 1 diabetes and showed both increased hypoglycaemic risk to a similar degree (Iscoe & Riddell, 2011).

The risk of exercise-induced hypoglycaemia can be minimized by careful glucose monitoring before and after exercise and the appropriate adjustment of medication and ingestion of carbohydrate-rich snacks (Seaquist et al., 2013). Campbell *et al* in a study of 11 individuals with type 1 diabetes exercising on a treadmill showed that a reduction of 75% in the dose of rapid acting insulin pre-exercise and 50% post-exercise protected participants from early-onset hypoglycaemia (≤ 8 h) but not late-onset post-exercise hypoglycaemia (Campbell et al., 2013). Yardley *et al*, in an observational study of physically active people with type 1 diabetes have shown a reduction in post-exercise hypoglycaemia by the judicious use of CSII (Yardley et al., 2013).

In type 2 diabetes, exercise is generally beneficial, with potential to improve glucose and lipid levels, reduce weight and improve insulin resistance (Chimen et al., 2012). Those with type 2 diabetes treated with insulin and/or insulin secretagogues are at risk of exercise-induced hypoglycaemia, if medication dose is not reduced or carbohydrate consumption increased. The risk of hypoglycaemia is greater when exogenous insulin levels are higher and if exercise is prolonged (Sigal, Kenny, Wasserman, Castaneda-Sceppa, & White, 2006). A meta-analysis conducted by MacLeod *et al* in individuals with type 2 diabetes treated by glucose lowering medication, insulin, or diet investigated the effect of exercise on blood glucose levels

by means of continuous glucose monitoring. Most studies showed that short-term exercise significantly decreased average glucose concentrations, with an acute glucose lowering via insulin sensitization being generally short-lived, but sometimes persisting up to 48-h post-exercise. They reported little effect on either fasting glucose levels or hypoglycaemic frequency (MacLeod, Terada, Chahal, & Boule, 2013). As in type 1 diabetes, the risk of exercise-induced hypoglycaemia can be minimized by careful glucose monitoring before and after exercise and the appropriate adjustment of medication and ingestion of carbohydrate-rich snacks (Seaquist et al., 2013).

**Diet, education and risk of severe hypoglycaemia**

Severe hypoglycaemia is defined as a hypoglycaemic event where the assistance of another person is needed to actively administer treatment (Seaquist et al., 2013). Donnelly *et al* in 2005, in a population-based study of 267 adults in Scotland over 1 m documented rates of severe hypoglycaemia of 1.15 events per patient per year, with the main predictors being a history of previous hypoglycaemia and coprescribing of any oral drug (Donnelly et al., 2005). Similarly, the UK Hypoglycaemia Study Group, in an observational study of 107 type 1 subjects over 9 - 12 m documented mean rates of 3.2 severe self-reported hypoglycaemic episodes per subject-year with a longer diabetes duration associated with loss of endogenous insulin secretion, increased counterregulatory failure and increased severe hypoglycaemia (UK Hypoglycaemia Study Group, 2007). Both reports show substantial rates of severe hypoglycaemia amongst those with type 1 diabetes, and increased rates with increasing duration of diabetes coincident with increased counterregulatory impairment and therefore hypoglycaemic unawareness. A study by Geddes *et al* of 518 people with type 1 diabetes over a 2-year period showed that insulin-treated people with hypoglycaemic unawareness had a six-fold higher frequency of severe hypoglycaemia in the previous year than those with normal awareness (Geddes, Schopman, Zammitt, & Frier, 2008).

When hypoglycaemic unawareness or undertreatment of severe hypoglycaemia allow progression of hypoglycaemia to the point where the sufferer becomes unable to self-treat, glucagon, can be given by injection in a non-medical setting by someone other than the sufferer. (Kedia, 2011).

The main preventative strategies for severe hypoglycaemia are patient education programs which aim to increase the competency of those with type 1 diabetes in

dovetailing diet and insulin doses to accommodate a flexible lifestyle. The two most well known of these are the HyPOS and the Dafne programs. The HyPOS program runs over 5 weeks and specifically targets prevention of hypoglycaemia, by training participants in symptom awareness by using diaries and performing blood glucose estimation. It has been shown that at 6-m follow-up, hypoglycaemic awareness significantly improved (Hermanns, Kulzer, Kubiak, Krichbaum, & Haak, 2007) and incidence of severe hypoglycaemia was lower in those who had completed the HyPOS program than in an untrained control group (0.1±0.2 vs 0.2±0.4 episodes/patient-year) (Hermanns, Kulzer, Krichbaum, Kubiak, & Haak, 2010).

The DAFNE program, similarly, is a 5-day education program which aims to teach 'dose adjustment for normal eating' emphasising (relatively) unrestricted diet with carbohydrate counting and using insulin-to-carbohydrate ratios. It has been shown variously to, 'not worsen' severe hypoglycaemia (Dafne Study Group, 2002), reduce severe hypoglycaemia (McIntyre et al., 2010) and also reduce emergency admissions for severe hypoglycaemia (Elliott et al., 2014).

### 2.2.7 *Consequences of hypoglycaemia*

**Physiological consequences**

Short-term: Hypoglycaemia can cause ongoing morbidity and even mortality in those with type 1 and advanced type 2 diabetes (Cryer, 2011; Seaquist et al., 2013). In the short-term, hypoglycaemia can cause confusion, coma, seizures, and death (Cryer, 2011). Hypoglycaemia has been reported to cause 4 - 10% of deaths in people with diabetes (Patterson et al., 2007; Skrivarhaug et al., 2006).

Driving-related morbidity: Hypoglycaemia also increases driving-related morbidity and mortality. Cox *et al,* in a study by questionnaire, reported that drivers with type 1 diabetes had significantly more self-reported car accidents, moving violations, episodes of hypoglycaemic stupor, need for assistance, and mild hypoglycaemia while driving compared to drivers with type 2 diabetes or spouse control subjects. Car accidents were shown to be associated with hypoglycaemia. Drivers with type 2 diabetes had similar rates to controls (Cox et al., 2003).

Trauma: Marchesini *et al* in a retrospective analysis of cases attending 46 Italian emergency departments for hypoglycaemia over a year showed that injuries associated with trauma accounted for 1.3 % of admissions. Diabetes treatment and increasing age were the main determinants (Marchesini et al., 2014). Bloomfield *et al*

in a meta-analysis looking at consequences of severe hypoglycaemia have commented that there is limited data on the association between hypoglycaemia and falls and traumatic injuries (Bloomfield et al., 2012) however Leckie *et al*, in a prospective 12-month survey of 243 employed people with insulin-treated diabetes, showed 0.14 episodes per person per annum of severe hypoglycaemia. This resulted in 2% sustaining a head injury, 2% suffering another injury,1% injuring someone else, and 1% damaging property (Leckie, Graham, Grant, Ritchie, & Frier, 2005).

Repeat hypoglycaemia: In the longer term mild symptomatic hypoglycaemia does not appear to have significant clinical effects, except for potentiating defects in counterregulatory responses and increasing unawareness to subsequent hypoglycaemic events (Amiel et al., 2008). However as hypoglycaemia in diabetes results from absolute or relative insulin excess as a byproduct of treatment with exogenous insulin and/or insulin segretagogues, insulin levels cannot decrease in response to falling glucose levels, as would happen in the normal situation (American Diabetes Association, 2005; Cryer et al., 2003) and the potential for repeat hypoglycaemic episodes exists. The bulk of research concerning repeat hypoglycaemia is focussed on the emergency treatment of a primary hypoglycaemic event by paramedics and the likelihood of a repeat hypoglycaemic episode necessitating a hospital admission within the subsequent 24 - 72 h (Cain, Ackroyd-Stolarz, Alexiadis, & Murray, 2003; Roberts & Smith, 2003; Socransky, Pirrallo, & Rubin, 1998; Strote, Simons, & Eisenberg, 2008). In the short-term situation, guidelines for food treatment of hypoglycaemia recommend follow-up with longer lasting carbohydrate after initial treatment of primary hypoglycaemia (American Diabetes Association, 2013c; Asian-Pacific Type 2 Diabetes Policy Group, 2002; Canadian Diabetes Association, 2012; Diabetes Education Study Group of the European Association for the Study of Diabetes, 1998; Diabetes New Zealand, 2008; Diabetes UK, 2011; Singapore Diabetes Society, 2010), and theoretically this would minimize the risk of repeat hypoglycaemia within several hours of a primary event, however the efficacy of this is poorly covered in the literature.

Nocturnal hypoglycaemia and 'dead in bed syndrome': Nocturnal hypoglycaemia - hypoglycaemia in type 1 diabetes occurs most frequently during sleep and can range in severity from asymptomatic mild hypoglycaemia to severe hypoglycaemia (American Diabetes Association, 2005). Wentholdt *et al* in a study using a glucose

sensor showed 33% incidence between 22h and 7h, with bedtime glucose levels as a predictor (Wentholt et al., 2007).

Nocturnal hypoglycaemia has been shown to be associated with 'dead in bed' syndrome, with ECG QT prolongation with subsequent ventricular tachyarrhythmia being a response to nocturnal hypoglycaemia. Gill *et al*, in a study using CGM and ECG in 25 people with type 1 diabetes, showed corrected QT interval was longer during nocturnal hypoglycaemia compared with normoglycaemia and that cardiac rate and rhythm disturbances were seen in 62% of nocturnal hypoglycaemic episodes. They concluded that this may support an arrhythmic basis for the 'dead in bed' syndrome (Gill, Woodward, Casson, & Weston, 2009). Hsieh and Twigg, in a recent review of 'dead in bed' syndrome, asserted that there was growing evidence implicating autonomic neuropathy and nocturnal hypoglycaemia as causative factors. They asserted that normally during sleep there is less sympathetic activity and relatively increased parasympathetic activity, and in diabetes this can combine with autonomic neuropathy induced impaired parasympathetic activity which may be associated with arrhythmias and subsequent death (Hsieh & Twigg, 2014).

Increased risk of cardiovascular disease: Severe hypoglycaemia has been associated with increased all-cause mortality and vascular risk. The Veterans Affairs Diabetes Trial randomised participants to very intensive or standard treatment and showed a large increase in the rate of sudden death in the intensive group, of whom 21% experienced severe hypoglycaemia compared to 10% of the conventional group (Duckworth et al., 2009). Similarly the ACCORD study randomised participants to an even stricter intensive treatment trial and showed rates of severe hypoglycaemia of 16.2% in the intensive compared to 5.1% in the conventional group, and a 22% increase in relative risk for all-cause mortality in the intensive group (Bonds et al., 2010). Severe hypoglycaemia imparts a two - fourfold increased risk of CVD. A specific mechanism for this increased risk has not been identified (Skyler et al., 2009). The follow-up to the DCCT, The Epidemiology of Diabetes Interventions and Complications study, found a decrease in CVD in association with intensive treatment (Nathan, 2014), however a study by Zoungas *et al* of 11,140 patients with type 2 diabetes over 5 y showed severe hypoglycaemia was associated with a significant increase in major macrovascular events, major microvascular events, death from cardiovascular causes, and all-cause mortality (Zoungas et al., 2010) and consistent with this Stahn *et al* in a study of 30 people with type 2 diabetes and CVD

showed that severe hypoglycaemic events were associated with increased risk of severe ventricular arrhythmias (Stahn et al., 2014). Similar results were obtained by Zhao et al in a retrospective cohort study over 2 y using the electronic medical records of veterans with type 2 diabetes. They identified 63,003 controls without documented hypoglycaemia and 2,187 veterans who had experienced at least one hypoglycaemic episode within the targetted period. The hypoglycaemic group had significantly higher risks of both cardiovascular events (HR 2.00 [95% CI 1.63–2.44]) and microvascular complications (1.76 [1.46–2.11]), but no statistical difference in mortality. Two or more hypoglycaemic episodes conferred increased risk (Zhao, Campbell, Fonseca, & Shi, 2012). Rana *et al* have suggested hypoglycaemia be viewed as another cardiac risk factor (Rana, Byrne, & Greaves, 2014).

Neurological risk: Neurologic syndromes are frequent during severe hypoglycaemia but usually reversible. Major irreversible brain damage is rare (Halimi, 2010) however cognitive decline and dementia appear to show an association with severe hypoglycaemia, at least in type 2 diabetes. Barrou *et al* are of the opinion that cognitive decline is largely related to poor metabolic control rather than hypoglycaemia (Barrou, Lemaire, Boddaert, & Verny, 2008). To the contrary, Feinkohl *et al* in a study of 4 y duration on cognition in 831 adults with diabetes aged 65 - 70 y concluded that there is a complex relationship between cognitive impairment and hypoglycaemia with severe hypoglycaemia associated with both poorer initial cognitive ability and accelerated cognitive decline (Feinkohl et al., 2014). Similarly, the Edinburgh study, which investigated 1066 people with type 2 diabetes, showed that self-reported history of severe hypoglycaemia was associated with reduced cognitive ability in later life (Aung et al., 2012).

**Psychological consequences – fear of hypoglycaemia**

Hypoglycaemia is the most common acute complication in type 1 diabetes and is also relatively common in advanced type 2 diabetes (Cryer et al., 2003). It can cause unpleasant symptoms such as shaking, sweating, drowsiness, nausea, poor coordination, confusion, unconsciousness and fitting. Severe hypoglycaemia can cause death. It is, therefore, unsurprising that many people with type 1 and advanced type 2 diabetes have a significant fear of hypoglycaemia (Wild et al., 2007).

Fear of hypoglycaemia is an accepted clinical syndrome. It can be measured by the use of a specific scale, the Hypoglycaemic Fear Scale (Cox, Irvine, Gonder-

Frederick, Nowacek, & Butterfield, 1987). Fear of hypoglycaemia has been shown to be associated with an individual's history of hypoglycaemia, duration of insulin treatment, and variability of BGL (Wild et al., 2007). Anderbro *et al* in a study of 1387 people with type 1 diabetes in Sweden showed the likelihood of an individual developing fear of hypoglycaemia was associated with frequency of severe hypoglycaemia, hypoglycaemic symptoms during mild hyperglycaemia, also higher number of symptoms, female gender, and hypoglycaemic unawareness (Anderbro et al., 2010).

McCoy *et al* in a cross-sectional analysis via a postal survey of 875 free-living adults with type 1 or 2 diabetes in Rochester reported a prevalence of fear of hypoglycaemia of 28.3% (type 1) and 16.9% (type 2). A limitation of this study was the low response rate (47.8%), however it does give an idea of the extent of the problem, especially among those with type 1 diabetes (McCoy et al., 2013). Myers *et al* in a study of 90 people with type 1 diabetes on intensive MDI and CSII (85.5%) reported that 30% of the sample reported fear of death from hypoglycaemia, with 25.5% of the total sample meeting the criteria for current posttraumatic stress disorder (PDS) (Myers, Boyer, Herbert, Barakat, & Scheiner, 2007). This prevalence of fear of hypoglycaemia induced PDS is slightly higher than identified PDS in Veterans of the Vietnam war (24.7%) (O'Toole, Catts, Outram, Pierse, & Cockburn, 2009).

The extent of the impact of fear of hypoglycaemia can be measured by a newly developed subscale of the Hypoglycaemic Fear Survey (Gonder-Frederick et al., 2013). It has been shown that the consequences of fear of hypoglycaemia can impact on diabetes control, self-treatment and lifestyle (Leiter, 2005). There is also evidence that fear of hypoglycaemia increases the risk of an individual keeping BGL high to avoid hypoglycaemic episodes, which then contributes to impaired diabetes control (Bohme, Bertin, Cosson, & Chevalier, 2013; Wild et al., 2007).

Bohme *et al* in an observational cross-sectional study of 485 people with type 1 diabetes showed that fear of hypoglycaemia had a major impact on quality of life (Bohme et al., 2013) and as such further research is needed, especially in the area of avoidance behaviours and their effect on long-term diabetes control (Wild et al., 2007).

### 2.2.8 *Alcohol and hypoglycaemia*

Alcohol acts to inhibit gluconeogenesis and glyconeogenesis. Post alcohol consumption, the dehydrogenation of alcohol by means of alcohol dehydrogenase using $NAD^+$ generates increased quantities of NADH which leads to reduced liver gluconeogenesis which decreases glucose 6-phosphate. Despite reduced liver gluconeogenesis, glucose output from the liver does not decrease significantly due to compensation which converts glycogen to glucose by glycogen phosphorylase. This depletes glycogen stores in the liver. Decreasing glucose 6-phosphate activates the glycogen phosphorylase. Some hours post alcohol metabolism gluconeogenesis in the liver returns to normal which restores glycogen stores. In the healthy person insulin secretion will decrease to prevent BGL falling, but in the insulin-treated individual insulin level is not able to respond by decreasing so there is a drop in BGL with resulting putative hypoglycaemia, the magnitude of the drop being dependent on the amount of alcohol consumed. By this mechanism the drop in BGL and hypoglycaemia are necessarily some hours after alcohol consumption (Evans, Kerr, & Flanagan, 2006; Plougmann, Hejlesen, Turner, Kerr, & Cavan, 2003; van de Wiel, 2004; Verlohren, 1981). This process does not occur in diet-treated people with type 2 diabetes but does occur with treatment by insulin secretagogues which potentiate insulin release (Pietraszek, Gregersen, & Hermansen, 2010; Rasmussen, Orskov, Schmitz, & Hermansen, 2001; van de Wiel, 2004).

Confirming this in the practical arena, a study involving 16 free-living people with type 1 diabetes given vodka (0.85 g/kg) or placebo and monitored with CGM for 36 h on 2 occasions reported twice as many hypoglycaemic episodes for the 24-h post-consumption in those who had drunk vodka compared to placebo (Richardson, Weiss, Thomas, & Kerr, 2005). In a similar smaller shorter-term study, 6 men with type 1 diabetes were admitted as inpatients on 2 different occasions, given basal and preprandial insulin, a standard meal and either white wine (0.75 g/kg alcohol) or mineral water. Evening and overnight BGL were the same in both groups but significantly lower in the morning in the wine group as compared to the mineral water group, although no subject suffered hypoglycaemia (Turner, Jenkins, Kerr, Sherwin, & Cavan, 2001).

Moderate and high doses of alcohol impair cognitive function. A study by Magrys et al investigating cognitive skills mediated by frontal and temporal brain regions in

healthy subjects showed that alcohol impaired sustained attention in males and verbal memory in both genders, exhibiting a U-shaped pattern, with those drinking moderate amounts of alcohol exhibiting the greatest impairment (Magrys & Olmstead, 2014). There is a complex relationship between cognitive impairment and hypoglycaemia with severe hypoglycaemia being shown to be associated with poorer cognitive ability older people with diabetes (Feinkohl et al., 2014). Alcohol has been shown to be a major contributor in the occurrence of severe hypoglycaemia in insulin-treated diabetes (Krnacova et al., 2012). So what is the effect on cognitive function when alcohol and hypoglycaemia are combined? Cheyne *et al* in an insulin clamp study investigated alcohol, hypoglycaemia and cognitive performance in 17 subjects with insulin-dependent diabetes. Cognitive function assessment was for reaction time, general intellectual skills, digit symbol substitution and visual information processing. They also tested hazard perception with respect to driving performance. The results showed that alcohol and hypoglycaemia independently impair cognitive function and their effect together is additive. With respect to driving ability, participants had blood alcohol levels below the UK legal driving limit, yet there was impaired reaction time (Cheyne et al., 2004).

Alcohol has been shown to be a major contributor in the occurrence of severe hypoglycaemia and also death. A study investigating the incidence of severe hypoglycaemia requiring admission for Emergency Services over a 1 y period in the Czech Republic identified alcohol as one of the major causes (Krnacova et al., 2012) and a study in Finland investigating trends in mortality showed that in people with type 1 diabetes diagnosed aged 15-29 y, 39% of deaths during the first 20 y of diabetes were from alcohol and drug-related causes (Harjutsalo & Forsblom, 2011). Finally, a retrospective audit of presentations with severe hypoglycaemia over a year, to a major hospital in the UK showed 10.2% causation by alcohol ingestion (Parfitt & Bhake, 2012).

### 2.2.9 *Hypoglycaemia in inpatients in the general ward*

**General ward inpatients**

Those with diabetes have a greater frequency of hospitalization and greater length of stay in hospital than people without diabetes (Moghissi et al., 2009). Hypoglycaemia is not uncommon in general ward inpatients with diabetes treated with insulin or insulin secretagogues. An accurate assessment of the extent of hypoglycaemia in

these inpatients is difficult to make due to lack of consensus on the definition of hypoglycaemia (see section 8.3) and differing methods of data collection between hospitals (Eiland, Goldner, Drincic, & Desouza, 2014), however it seems clear that inpatient hypoglycaemia is associated with both increased mortality, during and post-admission, and also increased length of hospital stay.

Turkin *et al* in a retrospective cohort study audited 4,368 admissions of 2,582 patients with diabetes hospitalized in the general ward over an 18-m period and documented hypoglycaemia in 7.7% of those admitted. They showed an association between each additional day with a hypoglycaemic event and an increase of 85.3% and 65.8% in the odds of inpatient death and death within 1 y post-discharge, respectively (Turchin et al., 2009). Similarly Brodovicz *et al* retrospectively investigated 107,312 admissions of insulin-treated patients, hospital stay $\geq$ 24 h and $\leq$ 30 d over 2 y and reported hypoglycaemia/severe hypoglycaemia in 20%/7%, respectively. The rate of inpatient mortality was 6.5%/7.6% in those with hypoglycaemia/severe hypoglycaemia and 3.8% in those without. Length of hospital stay was 8.2 d with hypoglycaemia compared to 5.2 d without (Brodovicz et al., 2013). Kim *et al* carried out a retrospective review of 1276 admissions where insulin was administered, 35% of patients experienced hypoglycaemia and they showed that hypoglycaemia was strongly associated with increased length of hospital stay and other adverse outcomes, more so than glycaemic variability (Kim, Rajan, Sims, Wroblewski, & Reutrakul, 2014). However Mendez *et al*, in a retrospective audit of 4,262 admissions over 2 y, showed that increased glycaemic variability was independently associated with longer length of hospital stay and increased mortality (Mendez et al., 2013). A case control study of 130 patients identified higher rates of hypoglycaemia with 65 (50 %) experiencing at least one episode of hypoglycaemia and 17% of severe hypoglycaemia (Maynard, Huynh, & Renvall, 2008). Kerry *et al,* in a bedside audit of BGL of 164 patients on insulin or sulphoylurea agents, identified an even higher proportion experiencing hypoglycaemia (74%), and also reported that 70% of hypoglycaemic events had occurred between 9pm and 9am (Kerry, Mitchell, Sharma, Scott, & Rayman, 2013) while Deusenberry *et al* in a case-control study involving 234 cases and controls treated with sulphonylurea agents reported 19% of patients experiencing hypoglycaemia (Deusenberry, Coley, Korytkowski, & Donihi, 2012). Boucai *et al* retrospectively studied 31,970 patients admitted to general wards over 1 y and reported similar rates of hypoglycaemia as

Turchin *et al* (10.5%) but on stratification into subgroups of spontaneous or drug-associated hypoglycaemia, reported that, after adjustment for comorbidities, neither drug-associated nor spontaneous hypoglycaemia were associated with increased mortality. They concluded that the hypoglycaemia might be a marker of disease burden rather than the direct cause of death (Boucai, Southern, & Zonszein, 2011).

Rates of hypoglycaemia are demonstrably higher in general inpatients than in free-living individuals (see section 2.2.5) and Eiland *et al* reason that illness gives variable insulin sensitivity which increases risk of hypoglycaemia in these inpatients (Eiland et al., 2014). Maynard *et al* in their case control study assessed the risk factors for general inpatient hypoglycaemia as prior inpatient hypoglycaemia, mismatch of insulin and nutrition, nutritional interruption and poor adherence to hypoglycaemia management and documentation (Maynard et al., 2008) and Anthony, in a retrospective case review of 484 inpatients with hypoglycaemia highlighted adherence to practice guidelines and poor documentation as major problems (Anthony, 2007). Elliott *et al* carried out a study to identify risk factors for severe hypoglycaemia and based on this developed an algorithm to predict severe hypoglycaemia. Risk factors identified were inadequate monitoring of trends in BSL, mismatch of diabetes treatment and nutrition, excessive insulin, nursing errors, and insufficient glucose with insulin for the acute treatment of hyperkalemia, many of the same factors identified by Maynard *et al* (M. B. Elliott, Schafers, McGill, & Tobin, 2012). Kerry *et al* in their charting of a diurnal pattern of hypoglycaemia theorised the risk factor for this was lack of carbohydrate to balance insulin at this time, essentially, again, an insulin food mismatch (Kerry et al., 2013). Patients treated with sulphonylureas exhibited a different pattern, with all risk factors relating to failure to clear sulphonylurea medication through the kidneys (age $\geq$ 65 y and reduced GFR) and also potentiation of medication effect (longer-acting sulphonylurea and concurrent intermediate or long-acting insulin). The authors concluded that sulfonylureas should be avoided or used with caution in these situations (Deusenberry et al., 2012).

**Patients in the general ward on nasogastric feeding**

It is well documented that hyperglycaemia in inpatients is independently associated with increased morbidity and mortality, increased length of hospital stay and increased cost (Lleva & Inzucchi, 2011; Moghissi et al., 2009). Therefore the bulk of

the literature on inpatients on nasogastric feeding focusses on factors, mainly feed types, designed to reduce hyperglycaemia, especially post-prandial hyperglycaemia (Elia et al., 2005), with the emphasis on nasogastric feeding products designed to blunt the postprandial blood glucose response (Alish et al., 2010; Vanschoonbeek et al., 2009).

In the general situation, the IDF recommends the consumption of foods with a low glycaemic index and preferably a low glycaemic load to improve postprandial glycaemia (Ceriello & Colagiuri, 2008). However Wolever *et al* have cast some doubt on the efficacy of this with a long-term study of free-living people with type 2 diabetes who showed no improvement in HbA1c after 12 m on a low GI diet compared to a high GI diet (Wolever et al., 2008). In addition to this, for those on bolus nasogastric feeding, it is difficult to retain sufficient feed volume to allow adequate energy intake and also reduce glycaemic load (which is partially dependent on quantity of carbohydrate), while using standard nasogastric feed products which have traditionally been high in carbohydrate and low in fat (Elia et al., 2005). For this and other reasons, diabetes specific-feeds (DSF) for enteral feeding have been developed. These products less contain less carbohydrate (35 - 40% of energy), more fat (40 - 50% of energy), with a high proportion of monounsaturated fatty acids (Vanschoonbeek et al., 2009). This runs contrary to the recommendations from the Evidence-Based Nutritional Approaches To The Treatment And Prevention Of Diabetes of the EASD, which specifies that in diabetes total fat intake should not exceed 35% of total energy (Mann et al., 2004), but not to the Evidence-Based Nutrition Principles and Recommendations for the Treatment and Prevention of Diabetes and Related Complications of the ADA which specify, more practically, that carbohydrate and monounsaturated fat together should provide 60 - 70% of total energy (Franz et al., 2003).

There are many studies comparing the efficacy of standard versus DSF in those with diabetes. Elia *et al* conducted a meta-analysis that included 23 studies of oral supplements and nasogastric feeding (7 studies), most of which compared standard formulas with DSF. The results showed that the DSF, in the main, reduced postprandial glycaemia and insulin requirements compared to standard feeds (Elia et al., 2005). Additional studies since the meta-analysis was published in 2005 have shown similar results. Alish *et al* used CGM to compare two different formula feeds in 12 patients with diabetes on enteral feeding. Subjects were fed 5 d of standard feed

and 5 d of DSF with assessment endpoints being postprandial glycaemia and insulinemia, glycaemic variability and mean glucose. They concluded that relative to the standard formula the DSF reduced all endpoints (Alish et al., 2010). Vanschoonbeek *et al* compared two formulas in a randomized, double-blind, crossover study involving 15 people with type 2 diabetes and showed peak plasma glucose was significantly lower and plasma insulin responses were lower without increasing the plasma triglyceride response with the DSF when compared with the standard formula (Vanschoonbeek et al., 2009) and Ceriello *et al* conducted a similar study in 12 people with type 2 diabetes showing lower individual and mean glucose peaks and less hyperglycaemic time over 24 h (Ceriello, Lansink, Rouws, van Laere, & Frost, 2009), as did Mori *et al* using CGM and concluding that a low carbohydrate feed improves postprandial and fasting BGL and decreases glucose variability (Mori et al., 2011) and Vaisman *et al* who showed over 12 weeks that postprandial glucose response and HbA1c were lower on a DSF compared to a standard enteral feed (Vaisman et al., 2009). Hofman *et al* compared three enteral feed products in a similar situation to Ceriello *et al* and showed both lower carbohydrate feeds gave lower glucose peaks and triglyceride levels (Hofman, Lansink, Rouws, van Drunen, & Kuipers, 2007) and in a similar study, Voss *et al* concluded that two lower carbohydrate DSF's resulted in a lower postprandial BGL compared to a standard feed (Voss et al., 2008). As can be seen, major endpoints in all these studies were measures of hypergycaemia, glucose variability and lipid levels.

In addition, many of these studies were of short duration, for example, 4 h (Vanschoonbeek et al., 2009; Voss et al., 2008), 6 h (Hofman et al., 2007) and 24 h (Ceriello et al., 2009; Mori et al., 2011). Short-term comparative studies of enteral feed products can give robust evidence of the hyperglycaemic effect of products but are not of sufficient duration to accuractly identify the hypoglycaemic effect, which has a more complex etiology (Eiland et al., 2014; Elliott et al., 2012; Maynard et al., 2008).

Stagnaro-Green *et al* investigated the mortality associated with both hyper and hypoglycaemia in a prospective audit of inpatient charts over 49 d and showed that compared with the mortality rate for general hospital patients of 2.3%, the mortality rate of hyperglycaemic patients was 11.1% and the mortality rate for hypoglycaemic patients was double this (22.2%) (Stagnaro-Green et al., 1995). There are many studies addressing hyperglycaemia in people with diabetes on nasogastric feeding in

the general ward but although hypoglycaemia is associated with a higher mortality rate, there is a dearth of information on this topic.

## 2.3 Summary

This chapter has reviewed ongoing research in the area of hypoglycaemia in diabetes and diabetes-related states and identified key areas where information is lacking in with respect to dietary treatment of hypoglycaemia.

NGT with elevated 1-h glucose is not formally recognized as prediabetes, but research has shown it to be associated with a high risk of progression to diabetes with associated increased risk of both vascular disease and all-cause mortality. Fasting and 2-h glucose levels are normal in this condition but BGL exceeds normal physiological levels at 1-h postload, subsequently dropping rapidly within 30 min, yet despite this, identification and dietary treatment of hypoglycaemia or relative hypoglycaemia in NGT and elevated 1-h postload glucose has not been documented.

The normal physiology of hypoglycaemia is well documented, as are the mechanisms of iatrogenic hypoglycaemia in diabetes, with much current research focussing on hypoglycaemia associated autonomic failure. Similarly, the level of BGL defining hypoglycaemia is well-researched but a consensus on a definitional level is yet to eventuate. Literature reports have highlighted the longer-term consequences of hypoglycaemia, both physical and psychological, with hypoglycaemia being shown to be associated with increased risk of ongoing hypoglycaemia and also cardiovascular disease. Severe hypoglycaemia has been shown to be associated with all-cause mortality and a complex relationship with cognitive impairment is slowly being unravelled. The psychological effects of hypoglycaemia are the subject of continuing research, with the development of the Hypoglycaemic Fear Scale allowing better assessment of its severity.

Ongoing research has enabled the development of more physiological insulin-types, analog insulins, and insulin-delivery systems that allow delivery of insulin in patterns that better mimic the normal situation. However, although these research-driven innovations can decrease the incidence of hypoglycaemia, they cannot eliminate it and dietary treatment remains the cornerstone of successful resolution of a hypoglycaemic event. The evidence base for dietary treatment of hypoglycaemia is not, however, well-researched, relying on expert opinion and laboratory based assessments using pre-analog or intravenous insulin. There is a dearth of studies

investigating optimum recommendations for dietary treatment and current dietary patterns in treatment of hypoglycaemia with the effect of this treatment on repeat hypoglycaemia also poorly researched.

Situational factors can increase hypoglycaemic risk for the person with diabetes. Alcohol ingestion in the presence of exogenous insulin has been shown to increase the risk of sustained hypoglycaemia. The mechanism and consequences of this are both well-researched, with several recent studies utilizing CGM demonstrating an increase in risk lasting 24 h post-alcohol consumption. This is crucial information for those with type 1 diabetes, however there is little published information assessing the extent of their knowledge in this area, or assessing the content of relevant easily accessed educational material on this topic.

Being hospitalized also increases hypoglycaemic risk, with numerous studies showing that hypoglycaemia is common among inpatients with diabetes and is significantly associated with both increased length of hospital stay and mortality. Those on nasogastric feeding in the general ward situation are potentially particularly vulnerable to this, and despite many studies identifying beneficial feed products and insulin regimes, there is a dearth of studies investigating hypoglycaemia in this population.

Optimal dietary treatment is crucial to the swift and effective resolution of hypoglycaemia, and research findings that increase knowledge of current dietary practices highlight areas where interventions may be beneficial. The gaps in the literature in this area are therefore the focus of the seven published studies in this thesis.

# CHAPTER 3: RELATIVE HYPOGLYCAEMIA, DIET AND ELEVATED ONE-HOUR POSTLOAD GLUCOSE.

## 3.1 Significance of study

### *3.1.1 Identification of relative hypoglycaemia in elevated 1-h postload glucose*

Individuals with NGT and elevated 1-h BGL do not fit the criteria for pre-diabetes; their fasting blood glucose is < 6.1 mmol/L, their 2-h glucose is < 7.8 mmol/L and their HbA1c < 5.7% (American Diabetes Association, 2013c). However because of their normal fasting and 2-h value in conjunction with their elevated 1-h level (> 8.6 mmol/L, > 10 mmol/L or > 11.0 mmol/L according to the different criteria), they exhibit enhanced glycaemic variability, with a spike in glucose at 1 h and then a rapid fall to normal levels by 90 min (Yen et al., 2008). A study by Yen *et al* recorded a fall from 1 h to 2 h of mean amplitude of the order of 6 mmol/L (Yen et al., 2008). Similarly, a study by Harada *et al* observed a mean amplitude of a similar order (5.3 mmol/L) (Harada et al., 2008). Kang *et al* in a study of 81 individuals with different subtypes of impaired glucose intolerance undergoing an OGTT showed a mean amplitude in those with IGT of (3.2 ± 1.2) mmol/L, which was significantly higher than in those with NGT (1.6 ± 0.5) mmol/L, and significantly lower than those with type 2 diabetes (5.2 ± 1.9) mmol/L (Kang et al., 2009). The amplitude and timescale of the fall in blood glucose observed over 30 minutes by those with 1-h elevated post-load glucose is similar in magnitude and timing to those with type 2 diabetes and also to falls in blood glucose recorded in those experiencing hypoglycaemia. For example, a recent study by Bergenstal *et al* investigating insulin-pump interruption for reduction of hypoglycaemia in people with type 1 diabetes, recorded mean nocturnal hypoglycaemic amplitudes of 4.8 ± 0.65 mmol/L in control subjects (± 13.6% error as values obtained from continuous glucose monitoring system (CGMS)) with mean duration of 39.4 min (Bergenstal et al., 2013). Similarly Fanelli *et al*, in a study of 11 subjects with type 1 diabetes observed a mean hypoglycaemic fall in blood glucose of approximately 4 mmol/L over approximately 40 minutes (Fanelli et al., 2003). In those with NGT and 1-h elevated glucose, this fall in BGL is not classifiable as hypoglycaemia (defined as an event during which typical symptoms of hypoglycaemia are accompanied by measured glucose ≤ 3.9 mmol/L (Seaquist et al., 2013)) but is consistent with relative or pseudo

hypoglycaemia (defined as an event with typical symptoms of hypoglycaemia with a measured glucose > 3.9 mmol/L, but approaching this level (Seaquist et al., 2013)).
Do those with NGT and elevated 1-h glucose experience hypoglycaemic symptoms? Fanelli *et al* showed a significant increase in counterregulatory response and thus symptoms, with a fast fall in blood glucose level (0.1 ± 0.003 mmol/L/min) as versus a slow fall (0.03 ± 0.003 mmol/L/min) (Fanelli et al., 2003) . Those with NGT and 1-h elevated postload glucose demonstrate this fast fall in blood glucose, for example, Yen *et al* observed a fall of 6 mmol/L in 60 minutes (Yen et al., 2008). It would therefore be a reasonable expectation that they would exhibit symptoms. The following paper is a (partly retrospective and partly prospective) case study. It reports relative hypoglycaemia in an individual with NGT and elevated 1-h glucose. Relative hypoglycaemia in this context has not been previously reported in the literature.

### *3.1.2 Normalisation of glucose variability in elevated 1-h postload glucose*

**Glycaemic variability in elevated 1-h postload glucose**

Cubeddu *et al* showed that NGT with 1-h elevated glucose was associated with greater postload glycaemia and hyperinsulinaemia than in those with 'true' NGT, thus potentially creating a state of enhanced glucose variability (Cubeddu & Hoffmann, 2010). Glycaemic variability in those with elevated postload glucose was investigated by Su *et al* in a study comparing 29 subjects with NGT and 1-h postload glucose ≥ 8.6 mmol/L and 29 age and sex matched controls with NGT and 1-h glucose < 8.6 mmol/L. They showed that those with NGT and 1-h glucose ≥ 8.6 mmol/L had increased glycaemic variability compared to those with NGT and 1-h glucose < 8.6 mmol/L (Su et al., 2013). Madhu *et al* using CGMS demonstrated progressively increasing glucose variability in evolving pre-diabetes (Madhu, Muduli, & Avasthi, 2013) and Kang *et al*, similarly using CGMS showed the amplitude of glycaemic excursion was lower in those with NGT than in those with type 2 diabetes but the frequency of glycaemic excursion was greater, and concluded that the deterioration in postprandial blood glucose levels preceded deterioration in fasting blood glucose levels (Kang et al., 2009).

**Consequences of increased glycaemic variability**

In those with NGT and elevated 1-h glucose, increased glycaemic variability has been shown to be consistently associated with indicators of declining β-cell function (Su et al., 2013). Similarly, glucose variability *per se* has been shown to affect β - cell function with Luo *et al* showing that fluctuating glucose inhibited β-cell function more than sustained hyperglycaemia (Luo et al., 2013). In those with diabetes, increased glucose variability has been shown to be associated with increased free radical production which was not associated with 24-h mean glucose, fasting plasma glucose levels, or HbA1c (Devaraj, Hirany, Burk, & Jialal, 2001). Glucose variability in those with type 2 diabetes has also been associated with vascular endothelial dysfunction (Torimoto, Okada, Mori, & Tanaka, 2013), severity of coronary artery disease (Su et al., 2011) and increased activation of oxidative stress (Zheng et al., 2010). Similar effects have been shown in IGT (Chen et al., 2013; Zheng et al., 2010). A study by Meynaar *et al* in critical care patients showed glucose variability was related to all-cause mortality irrespective of diabetic state.

**Treatment of glucose variability in 1-h elevated postload glucose**

Lifestyle and dietary changes have long been recommended in the official pre-diabetic states (IFG and IGT) with a view to prevention of progression to diabetes and minimisation of vascular complications recognised as being associated with pre-diabetes (Unwin, Shaw, Zimmet, & Alberti, 2002a). There have, however, been no such consensus recommendations for NGT with elevated postload glucose. Wang *et al,* in a recent study of glucose fluctuations in NGT (1-h level unspecified), IGT and type 2 diabetes, identified glucose fluctuations present in all three states gradually increasing from NGT to type 2 diabetes. Although not specifying NGT with elevated 1-h glucose, *per se,* they recommended early diet and lifestyle interventions with a view to minimizing glucose variability (Wang et al., 2012). Zhou *et al* in a study of glucose variability in healthy Chinese adults identified the 95th percentiles of the mean amplitude of glycaemic excursions as 3.86 ± 1.40 mmol/L and, based on this, suggested a normal reference range for glycaemic variability of < 3.9 mmol/L be adopted (Zhou et al., 2011). There is no documented evidence yet of application of lifestyle or dietary interventions in NGT with elevated 1-h postload glucose.

The following paper demonstrates the success over 4 years of interventions to normalise glucose variability in a woman with 1-h elevated postload glucose.

### *3.1.3 Relative hypoglycaemia, hunger and weight gain*

It is well documented that hunger is associated with hypoglycaemia in diabetes (Lawton et al., 2013) and induced hypoglycaemia in healthy subjects has been shown to increase subjective reports of hunger (Rodin, Wack, Ferrannini, & DeFronzo, 1985). Schmid *et al*, in a study of induced hypoglycaemia in 16 healthy subjects, showed that a linear drop in blood glucose level over 60 min to 2.2 mmol/L stimulated spontaneous food intake 4+ h later, with carbohydrate intake being especially affected (Schmid et al., 2008). It has also been shown that spontaneous meal initiations were triggered by a transient decline in blood glucose level within the normal range in healthy adults (Melanson, Westerterp-Plantenga, Saris, Smith, & Campfield, 1999). In NGT with elevated 1-h postload glucose there is a spike in glucose at 1h and then a rapid fall to normal levels by 120 min (Yen et al., 2008). Although not documented in the literature, it is postulated that this would lead to increased hunger due to the rapid fall in glucose, and further that this would involve putative increased energy intake resulting in weight gain, thus increasing the risk of progression to diabetes in these individuals who are already at high risk. Normalization of this fall in blood glucose should decrease hunger and putative weight gain. This is demonstrated in the following paper.

### 3.2 Expanded results

The figure below presents expanded results from published Paper 1, which presented data on meal composition and relative change in blood glucose from time 0 (preprandial level) to1h post-meal consumption under different treatment and dietary regimens. The treatments were not provided in randomised order. The graphs below present absolute blood glucose levels measured at 0, 1h and 2h, with 3 measurements/meal/regimen, which visually illustrates the marked 1h 'spike'. Analysis was performed using SPSS Statistics, v22,IBM Corporation, NY, USA.

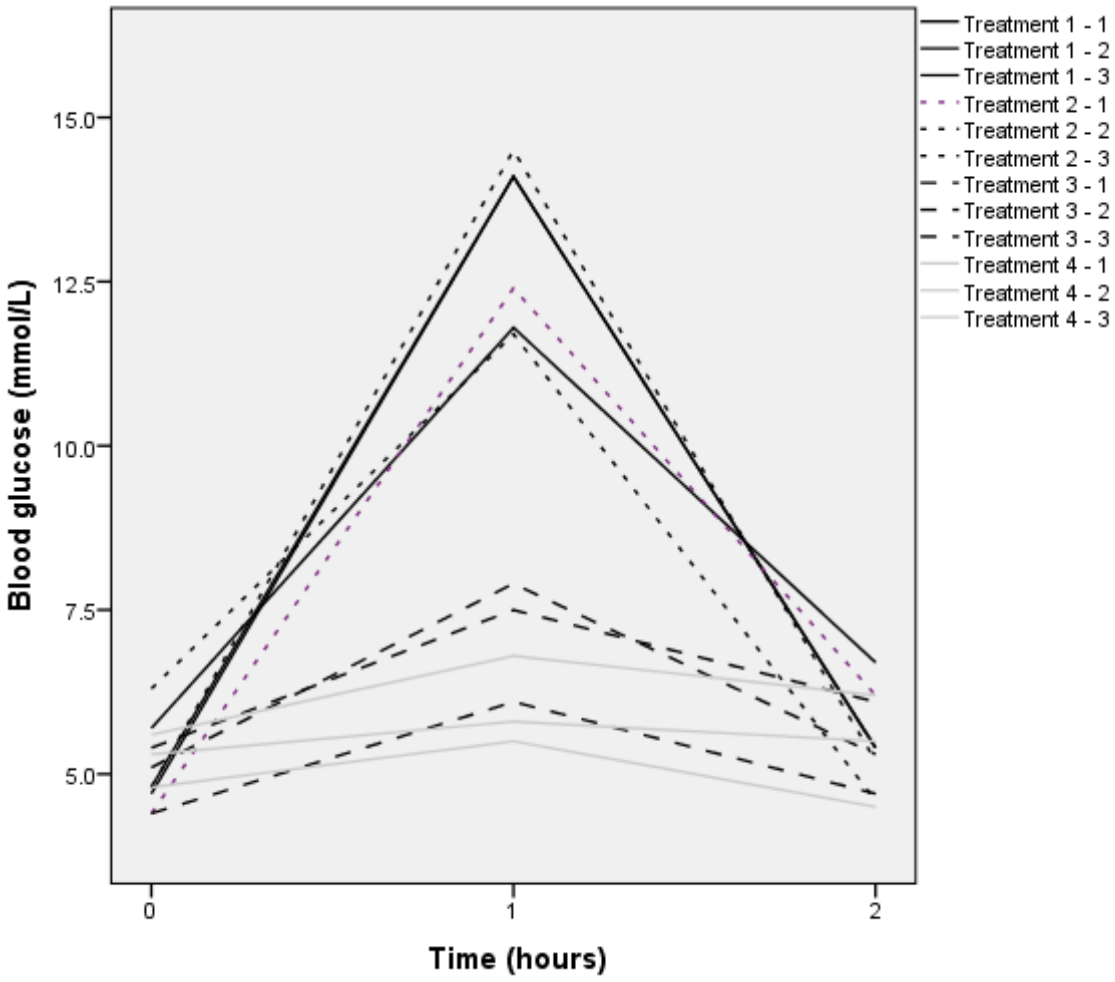



**Figure 3.1a) Blood glucose profiles for standard meal 1 (42 g carbohydrate) for four different treatments: 1 - untreated; 2 - sitagliptin; 3 - short-acting insulin; 4 - low carbohydrate. (**Note:Treatment 1-1 and 1-2 superimposed on graph).

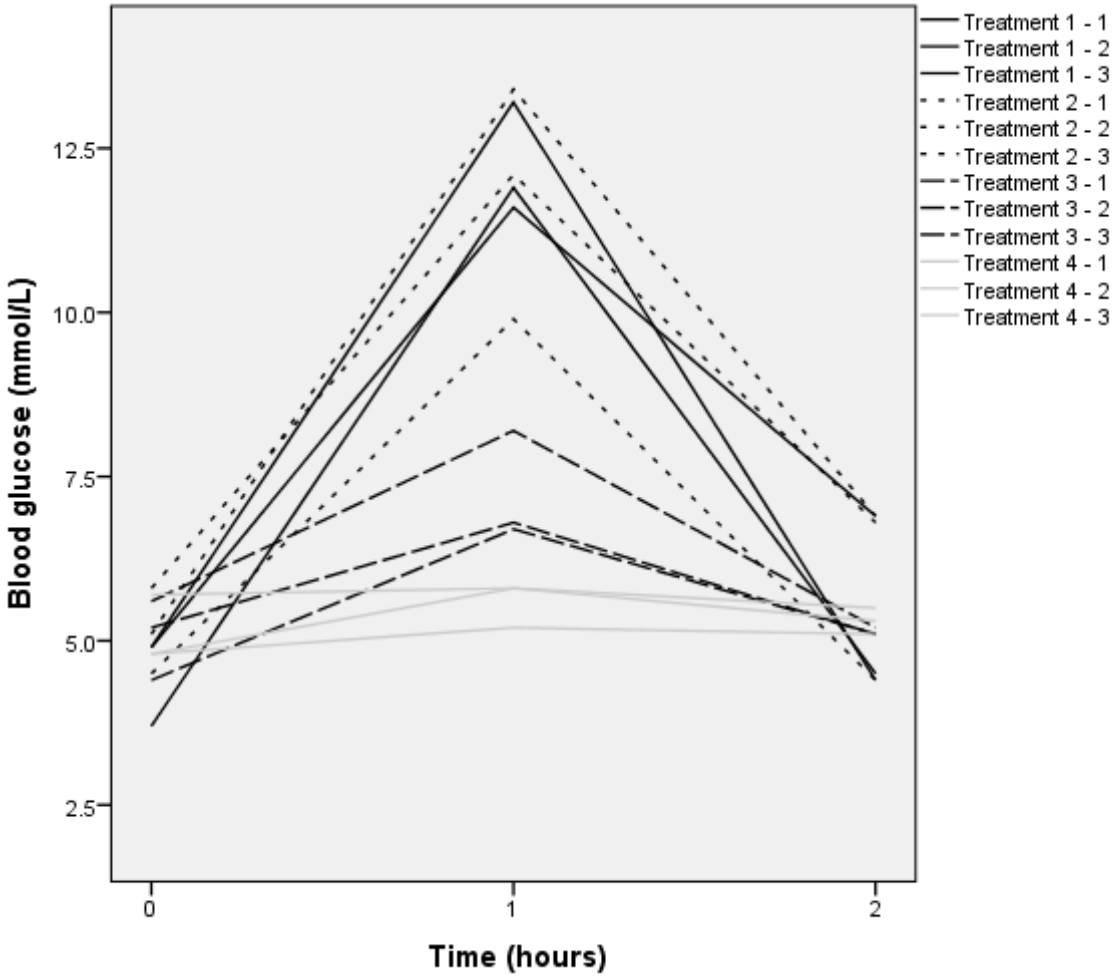



**Figure 3.1b) Blood glucose profiles for standard meal 2 (28 g carbohydrate) for four different treatments: 1 - untreated; 2 - sitagliptin; 3 - short-acting insulin; 4 - low carbohydrate.**

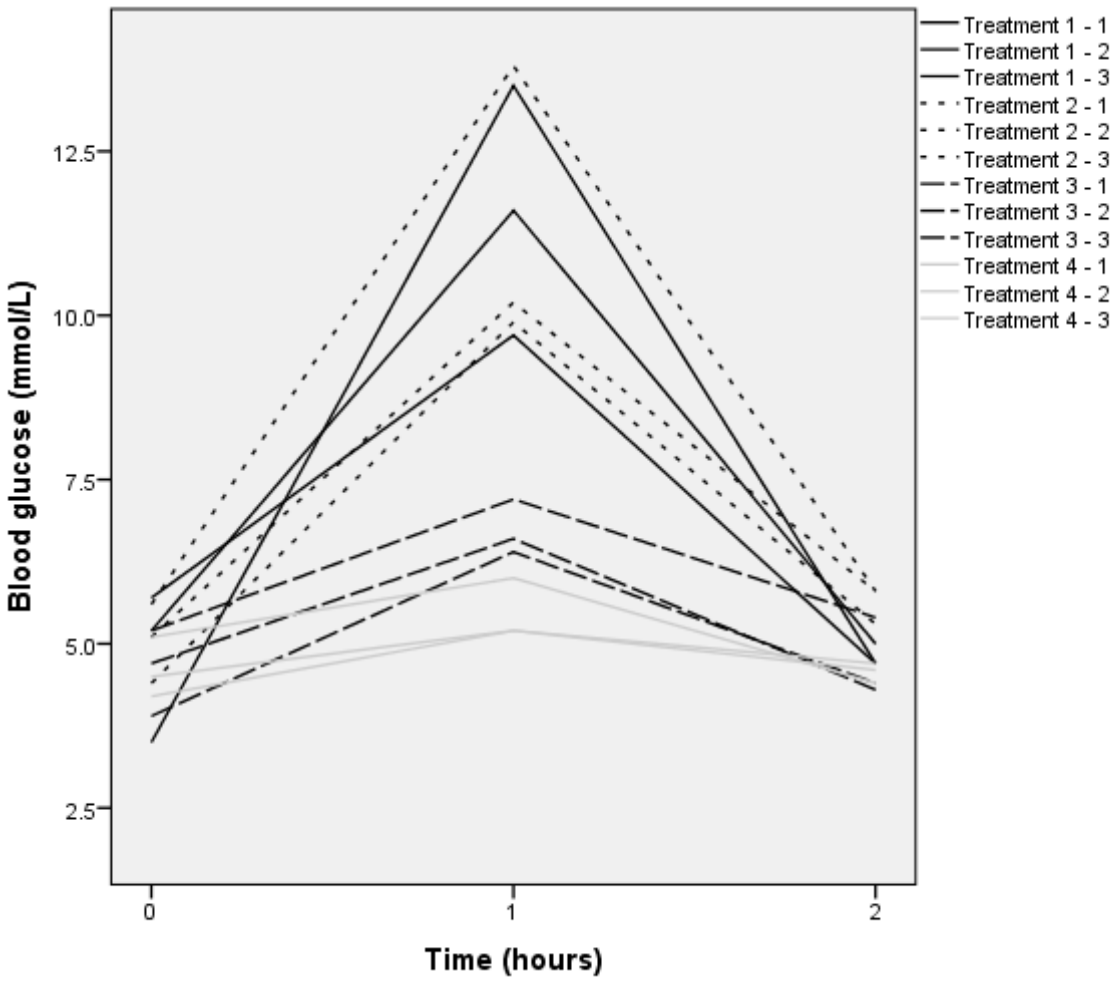



**Figure 3.1c) Blood glucose profiles for standard meal 3 (35 g carbohydrate) for four different treatments: 1 - untreated; 2 - sitagliptin; 3 - short-acting insulin; 4 - low carbohydrate.**

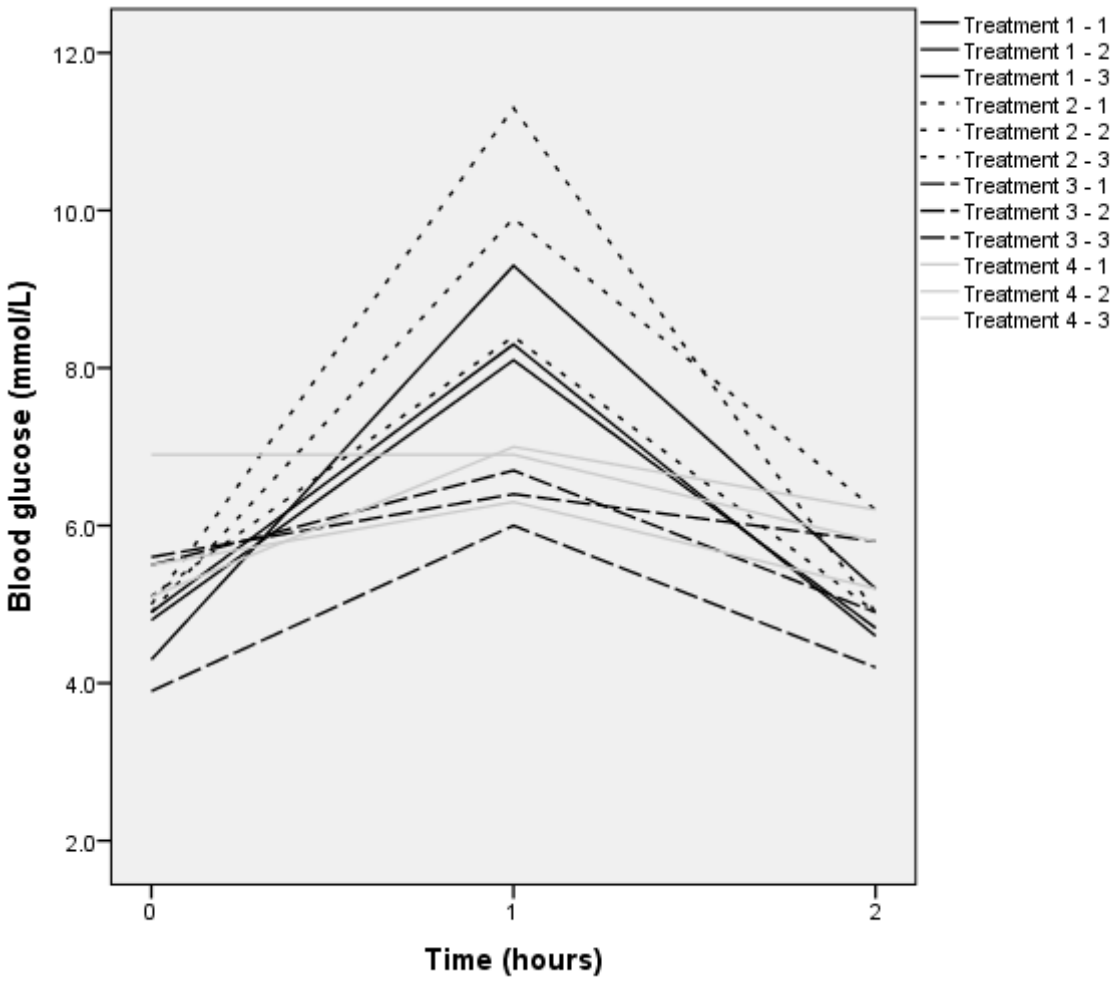



**Figure 3.1d) Blood glucose profiles for standard meal 4 (25 g carbohydrate) for four different treatments: 1 - untreated; 2 - sitagliptin; 3 - short-acting insulin; 4 - low carbohydrate.**

### 3.3 Paper 1

Vindedzis SA, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Low carbohydrate meals or a small dose of insulin normalises one-hour blood glucose in a woman with normal glucose tolerance and elevated one-hour postload glucose: a case report. The British Journal of Diabetes & Vascular Disease. 2013;13(2):103-5.

# Low carbohydrate meals or a small dose of insulin normalises one-hour blood glucose in a woman with normal glucose tolerance and elevated one-hour postload glucose: a case report

Sally A Vindedzis, Beryl Marsh, Jill L Sherriff, Satvinder S Dhaliwal and Kim G Stanton

*British Journal of Diabetes & Vascular Disease* 2013 13: 103
DOI: 10.1177/1474651412473343

THE BRITISH JOURNAL OF Diabetes & Vascular Disease

# Low carbohydrate meals or a small dose of insulin normalises one-hour blood glucose in a woman with normal glucose tolerance and elevated one-hour postload glucose: a case report

The British Journal of Diabetes & Vascular Disease
13(2) 103–105

DOI: 10.1177/1474651412473343
dvd.sagepub.com
SAGE

**Sally A Vindedzis,[1] Beryl Marsh,[1] Jill L Sherriff,[2] Satvinder S Dhaliwal[2], Kim G Stanton[1]**

## Introduction

Diabetes is diagnosed by 2-hour BGL ≥ 11.1 mmol/L on OGTT, fasting BGL ≥ 7.0 mmol/L or $HbA_{1C}$ ≥ 6.5%.[1] IFG and IGT are similarly diagnosed by elevated fasting and 2-hour BGLs.[1] Although 1-hour BGL is routinely measured, results are classified as NGT if fasting and 2-hour levels are normal, irrespective of elevation at 1 hour. It has, however, been shown that 1-hour postload BGL is a strong predictor of future risk for type 2 diabetes and vascular disease, even in those with NGT.[2,3] Additionally Meisinger *et al*. identified 1-hour postload glycaemia as a long-term predictor for all-cause mortality in men without diabetes.[4] There is no normal range for 1-hour glucose, but ≥ 8.6 mmol/L has been identified as a cut-off marking increased cardiovascular and diabetes risk.[2,3,5] It has been suggested that recognition and management of those with NGT and 1-hour glucose ≥ 8.6mmol/L may reduce incidence of diabetes and vascular events.[3,4]

This case report has been approved by Curtin University Human Research Ethics Committee, an institutional ethics committee, and a consent form has been signed.

## Case report

A.J., a 59-year-old Caucasian woman, had noted elevated BGLs soon after eating for about 10 years. In 2005 her OGTT showed a 1-hour level of 8.0 mmol/L with normal fasting and 2-hour levels (4.5 and 4.7 mmol/L respectively). When repeated in 2008 her BGL reached 11.7 mmol/L at 1 hour and was down to 7.2 mmol/L by 2 hours. Concurrent assessment of serum insulin showed a 1-hour level of 73 mU/L, remaining elevated at 2 hours (27 mU/L). SBGM had shown normal fasting levels on most occasions, but had risen to 6–8 mmol/L with acute illness. One-hour postprandial levels were often above 10 mmol/L when she ate a carbohydrate-containing meal. Apart from postprandial hyperglycaemia A.J. had no other vascular risk factors and did not fit criteria for metabolic syndrome. She had a raised LDL which responded to Lipitor but no evidence of a metabolic dyslipidaemia. Her blood pressure was 100/70. Until 2008 A.J. had noted increased postprandial hunger resulting in slow weight gain, although her BMI remained well within the normal range (2001, 60 kg, 20.5; 2008, 64.3 kg, 22.3).

Repeat SBGM over four standard meals showed a 1-hour postload rise significantly associated with meal carbohydrate quantity (p=0.024) but not glycaemic index (p=0.51) (Table 1). Mean 2-hour postload drop was 5.6±2.6 mmol/L.

A.J. commenced sitagliptin but after 4 months of treatment felt there was insufficient change in her 1-hour levels to warrant continuing. She elected to limit carbohydrate intake in most meals (5-10 g/meal) and use a small dose of short-acting insulin (½–1½units) before those meals when she elected to have more carbohydrate.

### Abbreviations:

| | |
|---|---|
| BGL | blood glucose level |
| BMI | body mass index |
| $HbA_{1C}$ | glycated haemoglobin $A_{1C}$ |
| IFG | impaired fasting glucose |
| IGT | impaired glucose tolerance |
| NGT | normal glucose tolerance |
| OGTT | oral glucose tolerance test |
| SBGM | self blood glucose monitoring |

[1]Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, WA, Australia
[2]School of Public Health, Curtin Health Innovation Research Institute, Curtin University, Bentley, WA, Australia

**Corresponding author:**
Sally Vindedzis, Department of Endocrinology and Diabetes, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia, 6001, Australia.
Email: sally.vindedzis@postgrad.curtin.edu.au

**Table 1.** Standard meals: content, carbohydrate load, glycaemic index and mean 1-hour postload rise in blood glucose.

| Stndard meal | Foods | CHO (g) | GI | 1-h BGL mmol/L |
|---|---|---|---|---|
| **Meal 1** | 1½ slice mixed grain toast<br>1 dsp dairy soft<br>1 dsp apricot jam<br>70 mL orange juice<br>Coffee + 50 mL soy milk | 41.8 | 47.8 | 8.2±1.8 |
| **Meal 2** | Long wheat roll<br>Mixed green salad<br>45 g cheese | 28.2 | 59 | 7.7±0.9 |
| **Meal 3** | Cannellini vegetable casserole<br>2 tbsp basmati rice<br>Green salad<br>Naan bread – palm sized<br>80 mL dry wine | 34.9 | 48.3 | 6.8±2.9 |
| **Meal 4** | 1 mixed grain toast<br>1 dsp dairy soft<br>2 tsp vegemite<br>80 mL orange juice<br>¼ apple | 25.1 | 46.1 | 3.9±0.9 |

**Key:** CHO: carbohydrate; dsp: dessert spoon; GI: glycaemic index; 1-h BGL: mean rise blood glucose 1-hour postload.
Carbohydrate content from Foodworks 7, Xyris Software (Aust) Pty Ltd 2012, Qld, Australia.
GI from Atkinson FS *et al.*[6]

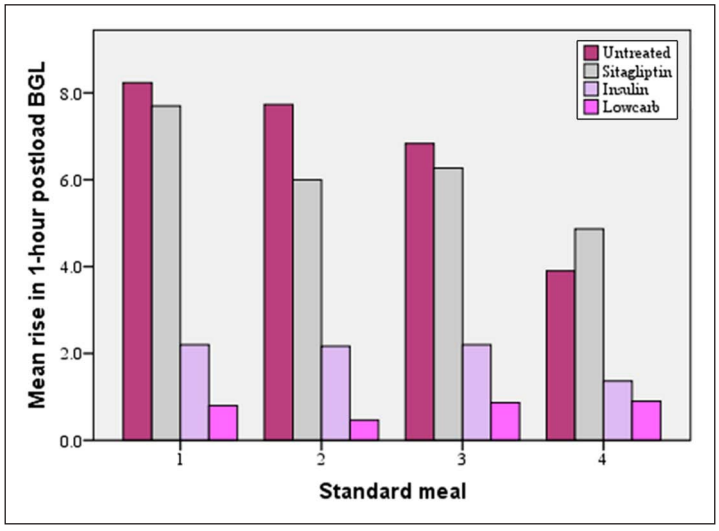



**Figure 1.** Mean rise in 1-hour postload blood glucose level (BGL) following four standard meals.

Mean repeat SBGM results are shown in Figure 1. Repeated measures ANOVA showed a significant difference between 1-hour postload rise for low carbohydrate and insulin-treated meals compared with no treatment or sitagliptin ($p<0.001$); there was no significant difference between no treatment and sitagliptin ($p=0.26$). On her current regime postprandial hunger has diminished with 3.6 kg weight loss over 4 years.

## Discussion

The significance of elevated postload 1-hour BGL is currently being debated. Whereas a diagnosis of IFG/IGT elicits advice on diabetes risk, diet, exercise and, more recently, metformin,[7] NGT with 1-hour BGL ≥ 8.6 mmol/L is classified normal and no preventative measures taken, despite evidence that these individuals have

an atherogenic profile similar to those with IGT[5] and a similarly increased risk of type 2 diabetes.[2]

We have described a case where two relatively straightforward interventions resulted in normalisation of elevated 1-hour postload BGL. Surprisingly sitagliptin, which has demonstrated positive effects on first phase insulin secretion,[8] had relatively little effect, although there was a trend to decreased 1-hour BGL with increased carbohydrate load. Our subject therefore chose a combination of mainly low carbohydrate meals combined with a small insulin dose before meals with > 10 g carbohydrate. One possible pitfall of low carbohydrate diets is increased saturated fat intake, but with proper design, this can be avoided. Such diets generally have good satiety and acceptance, although there is some evidence that adherence decreases over time.[9] Insulin treatment is more intrusive. A small dose before carbohydrate-containing meals only, minimises the risk of hypoglycaemic episodes, but still entails the necessity of SBGM. Our subject additionally noted that treatment appeared to reduce her postprandial hunger, thus facilitating weight loss. Her insulin profile at OGTT was consistent with Harada's thesis of decreased early phase insulin secretion giving rapid postprandial rise in BGL thus exaggerated second phase insulin response resulting in a rapid fall in BGL to normal levels by 90 minutes.[10] Her resulting postload drop at 2 hours is consistent with relative hypoglycaemia[11] and could well result in hunger and putative weight gain.

Cubeddu *et al*. showed that 8.3% of those with NGT have1-hour BGL ≥ 8.6 mmol/L,[3] so this condition is not unusual, but treatment of it is. This case demonstrates a practical intervention effective over 4 years. A case series is now needed to further investigate this.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Declaration of conflicting interests

The authors have no conflicts of interest to declare

## References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012; 35(supplement 1): S64-71.
2. Abdul-Ghani MA, Abdul-Ghani T, Ali N, DeFronzo RA. One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. *Diabetes Care* 2008; 31: 1650-55.
3. Cubeddu LX, Hoffmann IS. One-hour postload plasma glucose levels, a predictor of additional risk for diabetes: prevalence, mechanisms, and associated cardiovascular and metabolic risk factors in Hispanics. *Metab Syndr Relat Disord* 2010; 8: 395-402.
4. Meisinger C, Wölke G, Brasche S *et al*. Postload plasma glucose and 30-year mortality among nondiabetic middle-aged men from the general population: The ERFORT Study. *Ann Epidemiol* 2006; 16: 534-9.
5. Succurro E, Marini MA, Arturi F *et al*. Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. *Atherosclerosis* 2009; 207: 245-9.
6. Atkinson FS, Foster-Powell K, Brand-Miller JC. International Tables of Glycemic Index and Glycemic Load Values: 2008. *Diabetes Care* 2008; 31: 2281-3.
7. Nathan DM, Davidson MB, DeFronzo RA *et al*. Impaired fasting glucose and impaired glucose tolerance. *Diabetes Care* 2007; 30 :753-9.
8. Aaboe K, Knop FK, Vilsboll T *et al*. Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2010; 12: 323–33.
9. Berkow S, Barnard N, Eckart J, Katcher H. Four therapeutic diets: adherence and acceptability. *Can J Diet Pract Res* 2010; 71: 199-204.
10. Harada N, Fukushima M, Toyoda K *et al*. Factors responsible for elevation of 1-h postchallenge plasma glucose levels in Japanese men. *Diabetes Res Clin Pract* 2008; 81: 284-9.
11. Cryer PE, Axelrod L, Grossman AB *et al*. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; 94: 709-28.

# CHAPTER 4: GUIDELINES FOR FOOD TREATMENT OF HYPOGLYCAEMIA IN INSULIN-REQUIRING DIABETES

## 4.1 Background to study

### *4.1.1 The present guidelines*

First-line treatment for hypoglycaemia in the conscious person is dietary. Recommendations for self-treatment of hypoglycaemia are primarily made by national diabetes associations. General recommendations are fairly consistent worldwide: initial treatment with carbohydrate, preferably quickly absorbed, and eventual follow-up with longer lasting carbohydrate (American Diabetes Association, 2013c; Asian-Pacific Type 2 Diabetes Policy Group, 2002; Canadian Diabetes Association, 2012; Diabetes Education Study Group of the European Association for the Study of Diabetes, 1998; Diabetes New Zealand, 2008; Diabetes UK, 2011; Singapore Diabetes Society, 2010).

There is, however, less consensus on quantitative dietary treatment of hypoglycaemia, with recommendations for quantity of carbohydrate for initial treatment varying from 15 - 30 g (see Table 4.1) and recommendations for wait-time to retreatment (WTR) from 10 – 20 min (see Table 4.2).

Table 4.1 Recommendations for initial treatment of hypoglycaemia

| Amount Carbohydrate (g) | Recommended By: |
|---|---|
| 15 | • Diabetes Australia (Diabetes Australia, 2009)<br>• Singapore Diabetes Association (Singapore Diabetes Society, 2010)<br>• Diabetes New Zealand (Diabetes New Zealand, 2008) |
| 15 - 20 | • Diabetes UK (Diabetes UK, 2011)<br>• American Diabetes Association – Standards of Medical Care (2013) (American Diabetes Association, 2013)<br>• American Diabetes Society - Nutrition Recommendations (2008) (American Diabetes Association, 2008) |
| 20 - 25 | • National Health and Medical Research Council (Craig et al., 2011) |
| 15 - 30 | • Diabetes Educators Study Group (European Association for the Study of Diabetes) [Diabetes Education Study Group of the European Association for the Study of Diabetes, 1998 ] |
| Quantity unspecified | • Asian-Pacific Type 2 Diabetes Policy Group (Asian-Pacific Type 2 Diabetes Policy Group, 2002) |

Table 4.2 Recommendation for wait-time to retreatment if hypoglycaemia persists

| WTR (min) | Recommended By: |
|---|---|
| 10 | • Diabetes New Zealand (Diabetes New Zealand, 2008) |
| 10 - 15 | • Diabetes Australia (Diabetes Australia, 2009) |
| 15 | • American Diabetes Association – Standards of Medical Care (2013) (American Diabetes Association, 2013)<br>• Singapore Diabetes Association (Singapore Diabetes Society, 2010) |
| 10 - 20 | • American Diabetes Society - Nutrition Recommendations (2008) (Bantle et al., 2008) |
| Time unspecified | • Diabetes Educators Study Group (European Association for the Study of Diabetes) (Diabetes Education Study Group of the European Association for the Study of Diabetes, 1998)<br>• Diabetes UK (Diabetes UK, 2011)<br>• Asian-Pacific Type 2 Diabetes Policy Group (Asian-Pacific Type 2 Diabetes Policy Group, 2002) |

WTR, Wait-time to retreatment

### *4.1.2 Rationale for present guidelines*

What is the scientific basis for these recommendations made by the national diabetes associations? Grounds for recommendations are often not referenced (Asian-Pacific Type 2 Diabetes Policy Group, 2002; Diabetes Australia, 2009; Diabetes Education Study Group of the European Association for the Study of Diabetes, 1998; Diabetes New Zealand, 2008) or inter-referenced (Diabetes UK, 2011; Singapore Diabetes Society, 2010). Diabetes UK references a 1990 study by Slama *et al* (Slama et al., 1990) and a 1994 review by Cryer *et al* (Cryer et al., 1994) which in turn references Slama *et al* and two studies published in 1993 and 1984 by Wiethop and Cryer and Brodows *et al*, respectively (Brodows et al., 1984; Wiethop & Cryer, 1993). Singapore Diabetes Association in turn references Diabetes UK (Singapore Diabetes Society, 2010). The American Diabetes Association simply cites expert opinion (American Diabetes Association, 2013c).

### *4.1.3 Cited studies – laboratory conditions and atypical insulin regimes*

Aside from expert opinion, all referenced recommendations eventually cite three studies which were all conducted under laboratory conditions, in the absence of the subjects' normal insulin regimes (Brodows et al., 1984; Slama et al., 1990; Wiethop & Cryer, 1993). Two of these (Brodows et al., 1984; Slama et al., 1990) used intravenous regular insulin with normal evening insulin (Brodows et al., 1984) or medium acting insulin ceased 12 hours previously (Slama et al., 1990). The third used intravenous insulin overnight and regular insulin 2 h prior to testing but no longer-acting insulin (Wiethop & Cryer, 1993). Intravenous insulin is the most acute method of controlling BGL (Magee, 2012), having an onset of several min and a half life of 9 min (Mazer & Chen, 2009). Because of this short duration of action, it would be expected that hypoglycaemia would resolve quickly with the minimum quantity of dietary treatment. It is not possible to extrapolate results from these studies to the free-living situation where subject treatment would include medium-acting insulin with a duration of action of 12 - 18 h (Hirsch, 2005). Longer-lasting insulin which continues its action to decrease BGL over a prolonged period can cause longer-lasting hypoglycaemia and this may well affect the quantity of carbohydrate needed for treatment, and the WTR. An additional complicating factor in one study (Slama et al., 1990) was the subjects' short duration of diabetes (0.9 ±1.2 y). In this situation some subjects may still be producing significant intrinsic insulin (Fan et al., 2013) which may modify/enhance normalisation of hypoglycaemia. Their response to treatment of hypoglycaemia could not be presumed comparable to the general population of people with diabetes.

In Australia, the NHMRC in the 2011 National Evidence-Based Clinical Care Guidelines for Type 1 Diabetes in Children, Adolescents and Adults (Craig et al., 2011) references a 2009 guideline (Endocrinology Expert Group, 2009) for general dietary treatment of hypoglycaemia but cites the 1993 study of Wiethop and Cryer (Wiethop & Cryer, 1993) for quantitative recommendations (20-25g of carbohydrate with 'prompt' WTR). Diabetes Australia does not concur with this recommendation and continues to recommend 15 g and a 10 - 15 min WTR.

### *4.1.4 Current insulin regimes – analog insulins*

A major consideration is that all studies used as a basis for recommendations pre-date the introduction of analog insulin in 1998. Regular insulin, used in the above studies, contains zinc, which causes the molecules to associate and form hexamers which diffuse into the circulation and then slowly dissociate by way of dimers and then monomers (Hirsch, 2005). Lispro, the first analog insulin introduced, had an altered amino acid sequence, with the positions of proline and lysine, adjacent to each other in the B-chain, reversed. This resulted in rapid dissociation of the hexamer to the monomer, giving more rapid absorption and shorter duration of action than regular insulins. This shorter mode of action has been demonstrated to decrease the likelihood of hypoglycaemia (Kucera & Graham, 1998). Other short-acting analogs were subsequently developed with different modifications. Insulin aspart has proline on its B-chain replaced by aspartic acid. The aspartic acid residue has a negative charge which potentiates more rapid dissociation than the original configuration. This analog and those subsequently developed gave a similar reduction in hypoglycaemia to lispro (Heller et al., 1999; Hirsch, 2005). Other analogues produced by different substitutions on the insulin B-chain formed stable long-acting insulins suitable for use as basal insulin with a lower incidence of hypoglycaemia compared to previously used non-analog medium and longer-acting insulins (Hirsch, 2005; McKeage & Goa, 2001). Extrapolating data from studies based on regular insulins to current regimes using analog insulin has a shaky basis.

### *4.1.5 Issues of concern in the determination of food treatment of hypoglycaemia*

Issues of concern in determining quantity of treatment and WTR are the risk of progression to severe or extended hypoglycaemia with undertreatment and the possibility of subsequent hyperglycaemia with overtreatment (Choudhary & Amiel, 2011; Sommerfield et al., 2003). It is well documented that failure to identify, or undertreatment of mild hypoglycaemic episodes can lead to progression to severe or extended hypoglycaemia (Moghissi et al., 2009) which has been associated with increased morbidity (Cryer, 2012; Turchin et al., 2009), as has increased duration of hypoglycaemia (Braithwaite et al., 2004; Ng et al., 2009). There is abundant documentation showing post hypoglycaemic hypoglycaemia due to counter-regulatory responses (Hejlesen, Andreassen, Cavan, & Hovorka, 1996) but not for

subsequent hypoglycaemia resulting from excessive dietary treatment of mild hypoglycaemia.

### 4.2 Significance of study

Current recommended insulin therapy is for MDI of analog insulin with long-acting basal and short-acting pre-prandial insulin or CSII (continuous short acting analog insulin) (American Diabetes Association, 2013c) and it can be reasonably assumed that the majority of insulin-requiring individuals are being treated with these regimes. Recommendations for quantitative dietary treatment of hypoglycaemia need to be based on responses to that treatment by free-living subjects on these current regimes. The following paper addresses this issue in the context of current Australian recommendations for dietary treatment of hypoglycaemia and, as a secondary aim, investigates the poorly documented issue of post-hypoglycaemic hyperglycaemia.

### 4.3 Additional limitations of study and extended statistical analysis

Selection of subjects for the study reported in the following paper (section 4.4) was by time sequence, with each of 4 protocols continued for 16 weeks or until 20 participants had been audited. Study subjects were therefore not randomised for study groups.

The 4 study groups were based on treatment of hypoglycaemia: quantity of carbohydrate administered and wait-time to retreatment (15 g/5 min, 15 g/10 min, 20 g/5 min, 20 g/10 min), (see paper. section 4.4). Results from the paper stated that there was a significant association between treatment group and resolution of hypoglycaemia with one treatment ($^{\chi 2}$ $P < 0.01$), with 89.3% of the 20 g/10 min group attaining normoglycaemia with one treatment. A limitation of this result is that $\chi^2$ identifies a significant difference between groups but is unable to distinguish between specific groups. Further statistical analysis has therefore been performed to identify differences between specific groups as follows:

Independent samples median test was performed to compare number of treatments required to resolve hypoglycaemia with treatment group. This identified a significant difference between the 4 treatment groups ($p < 0.001$). Posthoc testing, pairwise multiple comparison, was then carried out. (see Table 4.1).

**Table 4.3 Post-hoc testing - independent samples median test pairwise multiple comparison**

| **Groups compared pairwise** | ***p*** |
|---|---|
| 20 g/10 min - 15 g/5 min | 0.000 |
| 20 g/5 min - 20 g/10 min | 0.017 |
| 15 g/10 min - 20 g/10 min | 0.032 |
| 15 g/10 min - 15 g/5 min | 0.395 |
| 20 g/5 min - 15 g/5 min | 0.663 |
| 15 g/10 min - 20 g/5 min | 0.839 |

Analysis was performed using SPSS Statistics, v22,IBM Corporation, USA.

This identifies a significant difference between the 20 g/10 min group compared to all other groups ($p$ = 0.000, 0.017, 0.032). This supports the result in published Paper 2.

### 4.4 Paper 2

Vindedzis S, Marsh B, Sherriff J, Dhaliwal S, Stanton K. Dietary treatment of hypoglycaemia: should the Australian recommendation be increased? Internal Medicine Journal. 2012;42(7):830-3.

*A Population Based Approach*. Canberra: PCA; 2005.
4 Department of Human Services. *Strengthening Palliative Care: A Policy for Health and Community Care Providers 2004–09*. Melbourne, Vic.: The Continuing Care Unit, Programs Branch, Metropolitan Health and Aged Care Services Division; 2004.
5 Shaw EA, Marshall D, Howard M, Taniguchi A, Winemaker S, Burns S. A systematic review of postgraduate palliative care curricula. *J Palliat Med* 2010; **13**: 1091–108.
6 Lofmark R, Mortier F, Nilstun T, Bosshard G, Cartwright C, Van Der Heide A *et al*. Palliative care training: a survey of physicians in Australia and Europe. *J Palliat Care* 2006; **22**: 105–10.
7 Fins JJ, Nilson EG. An approach to educating residents about palliative care and clinical ethics. *Acad Med* 2000; **75**: 662–65.
8 Chao C. Physicians attitudes toward DNR of terminally ill cancer patients in Taiwan. *J Nurs Res* 2002; **10**: 161–7.
9 Shulman-Green D. How do physicians learn to provide palliative care? *J Palliat Care* 2003; **19**: 246–52.
10 Duong PH, Zulian GB. Impact of a postgraduate six-month rotation in palliative care of knowledge and attitudes of junior residents. *Palliat Med* 2006; **20**: 551–6.

# Dietary treatment of hypoglycaemia: should the Australian recommendation be increased?

S. Vindedzis,[1] B. Marsh,[1] J. Sherriff,[2] S. Dhaliwal[2] and K. Stanton[1]

[1]Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth and [2]School of Public Health, Curtin University, Perth, Western Australia, Australia

**Key words**
hypoglycaemia, carbohydrate, diet, diabetes, hyperglycaemia.

**Correspondence**
Sally Vindedzis, Department of Endocrinology and Diabetes, Royal Perth Hospital, GPO Box X2213, Perth, WA 6001, Australia. Email: sally.vindedzis@health.wa.gov.au

Received 17 May 2011; accepted 3 October 2011.

doi:10.1111/j.1445-5994.2012.02831.x

## Abstract

Australian recommendations for treatment of hypoglycaemia are 15 g of carbohydrate repeated at 10–15 min if hypoglycaemia persists. Cited evidence is expert opinion or older studies not pertinent to current insulin regimens. This study aimed to determine the effect of increasing initial treating carbohydrate and decreasing wait-time to retreatment on resolution of hypoglycaemia in 92 free-living adults on current insulin regimens. The results support an initial treatment of 20-g carbohydrate, with a 10-min wait to repeat treatment as an optimal recommendation for the insulin-treated individual self-treating hypoglycaemia.

Hypoglycaemia in insulin-treated diabetes results from relative insulin excess.[1] The mechanisms of hypoglycaemia are well documented,[1,2] and programmes such as BGAT[3] and HyPOS[4] aid management; but as dovetailing insulin and lifestyle is an imperfect science, hypoglycaemia remains an unfortunate and feared by-product of insulin treatment.[5]

Treatment for hypoglycaemia in the conscious person is dietary and recommendations for this vary worldwide. All guidelines recommend initial treatment with quick-acting carbohydrate and follow-up with longer lasting carbohydrate.[6–10] The amount of carbohydrate recommended for initial treatment varies: 15 g (Australia, Singapore),[6,9] 10–20 g (UK),[7] 15–20 g (USA),[10] 15–30 g (Europe);[8] as does the recommended wait-time to repeat treatment (WTR) if hypoglycaemia persists: 10–15 min (Australia),[6] 15 min (Singapore, USA),[9,10] unspecified (UK, Europe).[7,8] Cited evidence for these recommendations is clinical opinion[7,9–11] or older studies[12–14] using intravenous, regular or medium-acting insulin, but no long-acting insulin. Free-living people treated with current insulin regimens incorporating short- and

Funding: None.
Conflict of interest: None.

long-acting insulins or continuous subcutaneous insulin infusion (CSII) may respond differently to dietary treatment of hypoglycaemia.

It therefore seems of value to determine if there are optimum recommendations for dietary treatment of hypoglycaemia in free-living individuals on current insulin regimens. We chose to assess 15- and 20-g carbohydrate quantities, as they are the most common recommendations. Recommendations for WTR range from 10 to 20 min. We assessed the shortest of these, and also a 5-min WTR, based on a substantial effect of glucose on blood glucose levels (BGLs) at 5 min.[15]

This study aimed to determine if there was a significant difference in the need for repeat treatment of hypoglycaemia following initial treatment with 15 or 20 g of fast-acting carbohydrate in free-living people experiencing spontaneous hypoglycaemia. A secondary aim was to determine if WTR could be reduced to 5 or 10 min without significantly increasing the need for repeat dietary treatment. The effect of carbohydrate quantity and WTR on subsequent hyperglycaemia was also investigated.

Participants were 92 free-living adults (50 male, 42 female) treated with subcutaneous insulin injection (SII) or CSII, attending scheduled diabetes clinic appointments and found to have hypoglycaemia on routine fingerprick blood testing during their clinic visit. As dietary treatment of hypoglycaemia in insulin-treated diabetes is a universal recommendation, consent, insulin treatment and hypoglycaemia were the only inclusion criteria. The project was approved by Curtin University Human Research Ethics Committee and registered as a clinical audit at Royal Perth Hospital.

Identification of hypoglycaemia was by blood glucose monitoring with a BGL <3.5 mmol/L defining 'clinical hypoglycaemia'.[16–18] Treatment was 15 or 20 g of glucose with WTR either 5 or 10 min, giving four different treatment protocols. Each protocol continued for 16 weeks or until 20 participants had been audited. Participants identified as hypoglycaemic were given a fluid containing 15 g (groups 1 and 2) or 20 g (groups 3 and 4) of glucose. They were retested in 5 min (groups 1 and 3) or 10 min (groups 2 and 4). If BGL remained <3.5 mmol/L, they were retreated as per protocol until BGL ≥3.5 mmol/L. Hypoglycaemic symptoms were recorded on a checklist by trained staff concurrent with blood testing. BGL assessment continued every 30 min while participants remained in clinic. On leaving, clinic participants were requested to blood test every 30 min to 4 h post-resolution of hypoglycaemia using their own blood glucose meter; record results, food and exercise on a standard form and return this to clinic. They were advised to follow normal procedure with meals and insulin. Trained staff measured clinic BGLs using the same blood glucose meter (Optium Xceed, Abbott, IL, USA) and measured glucose-containing fluid (carbotest) in the same premarked measuring cylinder.

As the study was not based on a hypothesised effect size, a formal calculation of statistical power was not applicable. The main objective of the study was to measure effectiveness of currently recommended dietary treatments for hypoglycaemia. The rate of incidental hypoglycaemic events in patients reporting for scheduled appointments to our clinics varies from 1 to 3 a week; therefore, we considered a 12-month audit (about 80 participants) that should be enough to answer the study questions.

Descriptive statistics were used for participant demographics, Shapiro–Wilk test was used to determine normality, and between-group differences were analysed using Kruskal–Wallis test for non-normally distributed continuous variables. The $\chi^2$ test was used to compare categorical variables. Mann–Whitney *U*-test was used to determine independent group differences.

Analysis was performed using PASW software (v18, SPSS Statistics, IBM Corporation, NY, USA).

Participant characteristics are shown in Table 1. Shapiro–Wilk test was significant for 12/20 continuous variables, indicating non-normal distribution, so non-parametric testing was performed. There was no significant difference between groups for age, gender, diabetes duration, haemoglobin A1c (HbA1c), body mass index (BMI) or presenting BGL. The numbers on CSII versus SII were too low to allow statistical testing.

Hypoglycaemic symptoms were reported by 35 (38%) of participants and resolved concurrently with the resolution of hypoglycaemia except in 10 participants who remained symptomatic for 10 min after their BGLs normalised.

The number of dietary treatments (quantity of carbohydrate as per protocol) required to resolve hypoglycaemia is shown in Table 2. There was a significant association between treatment group and resolution of hypoglycaemia with one treatment ($\chi^2$ $P < 0.01$), with 89.3% of the 20 g/10 min group attaining normoglycaemia with one treatment.

Short-term:BGLs were recorded for 45 participants at 30 min postresolution of hypoglycaemia. There was no significant difference between this group and non-recorders for age, gender, duration, HbA1c or BMI ($P > 0.05$). A BGL >10 mmol/L was arbitrarily defined as hyperglycaemia. Two out of 45 participants were hyperglycaemic at 30 min, but results were insufficient to compare treatment groups.

Longer term: Thirty-four participants returned BGLs recorded on personal blood glucose metres to 4 h

**Table 1** Characteristics of participants by hypoglycaemia treatment group

| Variables | Treatment group† | | | | *P*-value |
|---|---|---|---|---|---|
| | 15 g/5 min | 15 g/10 min | 20 g/5 min | 20 g/10 min | |
| *n* | 25 | 19 | 20 | 28 | |
| Age (years) | 47.5±17.8 | 50.2±16.2 | 45.3±17.8 | 52.5±16.8 | 0.52‡ |
| Gender (male/female) | 13/12 | 9/10 | 9/11 | 19/9 | 0.36§ |
| Diabetes duration (years) | 14.8±11.5 | 20.6±15.8 | 17.8±13.5 | 22.6±15.5 | 0.24‡ |
| Diabetes treatment (SII/CSII) | 24/1 | 16/3 | 18/2 | 25/3 | — |
| Haemoglobin A1c (%) | 8.8± 2.0 | 8.1± 1.9 | 8.8± 2.1 | 8.7± 2.2 | 0.63‡ |
| Body mass index (kg/m$^2$) | 28.0± 5.8 | 26.9± 4.6 | 25.4± 5.2 | 26.2± 8.1 | 0.63‡ |
| Presenting BGL (mmol/L) | 2.8± 0.5 | 2.7± 0.4 | 2.8± 0.5 | 2.9± 0.5 | 0.59‡ |

†Treatment group – carbohydrate quantity/wait-time to retreatment. ‡Independent samples Kruskal–Wallis test. §$\chi^2$ test. BGL, blood glucose level; CSII, continuous subcutaneous insulin infusion; SII, subcutaneous insulin injection.

post-resolution of hypoglycaemia. There was no significant difference between this group and non-recorders for age, gender, duration, HbA1c or BMI ($P > 0.10$). Fourteen recorded at least one BGL >10 mmol/L unrelated to food intake. To assess association between initial treating carbohydrate quantity and longer term hyperglycaemia categorical variables were generated as follows: carbohydrate 15g/20g; hyperglycaemia absent/present, present defined as at least one BGL >10 mmol/L ≥ 90 min post-hypoglycaemia. Association was tested using $\chi^2$ showing no significant association ($P > 0.10$).

Our results indicate that 20 g of fast-acting carbohydrate will resolve hypoglycaemia within 10 min in 89.3% of free-living individuals on current insulin regimes compared with 15 g that resulted in 63.2% resolving in 10 min. Decreasing the WTR to 5 min increased those needing repeat treatments with both 15 and 20 g treatments. Insufficient initial treating quantity of carbohydrate necessitating repeat treatments markedly increases the duration of hypoglycaemia. This is often accompanied by uncomfortable hypoglycaemic symptoms that last until clinical hypoglycaemia resolves, and in a third of symptomatic participants in this study, up to 10 min longer. Even where hypoglycaemic symptoms are minor or absent, repeated treatments, with the necessarily associated self-blood glucose monitoring, interrupt work, childcare and daily activities.

There is no consensus in the literature on a biochemical definition of hypoglycaemia. We identified hypoglycaemia as BGL <3.5 mmol/L, consistent with recommendations for 'clinical' hypoglycaemia.[16,17] The American Diabetes Association recommends 3.9 mmol/L as a level where individuals should consider the possibility of hypoglycaemia.[19,20] A lower level than this has been documented to decrease the incidence of hypoglycaemia, especially symptomless hypoglycaemia.[18] Had we used the 3.9 mmol/L level, we may have increased the numbers who resolved with one treatment of 15 g carbohydrate.

The rationale commonly given for restricting treating carbohydrate is that it causes subsequent hyperglycaemia. Fast-acting carbohydrate peaks at 30 min,[15] and hyperglycaemia at this time is probably attributable to treating carbohydrate. In this study, only 2 of 45 participants with BGLs recorded at 30 min post-hypoglycaemia were hyperglycaemic, but numbers were too small to relate to quantity of treating carbohydrate.

Hyperglycaemia after 60 min is unlikely to be related to initial treating carbohydrate. In this study, 34 participants returned BGLs recorded to 4 h postresolution of hypoglycaemia. The characteristics of those with records did not differ significantly from non-recorders. Fourteen recorded at least one BGL in the hyperglycaemic range

**Table 2** Number of dietary treatments required to resolve hypoglycaemia

| Treatment group† | 15 g/5 min | 15 g/10 min | 20 g/5 min | 20 g/10 min |
|---|---|---|---|---|
| *n* | 25 | 19 | 20 | 28 |
| Resolved with one treatment | 32.0% | 63.2% | 55% | 89.3% |
| Resolved after two treatments | 44% | 31.6% | 30% | 10.7% |
| Required >2 treatments | 24% | 5.2% | 15% | 0% |

†Treatment group – carbohydrate quantity/wait-time to retreatment.

90–240 min postresolution of hypoglycaemia. This was, unsurprisingly, not significantly associated with quantity of treating carbohydrate and is probably attributable to counterregulatory mechanisms.[1] These results need to be interpreted with caution because of possible selection bias in those who returned records and also because BGLs were from self-blood glucose monitoring records. They do, however, indicate that subsequent long-term hyperglycaemia following hypoglycaemia probably has more to do with physiology than diet. This warrants investigation with a cross-over study, which we have in progress.

Wild asserts that anxiety is lessened when an individual has a sense of control over their hypoglycaemia.[5] To this end, swift effective dietary treatment of hypoglycaemia is obviously desirable. This study supports an initial treatment of 20-g carbohydrate with a 10-min wait to repeat treatment as an optimal recommendation for the conscious insulin-treated individual self-treating hypoglycaemia.

## Acknowledgements

The authors wish to thank all participants who took part. We also wish to thank Anne Perry, Bee Choo Lim, Julie Pearse, Joyce Gwynne, Angela Sun and A. G. Tan, Royal Perth Hospital, Perth, for their help during the study.

## References

1 Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003; **26**: 1902–12.
2 Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER *et al*. Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2009; **94**: 709–28.
3 Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care* 2001; **24**: 637–42.
4 Hermanns N, Kulzer B, Kubiak T, Krichbaum M, Haak T. The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients with type 1 diabetes. *Diabetes Metab Res Rev* 2007; **23**: 528–38.
5 Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. *Patient Educ Couns* 2007; **68**: 10–5.
6 Diabetes Australia. [Homepage on the Internet]. Canberra: Diabetes Australia; 2009. [updated 2009; cited 2011 May 10]. Available from URL: http://www.diabetesaustralia.com.au/
7 Connor H, Annan F, Bunn E, Frost G, McGough N, Sarwar T *et al*. The implementation of nutritional advice for people with diabetes. *Diabet Med* 2003; **20**: 786–807.
8 Diabetes Education Study Group of The European Association for the Study of Diabetes. Teaching letter 2, hypoglycemia [Homepage on the Internet] 2003 [updated 2003; cited 2011 May 15] Available from URL: http://www.desg.org/component/option,com_docman/task,doc.../Itemid,61
9 Singapore Diabetes Society. Diabetes and hypoglycemia [Homepage on the Internet]. Singapore: Diabetic Society of Singapore; 2008 [updated 2008; cited 2011]. Available from URL: http://www.diabetes.org.sg/
10 American Diabetes Association. Standards of medical care in diabetes – 2011. *Diabetes Care* 2011; **34**: S11–S61.
11 Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A *et al*. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 2003; **26**: S51–61.
12 Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care* 1993; **16**: 1131–6.
13 Brodows RG, Williams C, Amatruda JM. Treatment of insulin reactions in diabetics. *JAMA* 1984; **252**: 3378–81.
14 Slama G, Traynard P-Y, Desplanque N, Pudar H, Dhunputh I, Letanoux M *et al*. The search for an optimized treatment of hypoglycemia: carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Arch Intern Med* 1990; **150**: 589–93.
15 Brand-Miller J, McMillan-Price J, Steinbeck K, Caterson I. Carbohydrates – the good, the bad and the whole grain. *Asia Pac J Clin Nutr* 2008; **17**: 16–9.
16 Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. *Diabet Med* 2008; **25**: 245–54.
17 Frier BM. Defining hypoglycaemia: what level has clinical relevance? *Diabetologia* 2009; **52**: 31–4.
18 Swinnen SG, Mullins P, Miller M, Hoekstra JB, Holleman F. Changing the glucose cut-off values that define hypoglycaemia has a major effect on reported frequencies of hypoglycaemia. *Diabetologia* 2009; **52**: 38–41.
19 Cryer PE. Preventing hypoglycaemia: what is the appropriate glucose alert value? *Diabetologia* 2009; **52**: 35–7.
20 American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on hypoglycemia. *Diabetes Care* 2005; **28**: 1245–9.

# CHAPTER 5: FOOD SELECTION FOR TREATMENT OF HYPOGLYCAEMIA IN INSULIN REQUIRING DIABETES

## 5.1 Expanded Methods

### *5.1.1 Rationale for use of a self-administered questionnaire*

Methodology for collecting data on health behaviours in free-living individuals can be problematic. Observational studies may disrupt the normal behaviour that is the target of observation. Self-reported data, while potentially overcoming this problem, requires that data acquisition be carried out in a standardized manner from a representative sample of a defined population to maximise accuracy (Rattray & Jones, 2007). In this type of survey, information is normally collected by interview, or self-administered questionnaire. Interview is the least burdensome method on the interviewees as they are only required to have basic verbal and listening skills (Bowling, 2005), however the presence of the interviewer may influence the accuracy of the answers, especially where questions are sensitive (Davis, Couper, Janz, Caldwell, & Resnicow, 2010). It has been reported that, compared to self-administered questionnaires, interviewer-administered questionnaires systematically elicited more socially desirable responses to questions relating to personal lifestyle, inferring the respondent was trying to please or impress the interviewer (Okamoto et al., 2002). It has been asserted that misreporting on sensitive topics is a conscious process where respondents edit the information they report to avoid embarrassment in the presence of an interviewer (Tourangeau & Yan, 2007).

A self-administered questionnaire requires more from the respondent, however, it allows anonymity and, where information may be sensitive, has been shown to be associated with better data quality compared to that obtained from interviewer-administered questionnaires (Durant, 2002; Ong & Weisse, 2007).

Can food treatment of hypoglycaemia be considered a sensitive topic? A sensitive question is defined as one requiring answers that may not conform to accepted social norms or that would be considered socially undesirable (Tourangeau & Yan, 2007). In a study involving 30 adults completing a Dose Adjustment for Normal Eating (DAFNE) course which includes instruction on food treatment of hypoglycaemia, almost all participants expressed a motivation to adhere to instructions on treatment of hypoglycaemia, but at interview 12 m post-course, only 50% had consistently

done so. Non-adherers gave a variety of rationales for non-adherent behaviour which included comments such as “I know that I shouldn’t but ....”, it’s “difficult to avoid overtreatment.....sweets are simply too nice” and ..... he ‘confessed’ to being unable to break a cycle of overmanagement (Lawton et al., 2013); all implying a felt betrayal of an accepted social norm. Similarly, it has been shown that fear of hypoglycaemia has been associated with non-adherence to treatment and this resulted in avoiding involvement with health professionals, presumably because it was thought this behaviour would be considered unacceptable (Tan, Chen, Taylor, & Hegney, 2012). It would seem that food treatment of hypoglycaemia could be seen, at least by some, as a ‘sensitive’ health issue. Thus the accuracy of research data obtained on this topic would be maximized by allowing participants to respond anonymously, and in the following study we utilized an anonymous self-administered questionnaire.

### *5.1.2 Readability*

Self-administered questionnaires require more from the respondent, with ability to respond being contingent on a certain level of literacy. Ability to respond accurately requires comprehension of the question, recall of requested information, and communication of the response in the manner specified by the question format (Bowling, 2005).

Low literacy is not a well-recognized problem in health care (Davis, Michielutte, Askov, Williams, & Weiss, 1998). Results from the 2006 Adult Literacy and Life Skills Survey showed that the proportion of Western Australians with literacy skills of Level 3 (the minimum literacy level required to deal with the complexities of everyday life) or above was about 55%. The lowest rates were in older Western Australians, with those aged 65-74 y having the smallest proportion at skill level 3+ (Australian Bureau of Statistics, 2011a). It is also well established that lower literacy levels are associated with lower socioeconomic status (Perry & McConney, 2010). The Australian Health Survey (2011 - 2012) showed that use of medical facilities increased with age (Australian Bureau of Statistics, 2011b). There is also a higher prevalence of use of general medical services among those who are educationally disadvantaged (Wiggers, Sanson-Fisher, & Halpin, 1995). It could, therefore, reasonably be expected that the literacy level in those attending a public hospital

clinic would be lower than in the community generally, and this may well affect health assessments by means of a questionnaire.

It has been shown that those with low literacy skills tend to interpret words literally, read slowly, and ignore unfamiliar words, which means that they tend to focus on details and miss key concepts. The simplification of text is seen as a partial solution to this. 'Readability' is a measure of the 'understandability' of a text (Ley & Florio, 1996). Readability formulas are quantitative measures of the reading difficulty of printed information, and there are numerous readability formulas available to provide quantitative estimates of the reading difficulty of printed health information by assessing the complexity of the vocabulary used (Friedman & Hoffman-Goetz, 2006). These formulae are multiple regression equations considering some combination of the number of syllables in words, the length of sentences and the proportion of common words used (Ley & Florio, 1996). Increasing readability usually leads to improvement in understanding (Ley & Florio, 1996) and the consensus on optimal level for health leaflets is $6^{th}$ grade level (Clauson, Zeng-Treitler, & Kandula, 2010), which is theoretically understandable by 91% of the population (Ley & Florio, 1996). There are many different readability formulas. We elected to use both Flesch Reading Ease and Flesch-Kincaid Formulae which are considered suitable for use in healthcare and require a relatively small amount of text for assessment, compared to some other formulae (Ley & Florio, 1996).

### *5.1.3 Validity and reliability*

The design of a questionnaire should be such that it accurately measures the health issues and behaviours it is designed to survey. The two most important issues in this context are the validity and reliability of the questionnaire. Validity is the degree that the questionnaire measures what it aims to measure. Reliability is the extent to which the questionnaire gives reproducible results, that is, its repeatability (Rattray & Jones, 2007; Saw & Ng, 2001).

**Validity**

Content, or face validity assesses whether the questionnaire is congruent with the concepts it is trying to measure. This includes both the relevance and scope of the questionnaire items (Scholtes, Terwee, & Poolman, 2011). This is a qualitative measure and is normally based on expert opinion (Saw & Ng, 2001). The following

paper was concerned with self-reported data on individual frequency and treatment of hypoglycaemia in people with insulin-treated diabetes. Item construction was carried out with reference to the literature and patient education material and items were subsequently reviewed by an experienced diabetes team. They were then piloted on a similar patient population (7% sample size of the full study population). There are no standards against which content validity can be measured. Its assessment is by subjective judgement (Scholtes et al., 2011).

Criteria validity is the extent to which measures are related to concrete criteria or a 'gold standard' (Manterola, Munoz, Grande, & Bustos, 2002). As this questionnaire was self-reported data on patient behaviour, a gold standard did not exist and criteria validity was not assessed.

**Reliability**

The two most common ways of measuring reliability of a questionnaire are to ask the question again in a different way in a different part of the questionnaire, or, secondly, to ask the question again to the same group at a different time; the test-retest method (Roberts, 2008; Saw & Ng, 2001). The results are then compared. There are advantages to both methods, but where a short questionnaire is considered optimum the second option is the obvious choice.

Test-retest agreement can be measured by percent agreement, which is calculated as the ratio of the number of times the test-retest results agree divided by the total number of questions in the questionnaire multiplied by 100. This does not, however, take into account the extent of agreement by chance (Stein, Devore, & Wojcik, 2005; Viera & Garrett, 2005). Statistical analysis of reliability is contingent on the form of information generated by the questionnaire. Zaki *et al* in a systematic review of statistical methods testing reliability in surveys using continuous variables reported that the intra-class correlation coefficient was the most popular method with 60% of studies utilizing this method. Other methods used were comparison of means (19%), Bland-Altman Limits of Agreement (17%) and simple correlation (5%) (Zaki, Bulgiba, Nordin, & Azina Ismail, 2013). Where variables are categorical, test-retest agreement is most commonly analysed by use of the Kappa coefficient (Roberts, 2008). The Kappa coefficient is calculated as: $\kappa = \{a - e\}/\{1 - e\}$, where a is the relative observed agreement between test-retest and e is the hypothetical probability of agreement by chance. The observed rate of agreement is used to calculate the hypothetical probability of test-retest agreement by chance and this is the calculated

value of e. The kappa coefficient therefore corrects, to some extent, for the proportion of agreement occurring by chance. It can therefore be seen that if the test-retest results agree completely then $\kappa = 1$, and if the converse, $\kappa = 0$. It is theoretically possible to have kappa values < 0 if there is systematic disagreement between the test and retest results. The generally agreed-on interpretation of kappa is: $\kappa = 0 - 0.2$ indicates slight agreement; 0.21 - 0.4, fair agreement; 0.41 - 0.6, moderate agreement; 0.61 – 0.8, substantial agreement; 0.81 – 1.00, almost perfect agreement (Saw & Ng, 2001; Viera & Garrett, 2005).

### *5.1.4 Response rates*

**Bias**

It is critical that the return rate of a self-administered questionnaire is adequate to avoid skewed sampling (Sitzia & Wood, 1998). Bias is introduced by non-response if those responding do not reflect the attitudes or behaviours of the whole population (Schalm & Kelloway, 2001). Cummings, in a review of physician surveys, asserted that similarities between responders and non-responders are almost impossible to assess and that non-response bias was one of the most important factors influencing validity of a survey (Cummings, Savitz, & Konrad, 2001).

Researchers cannot calculate the mean score of the non-responders and so cannot estimate the extent of the bias introduced by non-response. They can, however, calculate non-response and response rates as an indirect indication of the possibility of significant bias (Schalm & Kelloway, 2001). Baruch *et al*, in a study looking at response rates in questionnaires assessing organisational issues, commented that higher response rates are associated with larger sample sizes and more robust statistical conclusions. They also assert that an assessment of the response rate of a survey is a crucial factor in assessing the value of research results (Baruch & Holtom, 2008).

**Factors affecting response rates**

There is conflicting evidence on factors affecting response rates. Edwards *et al* reported that response rates were higher for shorter questionnaires and also if an incentive was offered for completion (Edwards et al., 2002), whereas Subar *et al*, investigating return rates in dietary questionnaires, showed that return rates were independent of length of questionnaire (Subar et al., 2001), as did Stizia *et al* in an

investigation of 210 patient satisfaction surveys. Contrary to the results of Edwards *et al*, Baruch *et al* showed that incentives did not increase response rates (Baruch & Holtom, 2008). It has also been shown that a questionnaire of interest to respondents increases response rates and that questionnaires containing sensitive questions are less likely to be returned (Edwards et al., 2002).

**Acceptable response rates**

There is no gold standard for an acceptable response rate for questionnaires. Several reviews have been published documenting average published response rates. Barush *et al* reviewing surveys used in organizational research looked at the response rate in 490 studies utilizing questionnaires. The average response rate for studies collecting data from individuals was 52.7 ± 20.4% (Baruch & Holtom, 2008). A review of results from mailed physician surveys published over 10 years reported that the average response rate was 61 percent (Cummings et al., 2001) and a review of 210 patient satisfaction surveys showed a response rate of 72.1% (Sitzia & Wood, 1998). Kelley *et al* assert that although it may not be wise to define a minimum acceptable response rate, their research indicates that a response rate of 75% for interviews and 65% for self-completed postal questionnaires should be both achievable and acceptable (Kelley, Clark, Brown, & Sitzia, 2003). As these figures are of the order of the existing reviews, we have adhered to this recommendation in the following paper.

## 5.2 Glycaemic index and hypoglycaemia

In the following paper, Paper 3 (see section 5.4), foods used for initial treatment of hypoglycaemia were categorised by two different methods: firstly, recommended/not recommended (a food was designated recommended if recommended by any of the recommending authorities); and, secondly, rate of action of carbohydrate. For the second categorisation, foods were grouped, then ranked by glycaemic index (GI) with GI of ≥70 categorised as quick-acting, 56 - 69 medium-acting and ≤55 slow-acting carbohydrate (Brand-Miller, Stockmann, Atkinson, Petocz, & Denyer, 2009).

Brand-Miller et al in a study of GI, postprandial glycaemia and the shape of the curve in healthy subjects investigated 1126 foods and compared GI and the shape of the curve. The average curve was then calculated for low-GI (<55), medium-GI (56 - 69), and high-GI (>70) foods. GI values correlated strongly with the food's

incremental peak. Differences in peak values between some foods classified as quick-acting compared to those classified as medium-acting were, in some instances, of the magnitude of 2 - 2.5 mmol/L at both 15 and 30 min post-consumption (Brand-Miller et al., 2009). This study was carried out using healthy subjects, and it is not clear if the results can be extrapolated to those with diabetes, however it has been shown that the correlation coefficient for 20 staple foods tested in subjects with and without diabetes was r = 0.94 ($p$ <0.001), which seems to indicate a very similar response (Atkinson, Foster-Powell, & Brand-Miller, 2008). If this is so, a difference of this magnitude 15 min post treatment of hypoglycaemia could be the difference between resolution of the event or ongoing hypoglycaemia, and would thus be of clinical significance.

### 5.3 Expanded results

The table below presents expanded results from published Paper 3 which were excluded from the paper due to the publishing journal's restrictions on length. It shows statistical analysis of test-retest results for items in the questionnaire utilized in the study. It can be seen from both the percent agreement and the kappa analysis that, in the main there was good agreement. It can be seen that where the CI for kappa are wide there is a large discrepancy between percent agreement and the kappa coefficient.

**Table 5.1 Reliability of questions in the hypoglycaemia questionnaire**

| | Test – Retest by interview | | |
|---|---|---|---|
| | %† | κ‡ | 95% CI§ |
| Frequency of hypoglycaemia (categorical) | 90.3 | 0.88 | 0.75 - 1.02 |
| Hypoglycaemic symptoms yes/no | 100 | 1.00 | 1.00 -1.00 |
| Specific symptoms of hypoglycaemia yes/no | 96.8 | 0.93 | 0.80 - 1.07 |
| - sweating | 93.5 | 0.82 | 0.57 - 1.06 |
| - hunger | 96.8 | 0.93 | 0.80 - 1.06 |
| - shaking | 93.5 | 0.86 | 0.68 - 1.05 |
| - irritability | 80.6 | 0.58 | 0.28- 0.88 |
| - headache | 87.1 | 0.74 | 0.50 - 0.98 |
| - behaviour change | 90.3 | 0.80 | 0.58 - 1.02 |
| - numbness | | | |
| Unique individual symptoms | 77.4 | 0.47 | 0.14 - 0.80 |
| Food used for initial treatment | 96.8 | 0.96 | 0.87 - 1.04 |
| Quantity of initial treating food(categorical) | 77.4 | 0.73 | 0.56 - 0.90 |
| Follow-up with food yes/no | 93.5 | 0.80 | 0.54 - 1.06 |
| Food used for follow-up (categorical) | 93.5 | 0.92 | 0.80 - 1.03 |

† %, Percent agreement; ‡ κ, Cohen's kappa; § CI, confidence interval

## 5.4 Paper 3

Vindedzis SA, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Food selection for treatment of hypoglycaemia in insulin-treated diabetes: what happens in real life? Practical Diabetes. 2012;29(7):271-4.

# Food selection for treatment of hypoglycaemia in insulin-treated diabetes: what happens in real life?

**Sally A Vindedzis**[1]
MSc, P/G Dip Nutrition and Dietetics, Dietitian – Diabetes

**Beryl Marsh**[1]
RN, Clinical Nurse Specialist – Diabetes

**Jill L Sherriff**[2]
PhD, MSc, P/G Dip Nutrition and Dietetics, Associate Professor (Nutrition and Dietetics)

**Satvinder S Dhaliwal**[2]
PhD, MSc, Associate Professor (Epidemiology and Biostatistics)

**Kim G Stanton**[1]
MB, BS, FRACP, Endocrinologist

[1]Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, Western Australia
[2]School of Public Health, Curtin University, Bentley, Western Australia

**Correspondence to:**
Sally Vindedzis, Department of Endocrinology and Diabetes, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia, 6001;
email: sally.vindedzis@health.wa.gov.au

**Received:** 20 May 2012
**Accepted in revised form:** 21 June 2012

## Abstract

Hypoglycaemia is a feared complication of insulin-treated diabetes. Treatment recommendations vary worldwide and their implementation is poorly documented. The primary study objective was to assess adherence to broad guidelines of hypoglycaemic treatment; initially with quick-acting carbohydrate and follow up with long-acting carbohydrate. The secondary objective was to assess if initial treating carbohydrate quantity complied with current worldwide recommendations.

Assessment was by questionnaire, which was validated, piloted and administered to all insulin-treated individuals attending routine outpatient diabetes clinic appointments over four weeks. The questionnaire response rate, readability and validity were acceptable at 74%, grade 6 level and 0.61 (Cohen's kappa), respectively.

Assessment of broad guidelines for treatment of hypoglycaemia showed 78% of responders reported initial treatment with recommended foods, but only 40.8% of these were quick-acting carbohydrate. Only 55.8% reported ingesting follow-up food. Assessment of initial treating carbohydrate quantity showed 20.6% of responders used quantities exceeding all guidelines. Of the remaining, 46.4% used quantities consistent with the most liberal recommendations (European Association for the Study of Diabetes).

Most study participants reported treating with recommended foods in quantities exceeding minimum recommendations, possibly attempting to resolve unpleasant symptoms of hypoglycaemia quickly. Failure of many to ingest follow-up food is concerning and warrants investigation. Increased patient education and standardisation of guidelines for treatment of hypoglycaemia are indicated. 
*Practical Diabetes* 2012; 29(7): 271–274

## Key words

questionnaire; hypoglycaemia; treatment; food; diabetes

## Introduction

Hypoglycaemia in diabetes is a by-product of treatment with exogenous insulin and/or oral hypoglycaemic agents. It is a common acute complication of diabetes. Reported rates of symptomatic hypoglycaemia in type 1 diabetes are one[1] to two[2,3] episodes per week with increased frequency of severe hypoglycaemia with longer duration of insulin treatment.[2,3] The reported rate in insulin-treated type 2 diabetes is lower,[1–3] with the UK Hypoglycaemia Study Group reporting four versus 36 episodes per subject-year for short duration insulin treatment in type 2 and type 1 diabetes respectively.[2]

Hypoglycaemia can cause neurogenic symptoms such as shaking, sweating and hunger and also neuroglycopenic symptoms, resulting from brain glucose deprivation, such as confusion, seizure and coma.[3] It has been estimated that 6–10% of deaths in people with type 1 diabetes are caused by hypoglycaemia.[4] People with diabetes are reported to fear hypoglycaemia more than the long-term complications of diabetes.[5]

It has been reported that 90.8% of people with type 1 and 84.5% of those with type 2 diabetes self-treat their hypoglycaemia.[6] Recommendations for this treatment fall into two parts. Firstly, all recommending authorities advise ingestion of quick-acting carbohydrate, reassessment of blood glucose levels and repeat treatment until blood glucose levels normalise.[7–13] Specific treatment foods recommended are glucose,[7–11,13] sugar,[8–13] carbonated beverages,[7–9,12,13] jelly beans, jelly babies etc,[8,9,12,13] honey[8,9] and fruit juice.[7–9,12,13] Subsequent ingestion of longer-lasting carbohydrate is then recommended to aid continued normalisation of blood glucose levels.[7–13] Secondly, there are specific recommendations for quantity of primary treating carbohydrate, ranging from 15g (Australia/Singapore/Canada)[8,9,12] to 15–30g (European Association for the Study of Diabetes [EASD]).[10] For others see Table 1.[7,11,13,14] All recommendations for

quantity of carbohydrate are based on expert consensus,[15] or older studies based on superseded insulin regimens.[16–18] Restriction of initial treating carbohydrate is based on the rationale that excess may contribute to subsequent hyperglycaemia although there is a paucity of studies supporting this.[19]

There is significant research on physiology and prevention of hypoglycaemia but little on the practical implementation of treatment recommendations for hypoglycaemia by people with diabetes.[20,21] This study was initiated to develop and validate a questionnaire to obtain information on self-treatment of hypoglycaemia in free-living people with insulin-treated diabetes. It aimed to assess if broad guidelines of hypoglycaemia treatment were being followed – i.e. initial treatment with recommended quick-acting carbohydrate and follow up with longer-lasting carbohydrate sources; and, secondly, if reported quantities of quick-acting carbohydrate were within recommended ranges.

## Methods

Participants were 119 free-living people (81 male, 38 female) over the age of 18 years with insulin-treated diabetes (type 1 and insulin-requiring type 2) attending routine outpatient diabetes clinic appointments. The sample size was determined by feasibility criteria. Treatment of diabetes was by subcutaneous insulin injection (SII) or continuous subcutaneous insulin infusion (CSII). Ethics approval was obtained from Curtin University Human Research Ethics Committee and the project was registered as a clinical audit at Royal Perth Hospital.

### *Procedure*

The questionnaire was given to all insulin-treated people attending routine diabetes clinics over a period of four weeks (n=161). Consent was presumed if it was returned to a designated sealed box. The questionnaire was short, with readability assessed as 6.2 on Flesch-Kincaid Grade Level Formula (grade 6 level, thus understandable by 85–90% of the population).[22] It commenced with an assurance of anonymity and an explanation of the aim: to investigate individual experiences of hypoglycaemia. Questionnaire items were identified from the literature, clinical experience and patient education material, and content validity was assessed qualitatively by a team consisting of a diabetologist, two diabetes educators and a dietitian. Test-retest reliability was assessed by comparing self-reported data with interview responses to the same questions by a convenience sample of 31 insulin-treated people from the same clinic population. Percent agreement was high for all questions (>70%) and Cohen's kappa, selected as it measures the amount by which agreement exceeds that expected by chance,[23] showed values >0.61 (substantial agreement) for 12 questions and 0.47–0.58 (acceptable agreement) for the other two.[24] The return rate for the questionnaire was 74% (n=119), above an acceptable rate of 65% for self-completed questionnaires.[25]

### *Measures*

**Demographics.** Descriptive statistics were used for subject demographics. The chi-square test ($\chi^2$) was used to compare categorical variables; and extended Fisher's exact test for age, diabetes treatment and duration (>2x2 contingency table with some cells <5).

**Broad guidelines for treatment of hypoglycaemia.** Initial treating foods were categorised by two different methods: firstly, recommended/not recommended (a food was designated recommended if recommended by any of the recommending authorities); and, secondly, rate of action of carbohydrate. Foods were grouped, then ranked by glycaemic index (GI). (GI of ≥70 was categorised as quick-acting, 56–69 medium-acting and ≤55 slow-acting carbohydrate.)[26] GI values were averaged from the Online Appendix To The International Tables of Glycemic Index.[26]

**Quantity of primary treating carbohydrate.** As most recommendations specify glucose as optimal treatment for hypoglycaemia,[7–11,13] initial treating food quantity was standardised by calculating glucose equivalents (GE). Glycaemic load (GL) is a stronger predictor of glycaemia than carbohydrate content alone[27] and was used as the GE. GL ≡ GE (g) = quantity carbohydrate eaten (g) x GI of food 100.

| Recommended carbohydrate | Recommended by: |
|---|---|
| 15g | • Diabetes Australia<br>• Singapore Diabetes Association<br>• International Diabetes Federation<br>• Canadian Diabetes Association |
| 15–20g | • Diabetes UK<br>• American Diabetes Association. Standards of Medical Care (2012) |
| 15–30g | • Diabetes Educators Study Group (European Association for the Study of Diabetes) |
| Unspecified | • Asian-Pacific Type 2 Diabetes Policy Group |

**Table 1.** Recommended quantity of carbohydrate for initial treatment of hypoglycaemia

**Statistical analysis.** This was performed using PASW, version 18, SPSS Statistics, IBM Corporation, USA, and extended Fisher's exact test by Gunma online database.[28]

## Results

Participant demographics are shown in Table 2. Median reported rate of hypoglycaemia was one per week, roughly consistent with reported rates in the literature.[1,2] The majority of responders to the question on symptoms of hypoglycaemia (n=118) reported experiencing symptoms (89%, 105). The most frequently reported symptoms were shaking (78.1% of symptomatic participants, n=82), sweating (72.4%, 76), behaviour change (54.3%, 57) and hunger (39%, 41).

### *Broad guidelines for treatment of hypoglycaemia*

**Recommended foods.** Of the 103 participants responding to this item, the majority (78%, n=80) reported initial treatment of their hypoglycaemia with recommended foods (Figure 1); jelly beans, jelly babies etc (34%, 35) and carbonated beverages (18.4%, 19) being the most common.

**Rate of action of carbohydrate.** Only 40.8% (n=42) of responders reported

| Variable | Result |
|---|---|
| Gender (M/F) | 81/38 |
| Age (yrs) (n,%) | |
| 18–25 | 7 (6) |
| 26–45 | 41 (35) |
| 46–65 | 48 (40) |
| >65 | 23 (19) |
| Treatment (SII/CSII)† | 104/15 |
| Duration (yrs) (n,%) | |
| 0–5 | 24 (20) |
| 6–15 | 33 (28) |
| 16–30 | 46 (39) |
| >30 | 16 (13) |

†(SII) subcutaneous insulin injection; (CSII) continuous subcutaneous insulin infusion.

**Table 2.** Participant demographics (n=119)

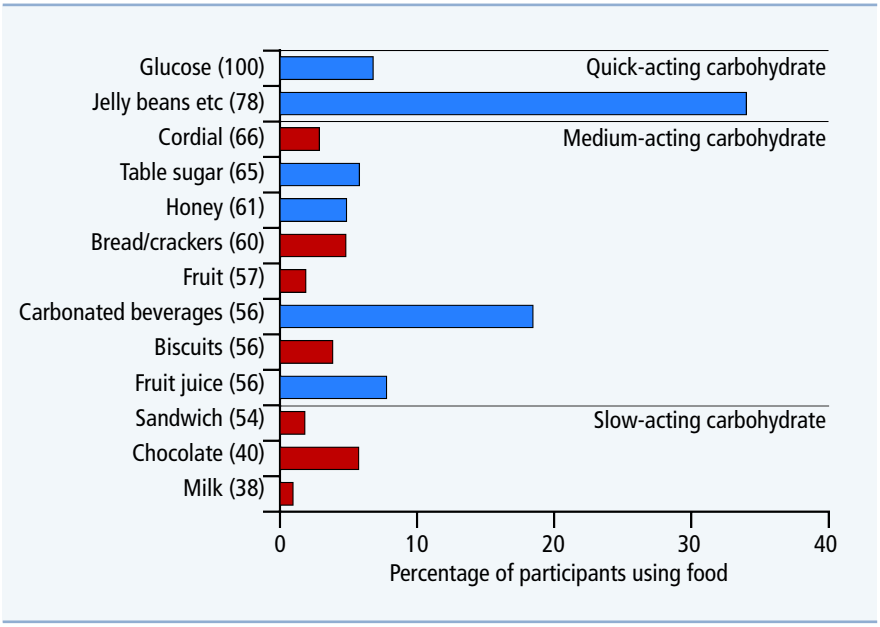



**Figure 1.** Foods used for initial treatment of hypoglycaemia ranked by action of carbohydrate: (a) numbers in parentheses denote average glycaemic index; (b) blue colour denotes recommended food for initial treatment

| Glucose equivalents | Responders using quantity | Quantity according to recommendations | |
|---|---|---|---|
| ≤15g | 32 (33%) | Less than or equal to lowest recommendations (Australia/Singapore/Canada) | |
| >15–20g<br>>20–30g | 22 (22.7%)<br>23 (23.7%) | Within USA/UK recommendations | Within EASD recommendations (i.e. 15–30g; 46.4%) |
| >30g | 20 (20.6%) | Greater than all recommendations | |

**Table 3.** Self-reported quantities of carbohydrate used for initial treatment of hypoglycaemia according to recommendations

initial treatment of hypoglycaemia with foods rated as quick-acting (GI ≥70) with the majority using medium-acting carbohydrate (50.5%, 52). (See Figure 1.)

**Follow-up treatment.** This question was answered by 104 participants, with 55.8% (n=58) of these reporting ingesting further food for follow up. Of these, medium-acting carbohydrate was the most commonly reported category of follow-up food (46.6%, 27), closely followed by long-acting carbohydrate (43.1%, 25). Sandwiches and bread/cereals tied as the most common follow-up treatment foods (22.4%, 13).

### *Quantities of carbohydrate used for initial treatment*

Self-reported quantities of carbohydrate used for initial treatment of hypoglycaemia are shown in Table 3, with 97 participants responding to this item. Only 20.6% (n=20) of responders reported quantities exceeding all recommendations, with a similarly small number (33%, 32) within minimum recommendations (15g, Australia/Singapore/Canada). Quantities falling within the recommendations of the EASD (15–30g) were reported by 46.4% (n=45) responders.

## Discussion

The purpose of this study was to investigate patterns of self-treatment of hypoglycaemia in people with insulin-treated diabetes and the extent to which guidelines for treatment were implemented. Response rates to questionnaire items addressing the broad guidelines for treatment of hypoglycaemia were high (≥87%). Consumption of recommended foods for initial treatment was reported by 78% of responders; however, only 40.8% were consuming quick-acting carbohydrate as defined by GI. This is understandable in that worldwide guidelines, while recommending ingestion of quick-acting carbohydrate, specify a range of foods, some of which are actually medium-acting carbohydrate. These recommendations are mirrored in other areas of the literature[3,29] and also in patient education material.[8,9,12] GI is now the universally accepted way of assessing rate of action of carbohydrate[27] but traditional specification of treatment foods preceded the advent of GI and some recommended foods may now be less than ideal.[17,30]

The response rate to the question on follow-up treatment was high, but only 55.8% of responders reported ingesting follow-up carbohydrate. The issue of follow up is important as quick-acting carbohydrate peaks at 30–45 minutes[31] and initial treatment may be effective for less than an hour[3,29,31,32] giving a subsequent drop in blood glucose level. A repeat episode of hypoglycaemia in the insulin-treated individual will be largely mitigated by insulin status and will be more likely where hypoglycaemia is due to relative excess of long-acting insulin or exercise, but lack of long-acting follow-up food

## Key points

- This study showed many responders reporting use of recommended, but medium-acting, carbohydrate for initial treatment of their hypoglycaemia. Increased education in the use of quick-acting carbohydrate and research on the efficacy of recommended medium-acting carbohydrate for treatment of hypoglycaemia seems indicated
- Many study participants reported using quantities of initial treating carbohydrate within EASD recommendations (15–30g) rather than the lower country of origin recommendation (15g). Non-adherence is not a reason to review recommendations, but in view of the relatively low evidence level on which recommendations are based and worldwide variation in recommendations, standardisation with the more liberal EASD recommendations seems timely
- In spite of recommendations, only 55.8% of responders reported ingesting follow-up food post initial treatment of hypoglycaemia. Further investigation to assess association between follow-up food and repeat hypoglycaemia would clarify the significance of this finding

increases the likelihood of repeat hypoglycaemic episodes.[3]

The questionnaire item addressing the second section of the guidelines, quantities of quick-acting carbohydrate used for initial treatment, was answered by 97 participants. Contrary to a finding by Sommerfield *et al.*,[21] only 33% of these reported using quantities consistent with the lowest recommendations (15g)[8,9,12] compared with 46.4% reporting quantities within the minimally increased EASD recommendations (15–30g).[10] Almost 90% of responders reported suffering unpleasant symptoms of hypoglycaemia, mainly shaking, sweating, behaviour change and hunger, and it is not surprising if they err towards larger quantities of initial treating carbohydrate with a view to possible faster resolution.

There were three main limitations of this study. As the questionnaire was anonymous there was no information available on the 26% of non-responders; however, the response rate was 74%, well above the 65% considered acceptable to minimise bias for a self-completed questionnaire.[25] A second limitation was lack of differentiation between diabetes types. All responders were insulin-treated, but self-reported data on diabetes type were considered to be of questionable accuracy. A third limitation was lack of data on the incidence of repeat episodes of hypoglycaemia; without this it is impossible to ascertain the significance of the large number of responders reporting lack of follow up with longer-acting carbohydrate.

### *Future directions*

This study showed many responders reporting use of recommended, but medium-acting carbohydrate for primary treatment of their hypoglycaemia. This indicates the need for increased education on the use of quick-acting carbohydrate in the treatment of hypoglycaemia. Research on the efficacy of currently recommended medium-acting foods for treatment of hypoglycaemia seems indicated, with a view to their possible removal from recommendations.

Many participants in this study reported quantities of initial treating carbohydrate within EASD recommendations rather than the lower, country of origin recommendations. Non-adherence in itself is not a reason to review recommendations, but in view of the relatively low evidence level on which recommendations are based and the variation in world recommendations, perhaps standardisation with more liberal EASD recommendations is indicated.

## Acknowledgements

The authors wish to thank all participants. Thanks also to Anne Perry, BeeChoo Lim, Angela Sun and AG Tan for their help during the study.

## Declaration of interests

There are no conflicts of interest declared.

## References

1. Donnelly LA, *et al.* Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabet Med* 2005;22:749–55.
2. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;50:1140–7.
3. Cryer PE, *et al.* Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902–12.
4. Cryer PE. Hypoglycemia in type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 2010;39:641–54.
5. American Diabetes Association. Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 2005;28:1245–9.
6. Leiter LYJ, *et al.* Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Can J Diabetes* 2005;29:186–92.
7. American Diabetes Association. Standards of medical care in diabetes – 2012. *Diabetes Care* 2012;35(Suppl 1):S11–S63.
8. Canadian Diabetes Association. Hypoglycemia. Canada: Canadian Diabetes Association. www.diabetes.ca/ [accessed June 2012].
9. Diabetes Australia. Hypoglycemia. Canberra: Diabetes Australia. www.diabetesaustralia.com.au/ [accessed June 2012].
10. Diabetes Education Study Group of The European Association for the Study of Diabetes. Teaching Letter 2, Hypoglycemia. www.desg.org/ [accessed June 2012].
11. Asian-Pacific Type 2 Diabetes Policy Group. Type 2 Diabetes Practical Targets and Treatments. International Diabetes Federation. www.idf.org/idf-wpr-type-2-diabetes-pratical-targets-and-treatments [accessed April 2012].
12. Singapore Diabetes Society. Diabetes and Hypoglycemia. Singapore: Diabetic Society of Singapore. www.diabetes.org.sg/ [accessed June 2012].
13. Treatment of hypoglycaemia. London: Diabetes UK. www.diabetes.org.uk/ [accessed June 2012].
14. Clinical Guidelines. Belgium: International Diabetes Federation. www.idf.org/ [accessed June 2012].
15. American Diabetes Association. Introduction. *Diabetes Care* 2008;31(Suppl 1):S1–S2.
16. Brodows RG, *et al.* Treatment of insulin reactions in diabetics. *JAMA* 1984;252:3378–81.
17. Slama G, *et al.* The search for an optimized treatment of hypoglycemia: carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Arch Intern Med* 1990;150:589–93.
18. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care* 1993;16:1131–6.
19. Heller SR. Diabetic hypoglycaemia. *Baillieres Best Pract Res Clin Endocrinol Metab* 1999;13:279–94.
20. Cox DJ, *et al.* Self-treatment of hypoglycemia while driving. *Diabetes Res Clin Pract* 2001;54:17–26.
21. Sommerfield AJ, *et al.* Self-treatment of mild symptomatic hypoglycaemia by people with insulin-treated diabetes. *Diabet Med* 2003;20:686–7.
22. Ley P, Florio T. The use of readability formulas in health care. *Psychol Health Med* 1996;1:7–28.
23. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med* 2005;37:360–3.
24. Saw SM, Ng TP. The design and assessment of questionnaires in clinical research. *Singapore Med J* 2001;42:131–5.
25. Kelley K, *et al.* Good practice in the conduct and reporting of survey research. *Int J Qual Health Care* 2003;15:261–6.
26. Atkinson FS, *et al.* International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* 2008;31:2281–3.
27. Brand-Miller J, Buyken AE. The glycemic index issue. *Curr Opin Lipidol* 2012;23:62–7.
28. Gunma University Faculty of Medicine. Fisher Exact Test. Japan: Shigenobu AOKI. http://aoki2.si.gunma-u.ac.jp/exact/exact.html [accessed June 2012].
29. Choudhary P, Amiel SA. Hypoglycaemia: current management and controversies. *Postgrad Med J* 2011;87:298–306.
30. Husband AC, *et al.* The effectiveness of glucose, sucrose, and fructose in treating hypoglycemia in children with type 1 diabetes. *Pediatr Diabetes* 2010;11:154–8.
31. Brand-Miller J, *et al.* Carbohydrates – the good, the bad and the whole grain. *Asia Pac J Clin Nutr* 2008;17(Suppl 1):16–9.
32. ADA. Nutrition Recommendations and Interventions for Diabetes. *Diabetes Care* 2008;31(Suppl 1):S61–S78.

# CHAPTER 6: FOOD AND REPEAT HYPOGLYCAEMIA IN INSULIN REQUIRING DIABETES

## 6.1 Paper 4

Vindedzis S, Marsh B, Sherriff J, Dhaliwal S, Stanton K. Omitting Follow-up Food After Initial Hypoglycaemic Treatment Does not Increase the Likelihood of Repeat Hypoglycaemia. Diabetes Therapy. 2013;4(1):67-75.

Diabetes Ther
DOI 10.1007/s13300-013-0019-x

ORIGINAL RESEARCH

# Omitting Follow-up Food After Initial Hypoglycaemic Treatment Does not Increase the Likelihood of Repeat Hypoglycaemia

Sally Vindedzis · Beryl Marsh · Jill Sherriff · Satvinder Dhaliwal · Kim Stanton

To view enhanced content go to www.diabetestherapy-open.com
Received: February 27, 2013


## ABSTRACT

***Introduction***: Guidelines for self-treatment of hypoglycaemia specify initial treatment with quick-acting carbohydrate until blood glucose levels normalize and then follow-up with longer-acting carbohydrate. The few studies investigating follow-up show 29–57% omission or undertreatment with follow-up carbohydrate but do not investigate the association of this with repeat hypoglycaemia. This study aimed to develop, validate and administer a questionnaire to delineate this association. The timeframe targeted was 2 h post primary hypoglycaemic event (PPHE), the time influenced by long-acting carbohydrate.

***Methods***: A questionnaire was generated, test–retest reliability assessed, and it was piloted on convenience samples from the target population. The final version was administered to all insulin-treated individuals attending an outpatient diabetes clinic over 4 weeks (169).

***Results***: Questionnaire development: readability (69.6—standard/easy), test–retest reliability (Cohen's kappa 0.57–0.91) and return rate (72.2%) were all acceptable. Questionnaire data: questionnaires were returned by 122 participants (63 males/59 females). Method of insulin administration was subcutaneous insulin injections (91%) and continuous subcutaneous insulin infusion (CSII) (9%). Repeat hypoglycaemia within 2 h PPHE was reported by 8.2% of respondents. There was no significant difference for age, gender and diabetes duration between those reporting repeat hypoglycaemia and those without. Consumption of follow-up longer-acting carbohydrate was reported by 58.2% of responders with 48% of these using long-acting and 52% medium-acting carbohydrate foods. Method of insulin administration and

S. Vindedzis (✉) · B. Marsh · K. Stanton
Department of Endocrinology and Diabetes, Royal Perth Hospital, GPO Box X2213, Perth, WA 6001, Australia
e-mail: sally.vindedzis@postgrad.curtin.edu.au

J. Sherriff · S. Dhaliwal
School of Public Health, Curtin Health Innovation Research Institute, Curtin University, Bentley, WA 6102, Australia

*Enhanced content for this article is available on the journal web site: www.diabetestherapy-open.com*

Published online: 12 April 2013

consumption of follow-up food were significantly associated with repeat hypoglycaemia ($P = 0.015$, 0.039) but presence or absence of symptoms and duration of action of carbohydrate were not significantly associated ($P = 0.103$, 0.629). Hierarchical logistic regression analysis showed omission of follow-up food PPHE was not a significant predictor of increased likelihood of repeat hypoglycaemia within 2 h PPHE, irrespective of method of insulin administration ($P = 0.085$).

***Conclusion***: This study supports guidelines that recommend judicious, rather than routine use of follow-up longer-acting carbohydrate PPHE.

**Keywords:** Repeat hypoglycaemia; Insulin-treated diabetes; Follow-up carbohydrate

## INTRODUCTION

Hypoglycaemia is a common complication of insulin treatment resulting from relative insulin excess and suboptimal glucose counterregulation [1]. Mean rates of hypoglycaemia in insulin-treated diabetes are reported as 42.89 (type 1) and 16.37 (type 2) events per person per year (population-based study) [2] and 29.0 (type 1 >15 years duration) and 10.2 (type 2 >5 years duration) events per person-year (secondary health based study) [3]. Hypoglycaemia is cited as the main impediment to euglycemia [4] and the most feared complication of insulin-treated diabetes [5].

It has been reported that 90.8% of adults with type 1 and 84.5% with type 2 diabetes self-treat their hypoglycaemia [6]. Recommendations for self-treatment advise ingestion of quick-acting carbohydrate, reassessment of blood glucose and repeat treatment until blood glucose levels normalise. Subsequent ingestion of longer-acting carbohydrate is then recommended [7–14] as quick-acting carbohydrate used for initial treatment peaks at 30 min and may return to baseline by 90–120 min [15], theoretically increasing the possibility of a repeat hypoglycaemic event within this timeframe. Longer-acting carbohydrate potentially stays above baseline to 210 min post-ingestion [16].

There are few reports in the literature on the extent of adherence to recommendations for follow-up treatment with longer-acting carbohydrate [17–19]. Sommerfield et al. in a survey of 101 insulin-treated individuals reported 29% undertreating with long-acting follow-up food [17], defining undertreatment as less than 10–20 g of long-acting carbohydrate (Diabetes UK Treatment Guidelines For Hypoglycaemia) [13]. Sumner et al. surveyed 125 individuals with type 1 diabetes reporting 57% omitted long-acting follow-up carbohydrate [18], and Vindedzis et al. reported 44.2% omitted follow-up carbohydrate in a survey of 119 insulin-treated individuals [19]. The association of omission or inadequate ingestion of follow-up food with repeat hypoglycaemia was not investigated in any of these studies.

Repeat hypoglycaemia per se does not have a formal definition, and the term is sometimes used interchangeably with recurrent hypoglycaemia [20] and multiple episodes of hypoglycaemia [21]. Current literature on repeat/recurrent hypoglycaemia examines a longer timeframe than would be affected by lack of follow-up food post-primary hypoglycaemic event (PPHE). Reports on paramedic treatment of hypoglycaemia identify repeat hypoglycaemia as occurring within 24–72 h PPHE [22], and reviews of mechanisms and prevention of hypoglycaemia identify repeat hypoglycaemia over 24 h PPHE,

or longer [23, 24]. This timescale for recurrence in the insulin-treated individual will be largely influenced by insulin status and also defective counterregulation, clinically indicated by reduced awareness of hypoglycaemic symptoms [23]. Method of insulin administration may be a modifier of hypoglycaemia within a shorter timeframe; there is mixed evidence of the association of continuous subcutaneous insulin infusion (CSII) with reduction in severe hypoglycaemia as compared with multiple daily injections [25, 26].

It could be reasonably assumed that the effect of follow-up longer-acting carbohydrate on blood glucose levels would be confined to 2–3 h PPHE depending on the source of the carbohydrate [16]. We therefore hypothesized that omission of follow-up longer-acting carbohydrate would increase the frequency of repeat hypoglycaemia within 2 h PPHE in free-living insulin-treated individuals. The aim of this study was therefore, first, to develop and validate a questionnaire to obtain data on treatment of primary hypoglycaemia, the presence or absence of symptoms of hypoglycaemia, and the frequency of repeat hypoglycaemia within 2 h PPHE and second, to administer this questionnaire to free-living insulin-treated individuals to assess the likelihood of repeat hypoglycaemia with and without follow-up food while controlling for other significant modifiers of hypoglycaemia.

## MATERIALS AND METHODS

### Development of the Questionnaire

The one-page questionnaire was couched in simple language with explanation of technical terms and aimed at completion within 10 min. It commenced with a brief preamble assuring anonymity and explaining the aim was investigation of individual experience of hypoglycaemia. Contact and ethics approval details were provided. Questionnaire items were generated from the literature, patient education material and clinical experience and were a mixture of multichoice and numeric and text open-ended questions. Readability of the questionnaire was assessed by the Flesch Reading Ease Formula and Flesch–Kincaid Grade Level Formula, which are considered suitable for use in health care settings [27]. Content validity was assessed qualitatively by a diabetologist, two diabetes educators and a dietitian. A convenience sample of 19 insulin-treated people from the population to be tested were recruited to assess test–retest reliability of the questionnaire, which was conducted by comparing self-administered responses with interview responses to the same questionnaire items. Interviews were carried out by one of five experienced diabetes educators blinded to the original responses. The questionnaire was then piloted on a convenience sample of nine people with insulin-treated diabetes (7% of sample size) to gain insight into item comprehension; this resulted in several minor rewordings. The return rate of the questionnaire was calculated by number of returned questionnaires against number distributed.

### Administration of the Questionnaire

The questionnaire was distributed to all insulin-treated adults attending routine outpatient diabetes clinic appointments over a period of 4 weeks ($n = 169$). Treatment of diabetes was by either subcutaneous insulin injection (SII) or CSII. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national)

and with the Helsinki Declaration of 1975, as revised in 2000. Study information was given and consent presumed on return of questionnaire. Ethics approval was obtained from Curtin University Human Research Ethics Committee and the project was registered as a clinical audit at Royal Perth Hospital. The questionnaire was designed for self-administration but was initially given to insulin-treated individuals, with a brief explanation, by one of five credentialled diabetes educators. The questionnaire was anonymous, filled out while waiting to see the doctor and consent was presumed on return of the questionnaire to a designated sealed box.

### Statistical Methods

#### *Questionnaire Development*

Test–retest reliability of the questionnaire was evaluated by percent agreement and also using the kappa statistic (κ), which measures the amount by which agreement exceeds that expected by chance. Kappa was calculated for the self administered—interview data with 95% confidence intervals based on 1,000 bootstraps.

#### *Data from Questionnaire*

Descriptive statistics were used for participant characteristics and hypoglycaemic frequency. The Chi-square test ($\chi^2$) was used to compare categorical variables and extended Fisher's exact test for age and duration of diabetes ($>2 \times 2$ contingency table with some cells $<5$). Glycaemic index (GI) was used to assess duration of action of follow-up carbohydrate with GI of $\leq 55$ categorized as long-acting and 56–69 as medium-acting carbohydrate [28]. Hierarchical logistic regression analysis was performed to predict the likelihood of repeat hypoglycaemia with respect to consumption/non-consumption of follow-up food while controlling for other significant variables. Analysis was performed using SPSS Statistics—version 21 (IBM Corporation, Somers, NY, USA) and extended Fisher's exact test by Gunma online database [29].

## RESULTS

### Development of Questionnaire

Readability of the questionnaire was assessed as 69.6 on Flesch Reading Ease Formula (standard—easy level) and 6.2 on Flesch–Kincaid Grade Level Formula consistent with a grade 6 level, thus theoretically understandable by 85–90% of the population [27]. Test–retest reliability and response rate for individual items are shown in Table 1. Response rates and percent agreement were uniformly high. Values for κ exceeded 0.61, indicating substantial agreement for six of the seven questions, with moderate agreement for the other [30].

### Data from Questionnaire

Questionnaires were returned by 122 out of 169 participants (63 males, 59 females) giving a return rate of 72.2%, well above the estimated acceptable rate of 65% for self-completed postal questionnaires [31]. Participant characteristics are shown in Table 2 and self-reported frequency, symptoms and treatment of hypoglycaemia in Table 3. Repeat hypoglycaemia was reported by 8.2% ($n = 10$) of participants and correlated well with a separate question on self-reported frequency of repeat hypoglycaemia ($P < 0.001$). There was no significant difference in the distribution of age, gender and duration of diabetes between those reporting repeat hypoglycaemia and those without ($P = 0.343$, 1.00, 0.458 respectively). All participants reported consuming initial treatment food.

**Table 1** Test–retest reliability and response rates of questionnaire items

| Question topic | Test–retest by interview | | | % Item response[b] |
|---|---|---|---|---|
| | %[a] | κ | 95% CI | |
| Frequency of hypoglycaemia | 94.7 | 0.91 | 0.71–1.00 | 97.5 |
| Hypoglycaemic symptoms yes/no | 78.9 | 0.69 | 0.39–0.92 | 94.3 |
| Repeat hypoglycaemia yes/no | 84.2 | 0.57 | 0.21–0.84 | 100 |
| Frequency of repeat hypoglycaemia | 94.7 | 0.89 | 0.63–1.00 | 100 |
| Initial treatment food | 88.9 | 0.84 | 0.60–1.00 | 100 |
| Follow-up with food yes/no | 89.5 | 0.76 | 0.53–1.00 | 98.4 |
| Food used for follow-up | 84.6 | 0.61 | 0.32–0.84 | 98.4 |

[a] Percent agreement
[b] Percent of total responders answering item
κ Cohen's kappa, *CI* confidence interval

**Table 2** Participant characteristics

| | | Percent responders |
|---|---|---|
| Gender (m/f) | 63/59 | 100 |
| Age (years) (*N*, %) | | 100 |
| 18–25 | 8 (6.6) | |
| 26–45 | 31 (25.4) | |
| 46–65 | 56 (45.9) | |
| >65 | 27 (22.1) | |
| Treatment (SII/CSII) (*N*, %) | 111/11 (91/9) | 100 |
| Duration (years) (*N*, %) | | 100 |
| 0–5 | 14 (11.5) | |
| 6–15 | 39 (31.9) | |
| 16–30 | 46 (37.7) | |
| >30 | 23 (18.9) | |

*CSII* continuous subcutaneous insulin infusion, *m/f* male/female, *N* number of responders, *SII* subcutaneous insulin injection, *y* years

Follow-up food ingestion was reported by 58.2% of item responders with 48% of these using long-acting and 52% medium-acting carbohydrate. Ninety percent of those using medium-acting carbohydrate chose food sources in the lower half of this category, i.e. GI <62 (Fig. 1).

Both method of insulin administration and consumption/non-consumption of follow-up food PPHE were significantly associated with presence/absence of repeat hypoglycaemia ($\chi^2$: $P = 0.015$, 0.039) but presence/absence of hypoglycaemic symptoms and duration of action of carbohydrate were not significantly associated ($\chi^2$: $P = 0.103$, 0.629). Hierarchical logistic regression analysis was then conducted to predict the likelihood of repeat hypoglycaemia using consumption/non-consumption of follow-up food PPHE as a predictor variable while controlling for method of insulin administration. A test of the full model against a constant only model was statistically significant, indicating that the predictor variables should distinguish between those with and without repeat hypoglycaemia ($\chi^2 = 4.445$, $P = 0.035$ with $df = 1$), the Hosmer–Lemeshow goodness of fit test was not significant ($P = 0.838$) indicating the model prediction was not significantly different from

**Table 3** Self-reported frequency and treatment of hypoglycaemia

| | | Percent responders |
|---|---|---|
| Frequency hypoglycaemia (events/wk) (*N*, %) | | 97.5 |
| 0–1 | 61 (50) | |
| 1–3 | 48 (39.4) | |
| 3–5 | 10 (8.1) | |
| >5 | 0 (0) | |
| Unanswered | 3 (2.5) | |
| Hypoglycaemic symptoms (y/n) (*N*, %) | 101/14 (82.8/11.5) | 94.3 |
| Unanswered | 7 (5.7) | |
| Repeat hypoglycaemia (y/n) (*N*, %) | 10/112 (8.2/91.8) | 100 |
| Frequency repeat hypoglycaemia (*N*, %) | | 100 |
| Often | 2 (1.6) | |
| Sometimes | 7 (5.7) | |
| Rarely | 14 (11.5) | |
| Never | 99 (81.2) | |
| Initial treatment food (y/n) (*N*, %) | 122/0 (100/0) | 100 |
| Follow-up food (y/n) (*N*, %) | 71/49 (58.2/40.2) | 98.4 |
| Unanswered | 2 (1.6) | |

*wk* week, *y* yes, *n* no, *N* number of responders

the observed values; however, the Wald criterion demonstrated that consumption/non-consumption of follow-up food PPHE was not a significant predictor of repeat hypoglycaemia ($P = 0.085$). All standard errors <2 indicated no multicollinearity between variables.

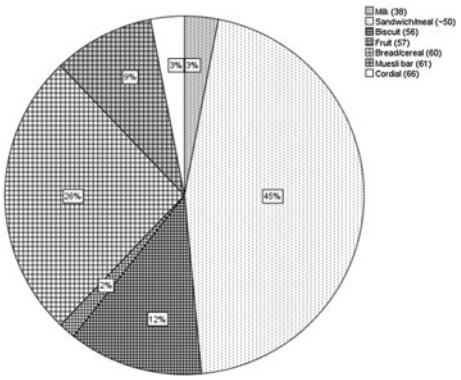



**Fig. 1** Follow-up carbohydrate—foods ingested and duration of action. Numbers in *brackets* in legend (x) denote average GI. *Slice labels* denote percent respondents ingesting specific food. *Dotted slices* denote long-acting carbohydrate. *Cross-hatched slices* denote medium-acting carbohydrate with GI <62

## DISCUSSION

Insulin-treated individuals in the target population are routinely taught to ingest follow-up food post-hypoglycaemia; therefore, it might be presumed they may be reluctant to admit they do not carry this out. In view of this, the data collection method considered optimal for this study was an anonymous self-administered questionnaire. This mode has been shown to decrease biased responses and result in more accurate and less 'socially desirable' responses to sensitive health-related questions than information obtained by interview [32]. A negative aspect of self-administered questionnaires is a possible decrease in reliability for open and more complex questions [33], but this was not demonstrated in this study. Advanced notification ahead of self-administration of a questionnaire has been shown to raise response rates and credibility without affecting questionnaire response type [33], and the initial contact by diabetes educators with

potential participants may partly account for the relatively high response rate.

Potentially many factors influence repeat hypoglycaemia [23]. We have investigated one of these (follow-up food) and sought to control for the other factor (method of insulin administration) that showed a significant association within the specified timeframe. Perhaps surprisingly, lack of symptoms of hypoglycaemia was not a modifier, possibly a function of the inclusion of individuals with insulin-treated type 2 diabetes and the associated lower rate of compromised counterregulation [34].

A limitation of this study was the inability to differentiate between type 1 and insulin-treated type 2 diabetes. It was considered that self-reported data on this may be inaccurate. Similarly, we collected no data on alcohol consumption, a modifier of hypoglycaemia, as this requires strategies to obtain accurate information outside the scope of this study [35].

Hierarchical binary logistic regression was the statistical test of choice as it assesses the likelihood of an event occurring given a set of conditions and does not require the statistical presumption of normality, which was not fulfilled in this data as all variables were categorical. Although only 10 participants reported repeat hypoglycaemia, the sample size (122) was considered adequate according to the rule of thumb $N - k - 1 \geq 50$ ($N =$ sample size, $k =$ number of predictor variables) [36]. The questionnaire item yes/no to experiencing repeat hypoglycaemia was used as the outcome variable, but only exhibited moderate test–retest reliability. It did, however, show excellent correlation with the separate questionnaire item on frequency of repeat hypoglycaemia, which exhibited high test–retest reliability, and was therefore taken as robust data.

The high reported rate (40.2%) of omission of follow-up food in this study is consistent with two other comparable studies [17, 19]. The use of medium-acting foods for follow-up is consistent with some recommendations [9, 13, 14], but notably, in this study, the majority of respondents selecting medium-acting follow-up foods tended towards those that were slower-acting in this category and this may account for the lack of association of duration of action of carbohydrate with incidence of repeat hypoglycaemia.

The relative percentages of reported repeat hypoglycaemia and omission of follow-up longer-acting carbohydrate PPHE suggest many individuals do omit follow-up food with impunity. The situation is rather complex, with some guidelines recommending routine consumption of follow-up food [7, 9, 12] and others stating follow-up food *may* be required [10, 13, 14]. CSII treatment is cited as one instance where follow-up food may be unnecessary as short-term insulin status is more controllable [14]; however, in this study omission of follow-up food PPHE did not significantly increase the likelihood of repeat hypoglycaemia irrespective of method of insulin administration.

## CONCLUSION

The results of this study support guidelines recommending judicious, rather than routine use of follow-up longer-acting carbohydrate PPHE.

## ACKNOWLEDGMENTS

The authors wish to thank all participants. Thanks also to Angela Sun, BeeChoo Lim, Anne Perry, and A.G. Tan for their help during

the study. Sally Vindedzis is the guarantor for this article, and takes responsibility for the integrity of the work as a whole. No funding or sponsorship was received for this study or publication of this article.

***Conflict of interest.*** Sally Vindedzis, Beryl Marsh, Jill Sherriff, Satvinder Dhaliwal, and Kim Stanton declare no conflicts of interest.

***Compliance with Ethics Guidelines.*** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Study information was given and consent presumed by return of questionnaire.



## REFERENCES

1. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care. 2003;26:1902–12.
2. Donnelly LA, Morris AD, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. Diabet Med. 2005;22:749–55.
3. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007;50:1140–7.
4. Cryer PE. Elimination of hypoglycemia from the lives of people affected by diabetes. Diabetes. 2011;60:24–7.
5. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. Patient Education Couns. 2007;68:10–5.
6. Leiter L, Yale J, Chiasson J, Harris S, Kleinstiver P, Sauriol L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. Can J Diab. 2005;29:186–92.
7. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care. 2013;36(Suppl 1):S11–66.
8. Canadian Diabetes Association [Homepage on the Internet]. Hypoglycemia. Canada: Canadian Diabetes Association. Available at: http://www.diabetes.ca/. Accessed 23 Jan 2013.
9. Diabetes Australia. [Homepage on the Internet]. Hypoglycemia. Canberra: Diabetes Australia. Available at: http://www.diabetesaustralia.com.au/. Accessed 16 Jan 2013.
10. Diabetes Education Study Group of The European Association for the Study of Diabetes [Homepage on the Internet]. Teaching letter 2, hypoglycemia. Available at: http://www.desg.org/. Accessed Jan 23 2013.
11. Asian-Pacific Type 2 Diabetes Policy Group. [Homepage on the Internet]. Type 2 diabetes practical targets and treatments. International Diabetes Federation. Available at: http://www.idf.org/idf-wpr-type-2-diabetes-pratical-targets-and-treatments. Accessed Jan 23 2013.
12. Singapore Diabetes Society [Homepage on the Internet]. Diabetes and hypoglycemia. Singapore: Diabetic Society of Singapore. Available at: http://www.diabetes.org.sg/. Accessed 23 Jan 2013.
13. Diabetes UK [Homepage on the Internet]. Treatment of hypoglycaemia. London: Diabetes UK. Available at: http://www.diabetes.org.uk/. Accessed Jan 23 2013.
14. National Health and Medical Research Council. National Evidence-Based Clinical Care Guidelines for Type 1 Diabetes for Children, Adolescents and Adults 2011. Department of Health and Aging. Available at: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp102.pdf. Accessed 13 Dec 2012.
15. Brand-Miller J, McMillan-Price J, Steinbeck K, Caterson I. Carbohydrates—the good, the bad and the whole grain. Asia Pac J Clin Nutr. 2008;17(Suppl 1):16–9.

16. Chlup R, Peterson K, Zapletalova J, Kudlova P, Seckar P. Extended prandial glycemic profiles of foods as assessed using continuous glucose monitoring enhance the power of the 120-minute glycemic index. J Diabetes Sci Technol. 2010;4:615–24.

17. Sommerfield AJ, Ewing FME, Strachan MWJ, Deary IJ, Aitken G, Frier BM. Self-treatment of mild symptomatic hypoglycaemia by people with insulin-treated diabetes. Diabet Med. 2003;20:686–7.

18. Sumner J, Baber C, Williams V. What do patients with type 1 diabetes know about hypoglycaemia? Pract Diabetes Int. 2000;17:187–90.

19. Vindedzis SA, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Food selection for treatment of hypoglycaemia in insulin-treated diabetes: what happens in real life? Practical Diabetes. 2012;29:271–4.

20. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2009;94:709–28.

21. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia. 2007;50:2553–61.

22. Roberts K, Smith A. Outcome of diabetic patients treated in the prehospital arena after a hypoglycaemic episode, and an exploration of treat and release protocols: a review of the literature. Emerg Med J. 2003;20:274–6.

23. Amiel S. Hypoglycemia: from the laboratory to the clinic. Diabetes Care. 2009;32:1364–71.

24. Kinsley BT, Weinger K, Bajaj M, et al. Blood glucose awareness training and epinephrine responses to hypoglycemia during intensive treatment in type 1 diabetes. Diabetes Care. 1999;22:1022–8.

25. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab. 2009;94:729–40.

26. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008;25:765–74.

27. Ley P, Florio T. The use of readability formulas in health care. Psychol Health Med. 1996;1:7–28.

28. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. Diabetes Care. 2008;31:2281–3.

29. Statistics database. Gumna University Website. Available at: http://aoki2.si.gunma-u.ac.jp/exact/exact.html. Accessed 16 Jan 2013.

30. Saw SM, Ng TP. The design and assessment of questionnaires in clinical research. Singapore Med J. 2001;42:131–5.

31. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care. 2003;15:261–6.

32. Okamoto K, Ohsuka K, Shiraishi T, Hukazawa E, Wakasugi S, Furuta K. Comparability of epidemiological information between self- and interviewer-administered questionnaires. J Clin Epidemiol. 2002;55:505–11.

33. de Leeuw E. To mix or not to mix data collection modes in surveys. J Off Stat. 2005;21:233–55.

34. de Galan BE, Schouwenberg BJ, Tack CJ, Smits P. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. Neth J Med. 2006;64:269–79.

35. Beck F, Peretti-Watel P. The impact of data collection methodology on the reporting of illicit drug use by adolescents. Population-E. 2002;57:571–92.

36. Peng CY, So TS, Stage FK, St. John EP. The use and interpretation of logistic regression in higher education journals: 1988–1999. Res High Education. 2002;43:259–93.

# CHAPTER 7: PATIENT KNOWLEDGE OF ALCOHOL AND HYPOGLYCAEMIA IN TYPE 1 DIABETES

## 7.1 Expanded significance of study

### *7.1.1 Alcohol intake in people with type 1 diabetes*

Consumption of alcohol is the norm in Australia and the results from the Australian 2011-2012 National Health Survey showed that in 2011-12, 82.4% of Australians ≥ 18 y had consumed alcohol in the past year with 19.5% of adults consuming more than two standard drinks per day on average, thus exceeding the drink-safe guidelines (Australian Bureau of Statistics, 2012).

Alcohol consumption in specific groups is difficult to assess as questions about 'typical' quantities of alcohol consumed tend to lead to underestimates (Stockwell et al., 2004), and it is well documented that survey questions on alcohol intake are 'sensitive' questions which are answered with less accuracy than other question types (Beck & Peretti-Watel, 2002; Tourangeau & Yan, 2007). This may be the reason there is a paucity of current information on alcohol intake by those with type 1 diabetes in Australia.

A 1991 US study of alcohol consumption in adolescents with type 1 diabetes showed approximately 50% had tried alcohol and 25% reported ongoing use, less than for the general population (Glasgow et al., 1991). A more recent study from Chile, also in adolescents, showed 30.1% of those surveyed had consumed alcohol compared to 39.2% of those without diabetes (Martínez-Aguayo et al., 2007) although conversely an Italian study showed alcohol consumption by 56% of those with type 1 diabetes compared to 51% of controls (Scaramuzza et al., 2010). Overall, from the available information consumption of alcohol may be less in those with type 1 diabetes than in equivalent populations without diabetes.

### *7.1.2 Associated risk*

**Health risks**

Although the intake of alcohol by those with type 1 diabetes may be less than that in the general population, the risk to health is greatly increased and includes reduced diabetes self-care, ketoacidosis and hypoglycaemia (Barnard, Sinclair, Lawton, Young, & Holt, 2012). Of these, the most common, associated with the greatest acute

risk, is hypoglycaemia (Choudhary & Amiel, 2011). In a study in adults with type 1 diabetes using CGMS, intake of alcohol at dinnertime has been associated with increased hypoglycaemic events the following day (Turner et al., 2001) and in a larger study using CGMS Richardson *et al* reported similar results and also showed decreased hypoglycaemic awareness (Richardson et al., 2005). Pedersen-Bjergaard *et al* in an analysis of 141 people with type 1 diabetes hospitalized with severe hypoglycaemia reported that 17% of these were associated with alcohol which was consistent with two other studies (Pedersen-Bjergaard et al., 2005). Cheyne *et al,* in a hyperinsulinaemic glucose clamp study, showed that the combination of alcohol and hypoglycaemia caused a marked decrease in cognitive function, and this posed a special risk to driving skills (Cheyne et al., 2004), which is especially concerning, as accidents while driving are often preceded by frequent mild symptomatic hypoglycemia (Cox et al., 2003).

**Alcohol-related mortality**

In 2003, alcohol consumption accounted for 3.3% of disease and injury in Australia and 13 per cent of deaths among Australians of 14 – 17 y (National Health and Medical Research Council, 2008) and worldwide, alcohol is reported to have caused 3.7% of all deaths (National Health and Medical Research Council, 2008). The figures for alcohol-associated mortality in those with type 1 diabetes in Australia are not available, however in Finland, where alcohol-related deaths are on a par with the world average (3.7%) (Official Statistics of Finland (OSF), 2012), a nationwide population-based cohort study examining trends in mortality among patients with type 1 diabetes showed that alcohol and drug-related mortality accounted for 39% of the deaths during the first 20 years of diabetes, 10 times that of the general population (Harjutsalo et al., 2011).

### *7.1.3 Education, hypoglycaemia and alcohol*

Richardson *et al* asserted that there is a lack of consistent advice given to those with type 1 diabetes concerning alcohol and hypoglycaemia (Richardson et al., 2005). Scaramuzza *et al* recommend educational intervention (Scaramuzza et al., 2010), Jaser *et al* recommend development and testing of standardized prevention programs (Jaser, Yates, Dumser, & Whittemore, 2011) and Engler *et al* in a review of alcohol use by diabetes patients strongly recommend assessment of alcohol intake and

intervention (Engler, Ramsey, & Smith, 2013). Cheyne *et al* state that patients with type 1 diabetes should be educated about hypoglycaemia and driving (Cheyne et al., 2004). The ADA, in a review of driving and diabetes recommend patients should be advised to self-monitor their glucose levels more frequently for several hours after moderate alcohol intake because of the risk of hypoglycaemia (American Diabetes Association, 2013a) and the NHMRC highlighted the need for education in this area (Craig et al., 2011).

How much, then, do people with type 1 diabetes know about alcohol and hypoglycaemia? Ahmed *et al* in a study of 65,996 people with diabetes showed that alcohol intake is inversely associated with adherence to diabetes self-care behaviours but did not identify the extent of knowledge of alcohol and hypoglycaemia (Ahmed, Karter, Warton, Doan, & Weisner, 2008), as did Thomas *et al* in a similar study on 3,930 veterans (Thomas et al., 2012). Ramchandani *et al* in a study on factors affecting glycaemic control in 42 college students with type 1 diabetes in the USA reported that of those surveyed, 35.7% drank alcohol once or twice a week with 33.3% drinking 4 - 6 drinks in an evening. Alcohol was rated as 6/16 of factors identified by students as causing deterioration in diabetes control but hypoglycaemia was not reported in association with this and students' knowledge of alcohol and hypoglycaemia not reported (Ramchandani et al., 2000). Engler *et al* in a recent publication, commented that although brief interventions can change alcohol-related behaviour in those with diabetes, there is only one study measuring the efficacy of this and this is in type 2 diabetes (Engler et al., 2013; Fleming, Brown, & Brown, 2004). And finally, looking at online education, Jones *et al* in a study investigating social networking and understanding of alcohol-associated risk for people with type 1 diabetes, identified 10 web sites with information/opinion/advice on alcohol and diabetes. No professional health information sites were identified and inaccurate information was common in the existing sites. No assessment or self-assessment of knowledge on these sites was reported (Jones, Sinclair, Holt, & Barnard, 2013). The only study reporting knowledge of hypoglycaemia and alcohol is a qualitative study by Miller-Hagen *et al* investigating perception and management of alcohol by college students in the USA, 11 of whom had type 1 diabetes. This study is reported as an unquantified narrative, and describes how some of the sample with type 1 diabetes developed knowledge/strategies. It recommends further research on how

education can improve drinking management in students with diabetes (Miller-Hagan & Janas, 2002).

There is, therefore, a dearth of information on assessment of current knowledge of alcohol and hypoglycaemia by those with type 1 diabetes. The following paper investigates this topic and compares assessed knowledge with current information provided on this topic by a variety of national diabetes associations.

### *7.1.4 Hypoglycaemia and alcohol - recommendations*

Recommendations for avoidance of alcohol-induced hypoglycaemia are presented in Appendix 4 (with thanks to Royal Perth Hospital Diabetes Clinic).

## 7.2 Paper 5

Vindedzis SA, Marsh B, Sherriff JL, Stanton KG. Alcohol and type 1 diabetes: Patient knowledge of alcohol-induced sustained hypoglycaemia. Diabetes Res Clin Pract. 2013 Nov;102(2):e19-20. doi: 10.1016/j.diabres.2013.08.010. Epub 2013 Sep 26. No abstract available

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

## Letter to the Editor

### Alcohol and type 1 diabetes: Patient knowledge of alcohol-induced sustained hypoglycaemia

In type 1 diabetes alcohol can significantly reduce blood glucose 6–8 h post-consumption [1] with increased risk lasting 24 h [2]. Risk is dose-related and can be reduced with judicious carbohydrate consumption and long-acting insulin reduction where necessary [1]. There are, however, few studies assessing, firstly, easily available information and secondly, patients' knowledge in this area. We accessed and assessed National Diabetes Association guidelines, as typical information retrievable from an Internet search for 'alcohol and type 1 diabetes' and also assessed knowledge of alcohol and hypoglycaemia in adults with type 1 diabetes by questionnaire.

Questionnaire items assessed knowledge of the hypoglycaemic effect of alcohol, duration of hypoglycaemia post-consumption and number of standard drinks perceived to cause hypoglycaemia. Standard drink quantity was depicted for comparison. Risk reduction (dietary or insulin modification) was not addressed to minimize prejudicing assessment of knowledge of hypoglycaemic effect *per se*. Questionnaire readability was 7.3 on Flesch–Kincaid Grade-Level score, thus understandable by a seventh grader. It was distributed to 50 consecutive adults with type 1 diabetes ≥18 y attending routine outpatient clinics; was anonymous, and consent was presumed by return to a designated sealed box.

## 1. Results

Information on alcohol and hypoglycaemia provided by 6 National Diabetes Associations [3–8] is shown in Table 1. All provided general information on alcohol and hypoglycaemia, eating with, and snacking after alcohol, and sustained hypoglycaemic effect, but the possible duration of hypoglycaemia varied from not specified to 16–24 h. Only 2 guidelines provided information on reduction of long-acting insulin. Questionnaires were returned by 37 (74%) participants, exceeding the acceptable return rate of 65% for self-completed questionnaires [9]. Diabetes duration was 16.5 ± 11.9 y and treatment was by basal-bolus (83.8%)/CSII(16.2%). The hypoglycaemic effect of alcohol was correctly identified by 88.2% of responders, but only 32.4% postulated duration of 4 + h post-consumption. Standard drink quantity perceived to lower blood glucose level was 1–3 (50%) and 4+ (41.2%). Study limitations were small sample size (50) and the notorious difficulty of obtaining accurate information on alcohol consumption. We aimed to maximize accuracy by the proven strategy of anonymity [10] and assessment of knowledge rather than behaviour.

**Table 1 – Alcohol and insulin: information provided by guidelines.**

| National associations | Information provided | | | | | |
|---|---|---|---|---|---|---|
| | Potential hypoglycaemic effect | Duration of hypoglycaemia • y/n • time | Food with alcohol | Snack later | Possible insulin reduction | Recommends further information |
| American Diabetes Association | y | • y • up to 24 h | y | y | n | y |
| Canadian Diabetes Association | y | • y • up to 24 h | y | y | n | y |
| Diabetes Australia | y | • y • up to 24 h | y | y | y | y |
| Diabetes New Zealand | y | • n • n.s. | y | n | y | y |
| Diabetic Society Singapore | y | • y • n.s. | y | y | n | y |
| Diabetes UK | y | • y • up to 16 h | y | y | n | y |

## 2. Conclusions

Knowledge of alcohol and hypoglycaemia was acceptable in this group, except in the important area of duration of alcohol-induced hypoglycaemia. This is congruent with accessed guidelines and may reflect an identified lack of consistency in information given to patients regarding alcohol-induced hypoglycaemia [2]. Additionally not all guidelines provided information on reduction of long-acting insulin, an important strategy to minimize hypoglycaemic risk.

## Funding

None.

## Conflict of interest

None.

REFERENCES

[1] Choudhary P, Amiel SA. Hypoglycaemia: current management and controversies. Postgrad Med J 2011;87:298–306.
[2] Richardson T, Weiss M, Thomas P, Kerr D. Day after the night before: influence of evening alcohol on risk of hypoglycemia in patients with type 1 diabetes. Diabetes Care 2005;28:1801–2.
[3] American Diabetes Association [Homepage on the Internet]. Alcohol. Virginia: American Diabetes Association; 2013 Available at:http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/alcohol.html [accessed 30.06.13].
[4] Canadian Diabetes Association [Homepage on the Internet]. Alcohol and diabetes. Canada: Canadian Diabetes Association; 2013 Available at:http://www.diabetes.ca/for-professionals/resources/nutrition/alcohol/ [accessed 30.06.13].
[5] Diabetes Australia [Homepage on the Internet]. Alcohol and diabetes. Canberra: Diabetes Australia; 2013 Available at:http://www.diabetesaustralia.com.au/Living-with-Diabetes/Eating-Well/Alcohol/ [accessed 30.06.13].
[6] Diabetes New Zealand [Homepage on the Internet]. Hypoglycaemia. New Zealand: Diabetes New Zealand; 2013 Available at:http://www.diabetes.org.nz/living_with_diabetes/type_1 diabetes/low_blood_glucose_hypo [accessed 29.06.13].
[7] Singapore Diabetic Association [Homepage on the Internet]. Hypoglycaemia. Singapore: Singapore Diabetic Association; 2013 Available at:http://www.diabetes.org.sg/resources/0111-hypo.pdf [accessed 30.06.13].
[8] Diabetes UK [Homepage on the Internet]. Alcohol Diabetes, Hypoglycaemia. UK: Diabetes UK; 2013 Available at:http://www.diabetes.org.uk/Guide-to-diabetes/Healthy_lifestyle/Alcohol_and_diabetes/ [accessed 30.06.13].
[9] Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care 2003;15:261–6.
[10] Beck F, Peretti-Watel P. The impact of data collection methodology on the reporting of illicit drug use by adolescents. Population-E 2002;57:571–92.

Sally A. Vindedzis*
Beryl Marsh
*Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, WA 6001, Australia*

Jill L. Sherriff

*School of Public Health, Curtin Health Innovation Research Institute, Curtin University, Bentley, WA 6102, Australia*Kim G. Stanton

*Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, WA 6001, Australia*

**Corresponding author at*: Department of Endocrinology and Diabetes, Royal Perth Hospital, GPO Box X2213, Perth, WA 6001, Australia. Tel.: +61 08 64775213; fax: +61 08 64775238
E-mail addresses: sally.vindedzis@postgrad.curtin.edu.au salvindedzis@bigpond.com (S.A. Vindedzis)

1 August 2013
Received in revised form 8 August 2013
Accepted 12 August 2013

0168-8227/$ – see front matter

http://dx.doi.org/10.1016/j.diabres.2013.08.010

# CHAPTER 8 HYPOGLYCAEMIA IN INPATIENTS WITH INSULIN-REQUIRING DIABETES ON NASOGASTRIC FEEDING

## 8.1 Expanded significance of studies

Those with diabetes have a greater frequency of hospitalization and longer length of hospital stay than people without diabetes (Moghissi et al., 2009). Prevalence of hypoglycaemia is demonstrably higher in general inpatients than in free-living individuals, with 3 - 29% of inpatients suffering at least one hypoglycaemic event during their hospital admission (Umpierrez et al., 2009; Umpierrez et al., 2011). Eiland *et al* have asserted that illness gives variable insulin sensitivity which increases risk of hypoglycaemia in inpatients with diabetes (Eiland et al., 2014). Other specific identified risk factors for inpatient hypoglycaemia in those with diabetes are mismatch of insulin and nutrition (Elliott et al., 2012; Kerry et al., 2013; Maynard et al., 2008), unexpected nutritional interruption (Maynard et al., 2008), prior inpatient hypoglycaemia (Maynard et al., 2008; Varghese et al., 2007), inadequate monitoring of trends in BSL (Elliott et al., 2012) and poor adherence to practice guidelines and documentation (Anthony, 2007; Maynard et al., 2008).

Arguably, those on established nasogastric feeding in the general ward are a vulnerable subgroup of inpatients with an enhanced risk from all of these factors. They are on a relatively inflexible nutrition delivery schedule to which it may be difficult to match an appropriate insulin regimen within staff time constraints (Ng et al., 2009) and interruption of feeds for medical procedures and tests may further exacerbate hypoglycaemic risk (Maynard et al., 2008). Decreased nutritional intake is an indicator for the introduction of nasogastric feeding (Lloyd & Powell-Tuck, 2004) and also often a trigger for an initial hypoglycaemic event and thus a risk factor for subsequent hypoglycaemic episodes (Maynard et al., 2008). Studies in critical care have shown that frequent measurement of blood glucose levels is essential to attain good glycaemic control and chart trends in BGL (Harper, 2007), yet the recommended frequency of blood glucose monitoring in the general ward for those on nasogastric feeding is 4 - 6 hourly testing (American Diabetes Association, 2014b), and finally there is evidence that, at least in some hospitals, there is less than acceptable adherence to practice guidelines and documentation of nasogastric feeding practice (Dobson & Scott, 2007; Persenius, Hall-Lord, Baath, & Larsson, 2008).

Aside from critical care and short-term post-operative care, nasogastric feeding is most often used to deliver nutrition to patients who have an altered conscious state or impaired swallowing ability (Lloyd & Powell-Tuck, 2004). There is little information on the prevalence of hypoglycaemia in inpatients with diabetes with altered conscious state, however, a parallel could perhaps be drawn with free-living individuals with hypoglycaemic unawareness, who are similarly unable to respond to symptoms of impending hypoglycaemia and have been shown to have a six-fold higher frequency of severe hypoglycaemia than those with normal awareness of hypoglycaemia (Geddes et al., 2008).

Turchin et al have shown that in patients in the general ward, each additional day with hypoglycaemia is associated with an increase of 85.3% in the odds of death (Turchin et al., 2009). It could be surmised that inpatients on nasogastric feeding may be at even greater risk. Interventions to decrease hyperglycaemia in people on nasogastric feeding are well researched (Alish et al., 2010; Ceriello et al., 2009; Elia et al., 2005; Vanschoonbeek et al., 2009), but this is not the case with hypoglycaemia. The following papers add information to this crucial yet under-researched area.

## 8.2 Paper 6

Vindedzis SA, Marsh B, Sherriff JL, Stanton KG. Hypoglycaemia in inpatients with diabetes on nasogastric feeding. Practical Diabetes. 2014; 31(1):29-31. DOI:10.1002/pdi.1824.

# Hypoglycaemia in inpatients with diabetes on nasogastric feeding

**Sally A Vindedzis**[1]
MSc, P/G Dip Nutrition and Dietetics, Dietitian – Diabetes

**Beryl Marsh**[1]
RN, Clinical Nurse Specialist – Diabetes

**Jill L Sherriff**[2]
PhD, MSc, P/G Dip Nutrition and Dietetics, Associate Professor (Nutrition and Dietetics)

**Kim G Stanton**[1]
MB, BS, FRACP, Endocrinologist

[1]Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, Western Australia
[2]School of Public Health, Curtin Health Innovation Research Institute, Curtin University, Bentley, Western Australia

**Correspondence to:**
Sally Vindedzis, Department of Endocrinology and Diabetes, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia 6001; email: sally.vindedzis@postgrad.curtin.edu.au

**Received:** 16 August 2013
**Accepted in revised form:** 11 October 2013

## Abstract

Hypoglycaemia in patients with diabetes on nasogastric feeding is both potentially damaging and under-researched. We retrospectively reviewed 50 such inpatients to determine factors influencing hypoglycaemia. Our results showed 10.9% patient-days with ≥1 hypoglycaemic episode and 3.5% total blood glucose values <3.5mmol/L. There was an association between sulphonylurea treatment and increased and extended hypoglycaemia. Reducing diabetes treatment post-hypoglycaemia was associated with reduced subsequent hypoglycaemia but not increased hyperglycaemia.

This study supports optimal blood glucose monitoring, insulin treatment and judicious medication reduction post-hypoglycaemia. 
*Practical Diabetes* 2014; 31(1): 29–31

## Key words

hypoglycaemia; nasogastric feeding; diabetes; retrospective

## Introduction

Hypoglycaemia is a common complication of treatment with insulin and sulphonylurea agents.[1] Swift identification and management of mild hypoglycaemic episodes prevent progression to severe hypoglycaemia[2] which has been associated with increased morbidity,[3,4] as has increased duration of hypoglycaemia.[5,6] The majority of inpatients with diabetes on nasogastric feeding have altered conscious state and are unable to respond to symptoms of hypoglycaemia, making them reliant on often busy staff, to identify and treat their hypoglycaemia. In this context, even with regular blood glucose monitoring (BGM) there may be considerable progression of a hypoglycaemic episode prior to its identification.[5,6] There is extensive literature on diabetes specific formula feeds, mainly with regard to post-feed hyperglycaemia,[7] but less quantifying hypoglycaemia.[8–10]

We carried out a retrospective case note review to determine the frequency and timing of hypoglycaemia in hospitalised patients with diabetes on established nasogastric feeding in a tertiary hospital.

## Methods

Subjects were 50 inpatients with diabetes (27 male, 23 female) fed entirely by nasogastric feeding for ≥3 days as per hospital protocol (Table 1). Patients on insulin infusions or in ICU were excluded. Subjects were consecutively flagged by the treating dietitian. Data were collected from medical notes, BGM records, and medication charts. Goals of treatment were blood glucose level (BGL) ≥4 and <10mmol/L. Initial treatment of hypoglycaemia was liquid carbohydrate as per hospital protocol. No identifying information was collected. The study was approved by the Human Ethics Research Committee (Curtin University, Western Australia) and as a tertiary hospital clinical audit.

### *Measures*

Hypoglycaemia was defined as BGL <3.5mmol/L, as a level having clinical relevance.[11,12] Severe hypoglycaemia is formally defined as 'an event requiring assistance of another person to actively administer carbohydrate';[13] but as this was applicable to all events in this study, we arbitrarily defined severe hypoglycaemia as BGL <2.0mmol/L, and extended hypoglycaemia as duration >2 hours or repeat episode within 2 hours. There is no standardised reporting method for frequency of hypoglycaemia[14] so we have reported it both as percentage of patient-days with ≥1 hypoglycaemic episode (PPD) and percentage of total blood glucose values <3.5mmol/L (PTG), to allow for variable feed duration and consistent with two other studies.[8,9]

| BGM (h) | Insulin | Feed (h) |
|---|---|---|
| 06.00 | 6.30 (SA) | 6.45<br>09.00 |
| 11.30 | 12.00 (SA) | 12.15<br>14.30 |
| 16.30 | 17.00 (SA) | 17.15<br>20.00 |
| 21.00 | 21.30 (LA) | |

BGM: blood glucose monitoring; SA: short acting; LA: long acting.

**Table 1.** Bolus nasogastric feeding – timing

| Variable | Result |
|---|---|
| **Gender:** M/F | 27/23 |
| **Age:** years | 67.8±13.9 |
| **NG duration:** days[range] | 13.0±9.2[3–41] |
| **NG content (CHO):** ≤40%/>40% | 19/31 |
| **NG administration** (bolus/continuous) | 49/1 |
| **Treatment:** SCII/SU | 42/8 |
| SCII: | |
| Basal bolus | 28 |
| Twice daily | 7 |
| Long acting | 1 |
| Correctional | 6 |

NG: nasogastric feed; CHO: carbohydrate; SCII: subcutaneous insulin injection; SU: sulphonylurea.

**Table 2.** Patient characteristics (n=50)

| Variable | Percent | P-value |
|---|---|---|
| **PPD** | 10.9 | |
| **PTG** | 3.5 | |
| SCII | 3.1 | 0.001 |
| SU | 5.8 | |
| **PTG <2h** | 0.72 | |
| SCII | 0.63 | 0.179 |
| SU | 1.13 | |
| **PTG >2h** | 0.23 | |
| SCII | 0.14 | 0.038 |
| SU | 0.65 | |

PPD: percent of patient days with 1+ hypoglycaemic event; PTG: percent of total blood glucose level <3.5mmol/L; SCII: subcutaneous insulin injection; SU: sulphonylurea; PTG <2, percent of total blood glucose level <2.0 mmol/L (severe hypoglycaemia); PTG >2h, percent of total blood glucose level >2h (extended hypoglycaemia).

**Table 3.** Frequency of hypoglycaemia

Descriptive statistics were used for subject demographics, $\chi^2$ test to compare categorical variables and proportions, Shapiro-Wilk test to determine normality, Spearman rank-order correlation to determine strength of association between non-normally distributed continuous variables, and log-rank test to compare time to event data. Analysis was performed using IBM SPSS Statistics, v21, IBM, NY, USA, and GraphPad Prism 6, GraphPad Software Inc, USA.

## Results

Subject characteristics are shown in Table 2. Frequency of hypoglycaemia was: PPD 10.9%, PTG 3.5%, and this was not statistically associated with gender, age, or feed carbohydrate content (p>0.05). Increased total hypoglycaemia was associated with increased duration of nasogastric feeding (p=0.016).

Hypoglycaemia was prevalent before the next medication dose and rare between medication administration and feed bolus: 34.8% and 4.3% of hypoglycaemic patients respectively.

It was not possible to assess the impact of withheld feeds from available documentation. Frequencies of hypoglycaemia, severe hypoglycaemia and extended hypoglycaemia are shown in Table 3. Sulphonylurea treatment (SU) was associated with increased incidence of hypoglycaemia (p<0.001) and extended hypoglycaemia (p=0.038). All hypoglycaemic patients had increased BGM post-hypoglycaemia (6.1±1.6/day) and based on this 78% had medication decreased in response to hypoglycaemia. Survival analysis showed a significantly longer time to a subsequent hypoglycaemic episode between patients whose treatment was reduced in response to hypoglycaemia and those whose treatment remained unchanged (p=0.008) (see Figure 1). There was no association with subsequent hyperglycaemia (p=0.33).

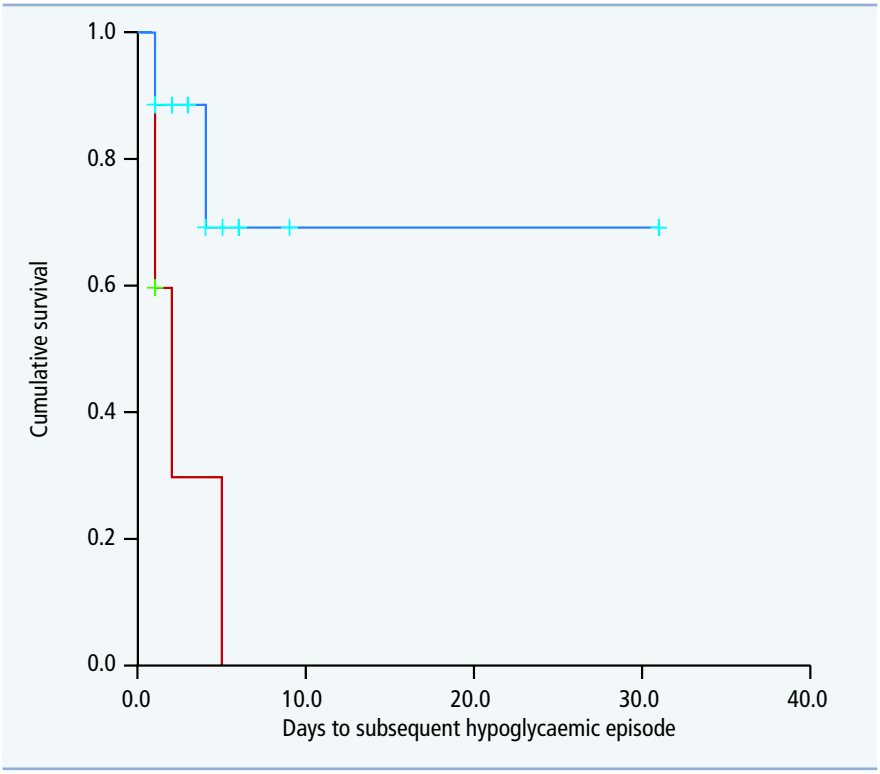



**Figure 1.** Kaplan-Meier survival curves for patients with treatment changed post-hypoglycaemia (blue line) and unchanged (red line); + denotes censored data

## Discussion

Hypoglycaemic episodes were not uncommon in these patients. Comparison with other nasogastric studies is difficult due to lack of quantification of hypoglycaemic events.[15] Rates of hypoglycaemia in this study (PPD 10.9%; PTG 3.5%) were higher than the two comparable studies (PPD – not reported[8] and 1.1–1.3%[9]; PTG – 1.4–5.4[8] and 1.1–1.3[9]), especially as both defined hypoglycaemia as <3.9mmol/L; the higher cut-off point would be expected to identify more hypoglycaemic episodes.[16] Frequency of BGM also varied from 6.1±1.6/day (this study) compared to 4/day,[8] and 4/day+ (maximum 6/day).[9] However, it has been shown that increased BGM can increase documented inpatient hypoglycaemia and severe hypoglycaemia.[17] Additionally, one study[9] included subjects on dual oral and enteral feeding which may tend to decrease frequency of hypoglycaemia.[6,18]

Severe and extended hypoglycaemia are not quantified in the literature on nasogastric feeding but the high frequency of BGM in our study may have increased documentation of these.[17] Hypoglycaemia and extended hypoglycaemia were statistically associated with SU, consistent with other reports documenting increased frequency of hypoglycaemia in SU treated individuals, especially those >65 years of age.[19,20]

As this was a retrospective observational study, duration of nasogastric feeding varied. We therefore used Kaplan-Meier survival curves for time to event analysis of the effect of reduction in medication post-hypoglycaemia on a subsequent hypoglycaemic episode. This meant that censored data which arose from cessation of nasogastric feeding before a subsequent hypoglycaemic event was observed, were taken into account. As a consequence, we have shown a significantly increased time to a subsequent hypoglycaemic event in those whose medication was reduced. There was no association with subsequent hyperglycaemia.

### Key points

- This study showed hypoglycaemia was prevalent in inpatients with diabetes on established nasogastric feeding in the general ward, with increased frequency associated with longer duration of feeding but not with feed carbohydrate content
- There was an association between sulphonylurea treatment and increased and extended hypoglycaemia. Reducing diabetes treatment post-hypoglycaemia was associated with reduced subsequent hypoglycaemia but not increased hyperglycaemia
- This study supports insulin treatment, optimal blood glucose monitoring, and judicious medication reduction post-hypoglycaemia

### *Limitations of study*

Neither type nor duration of diabetes or interruption of feeds are quantified as they were not consistently recorded in patient notes.

## Conclusions

This study highlights the prevalence of hypoglycaemia in patients on nasogastric feeding. It supports optimal blood glucose monitoring and treatment with insulin rather than sulphonylureas, and highlights the need for appropriate medication reduction based on blood glucose monitoring results.

## Declaration of interests

There are no conflicts of interest declared. Funding: none.

## References

1. Wexler DJ, *et al.* Prevalence of hyper- and hypoglycemia among inpatients with diabetes. *Diabetes Care* 2007;30(2):367–9.
2. Moghissi ES, *et al.* American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;32(6):1119–31.
3. Cryer PE. Severe hypoglycemia predicts mortality in diabetes. *Diabetes Care* 2012;35(9):1814–6.
4. Turchin A, *et al.* Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care* 2009;32(7):1153–7.
5. Ng JM, *et al.* Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care* 2009;32(12):e151.
6. Braithwaite SS, *et al.* Hospital hypoglycemia: not only treatment but also prevention. *Endocr Pract* 2004;10(Suppl 2):89–99.
7. Elia M, *et al.* Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes. *Diabetes Care* 2005;28(9):2267–79.
8. Hsia E, *et al.* Comparison of 70/30 biphasic insulin with glargine/lispro regimen in non-critically ill diabetic patients on continuous enteral nutrition therapy. *Nutr Clin Pract* 2011;26(6):714–7.
9. Korytkowski MT, *et al.* Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. *Diabetes Care* 2009;32(4):594–6.
10. Pohl M, *et al.* Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: stage II of a randomized, controlled multicenter trial. *J Parenteral Enteral Nutr* 2009;33(1):37–49.
11. Amiel SA, *et al.* Hypoglycaemia in type 2 diabetes. *Diabet Med* 2008;25(3):245–54.
12. Frier BM. Defining hypoglycaemia: what level has clinical relevance? *Diabetologia* 2009;52(1):31–4.
13. Cryer PE, *et al.* Evaluation and management of adult hypoglycemic disorders: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2009;94(3):709–28.
14. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: A report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005;28(5):1245–9.
15. Elia M, *et al.* Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. *Diabetes Care* 2005;28(9):2267–79.
16. Swinnen SG, *et al.* Changing the glucose cut-off values that define hypoglycaemia has a major effect on reported frequencies of hypoglycaemia. *Diabetologia* 2009;52(1):38–41.
17. Weinberg ME, *et al.* Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *J Diabetes Sci Technol* 2010;4(3):577–82.
18. Donnelly LA, *et al.* Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabet Med* 2005;22(6):749–55.
19. Breuer HW, Ptak P. Hypoglycemia – frequency, causes, induced costs. *Dtsch Med Wochenschr* 2012;137(19):988–92.
20. Deusenberry CM, *et al.* Hypoglycemia in hospitalized patients treated with sulfonylureas. *Pharmacotherapy* 2012;32(7):613–7.

## 8.4 Paper 7

Vindedzis SA, Sherriff JL, Stanton KG. Hypoglycemia in Insulin-Treated Adults on Established Nasogastric Feeding in the General Ward: A Systematic Review. Diabetes Educ. 2014. DOI: 10.1177/0145721714523510

## Hypoglycemia in Insulin-Treated Adults on Established Nasogastric Feeding in the General Ward: A Systematic Review


Sally A. Vindedzis, Jill L. Sherriff and Kim G. Stanton



*The Diabetes Educator* published online 13 February 2014
DOI: 10.1177/0145721714523510

The Diabetes Educator OnlineFirst, published on February 13, 2014 as doi:10.1177/0145721714523510



# Hypoglycemia in Insulin-Treated Adults on Established Nasogastric Feeding in the General Ward

## A Systematic Review


## Purpose

This study aimed to address 2 questions: First, what are the existing summary statistics of frequency of hypoglycemia in insulin-treated adults on established nasogastric feeding in the general ward? Second, to what extent does lack of homogeneity in defining, identifying, and reporting hypoglycemia affect these statistics?

## Methods

A systematic review of the literature documenting hypoglycemia in insulin-treated adults on nasogastric feeding for ≥ 3 days in the general ward was carried out. Data sources were PubMed, Embase, ProQuest, Cochrane, Directory of Open Access Journals, and PLoS. Search period was 1999 onward, postdating introduction of analog insulin.

## Results

Initially, 231 studies were identified, with 9 judged suitable for inclusion, according to inclusion/exclusion criteria. All included studies had as their primary objective the assessment of efficacy of insulin/feed regimens in the target population. Studies exhibited major heterogeneity. Definitions of hypoglycemia varied from < 60 mg/dL (3.3 mmol/L) to < 80 mg/dL (4.4 mmol/L), and 5 methods of reporting frequency of hypoglycemia were utilized, precluding pooled analysis. A descriptive synthesis


Sally A. Vindedzis, MSc

Jill L. Sherriff, PhD

Kim G. Stanton, MB

From the Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, Australia (Ms Vindedzis, Dr Stanton), and the School of Public Health, Curtin Health Innovation Research Institute, Curtin University, Bentley, Australia (Dr Sherriff).

Correspondence to Sally A. Vindedzis, MSc, P/G Dip Nutrition and Dietetics, Dietitian-Diabetes, Department of Endocrinology and Diabetes, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia, 6001, Australia (sally.vindedzis@postgrad.curtin.edu.au).

*Conflict of Interest:* The authors have declared no conflicts of interest.

DOI: 10.1177/0145721714523510

of results was generated with some comparable results presented on a modified forest plot, showing 2.1% to 10.2% of patients with a hypoglycemic event and 1.1% to 5.4% blood glucose level < 70 mg/dL (3.9 mmol/L).

## Conclusions

Hypoglycemia is not uncommon in this population, but further research is needed for quantification. Standardized documentation and reporting methods incorporating sample size and study duration, such as hypoglycemic events per patient-days, would facilitate interstudy comparisons, as would documentation of hypoglycemia at the 2 most commonly defined levels: < 63 mg/dL (3.5 mmol/L) and < 70 mg/dL (3.9 mmol/L).

Hypoglycemia is common among inpatients with diabetes,[1] with a reported incidence ranging from 7.7%[2] to 20%.[3,4] It has been shown to be significantly associated with both increased length of hospital stay and mortality.[2,3,5] Turchin et al have reported that each additional day with hypoglycemia is associated with an increase of 85.3% in the odds of inpatient death.[2] Curkendall et al showed similar results with an additional economic impact of higher hospital charges and increased discharge to a skilled nursing facility associated with documented hypoglycemia.[6]

Variation in definition and reporting of inpatient hypoglycemia affects both strength of association with adverse effects and interstudy comparisons. The NICE-SUGAR Study showed increased mortality (hazard ratio, 1.41) associated with a hypoglycemic level of 41 to 70 mg/dL (2.3-3.9 mmol/L). This increased (2.1) with a hypoglycemic level of ≤ 40 mg/dL (2.2 mmol/L).[7] Krinsley et al used different cutoff points (< 40, 40-54, and 55-69 mg/dL [2.2, 2.2-3.0, 3.1-3.9 mmol/L]) and showed increased relative risk of mortality of 3.55, 2.70, and 2.18, respectively.[8] A recent retrospective study by Sechterberger et al identified < 63 mg/dL (3.5 mmol/L) as a cutoff for detrimental low blood glucose level in critical care patients,[9] while Curkendall et al used different cutoff levels (70 mg/dL [3.9 mmol/L] and 50 mg/dL [2.8mmol/L]).[6]

In the critical care situation, intensive blood glucose monitoring is in place, allowing swift identification and treatment of hypoglycemic episodes,[10] but in the general ward, staffing and routine monitoring are reduced, and there is evidence that reduced staffing has a detrimental effect on resolution of hypoglycemic episodes.[10,11] Patients on established nasogastric feeding in a general ward situation are particularly vulnerable, often having altered conscious state, and are dependent on staff to identify and treat their hypoglycemia.

Despite numerous studies assessing the short-term glycemic effects of enteral feeding products[12-15] and similar longer-term assessments of insulin regimens[16,17] and formula feeds,[18-20] there are few studies directly quantifying hypoglycemia in those on nasogastric feeding outside the critical care unit. This systematic review therefore aimed to address 2 questions: First, what are the existing summary statistics of frequency of hypoglycemia in insulin-treated adults on established nasogastric feeding in the general ward? Second, to what extent does lack of homogeneity in defining, identifying, and reporting hypoglycemia affect these statistics?

## Methods

### Search Strategy

The review was carried out in accordance with PRISMA and QUOROM statement guidelines.[21-23] A systematic search to retrieve potentially relevant articles was conducted, from 1999 onward. This time frame was chosen as postdating the introduction of analog insulin, whose shorter mode of action has been demonstrated to decrease the likelihood of hypoglycemia.[24] Databases searched were as follows:

*PubMed:* Accessed April 19, 2013. Search terms—insulin AND (diabetes OR diabetic) AND (enteral OR "tube feed" OR nasogastric) AND (hypoglycemia OR hypoglycemia) NOT children NOT critical NOT "critically ill" NOT "intensive care" NOT neonates NOT pediatric [All Fields] and accessed again 21/04/2013 using search terms (diabetes OR diabetic) AND "tube feeding" AND insulin NOT children NOT critical NOT "critically ill" NOT "intensive care" NOT neonates NOT pediatric [All Fields].

*ProQuest:* Accessed April 20, 2013. Search terms—insulin AND (diabetes OR diabetic) AND (enteral OR "tube feed" OR nasogastric) AND (hypoglycemia OR hypoglycemia) NOT children NOT critical NOT "critically ill" NOT "intensive care" NOT neonates NOT pediatric [All Fields].

*Embase and Cochrane Library:* Accessed April 21, 2013. Same search terms [All Fields]. Cochrane systematic reviews were searched April 24, 2013, by topic (diabetes), then subtopic (effective practice, general, type 1, type 2).

PLoS clinical trials and Directory Open Access Journals were searched April 21 and 22, 2013, respectively, with the following search terms: diabetes AND (enteral OR nasogastric OR "tube feed") [All Fields]. Key journals in the field of enteral feeding and practical diabetes management were hand searched—*Nutrition in Clinical Practice, Clinical Nutrition, Practical Diabetes, Diabetes Care, Clinical Diabetes, Diabetic Medicine*—as were citations from retrieved articles.

### Initial Retrieval, Selection Criteria, and Study Inclusion

Papers were initially identified from electronic and hand searches by screening of titles, abstracts, and extracts by one author (S.A.V.). Papers were retrieved if they met study inclusion/exclusion criteria. Inclusion criteria were studies referencing hypoglycemia with participants ≥ 18 years old who had insulin-treated diabetes and were on nasogastric feeding. Papers were excluded if participants were critically ill or in intensive care, were receiving significant oral supplementation (> 25% total energy intake orally), or were on nasogastric feeding < 3 days, PEG feeding, or total parenteral nutrition. The full documents were then read by 2 authors (S.A.V. and J.L.S.). Papers were excluded if they did not meet inclusion/exclusion criteria, were not original studies, or demonstrated ineligible methodology. Papers were included on consensus from both authors.

### Data Extraction and Analysis

Data were extracted by one author (S.A.V.) and verified by another (J.L.S.). Quality was assessed via SIGN checklists.[25] Qualitative data extracted were study design, outcomes, and study mode of reporting hypoglycemia. Quantitative variables extracted were duration of data collection, level of blood glucose used to define hypoglycemia, reporting methodology, frequency of hypoglycemia, and frequency of routine assessment of blood glucose. Due to the small number of studies suitable for inclusion and the heterogeneity of data, we largely took a descriptive approach to combining results; however, where data were comparable, they were presented as a modified forest plot to give a better picture of variability in reported frequency of hypoglycemia. Analysis was carried out with GraphPad Prism 6 (GraphPad Software Inc, La Jolla, California, USA).

## Results

Of the total 231 studies initially identified by the search strategy, 185 were excluded after review of the title/abstract and a further 37 on the basis of the full paper (see Figure 1). The major reasons for exclusion were study overlap, inadequate duration of nasogastric feeding, and critical care setting. Studies were listed according to evidence level, with 9 papers[16,17,19,26-31] that referenced hypoglycemia judged suitable for inclusion (Table 1). In these studies, hypoglycemia was variously referenced as an outcome,[16,17,26,27,31] clinical data,[28,30] or an adverse event,[19,29] with the primary study objective being the assessment/comparison of insulin regimens[16,17,26-28,30,31] or nasogastric feed products.[19,29] As the stated aim of this review was to assess published summary statistics of frequency of hypoglycemia in insulin-treated adults on established nasogastric feeding in the general ward irrespective of insulin or feeding regimen, groups within studies have been assessed autonomously rather than comparatively.

### Level of Blood Glucose Defined as Hypoglycemia

The level of blood glucose defined as hypoglycemia and the referenced rationale for this definition varied greatly among studies (see Table 2). It was variously defined as follows: < 80 mg/dL (4.4 mmol/L),[27,28] referencing Finney et al[32]; < 70 mg/dL (3.9 mmol/L),[16,17] referencing Dinardo et al[33] and the American Association of Clinical Endocrinologists and American Diabetes Association consensus statement[34]; < 60 mg/dL (3.3 mmol/L),[19,26,29] 2 unreferenced and 1 referencing Centennial Medical Center policies[35]; and 2 studies[30,31] with undefined levels, with one of these specifying no hypoglycemic events requiring treatment, presumably referring to symptomatic hypoglycemia rather than biochemical definition.

### Identification of Hypoglycemia

With the exception of 2 studies, identification of hypoglycemia was specified by level of blood glucose. Frequency of routine blood glucose monitoring varied widely among studies (median, 4 assessments/day; range,

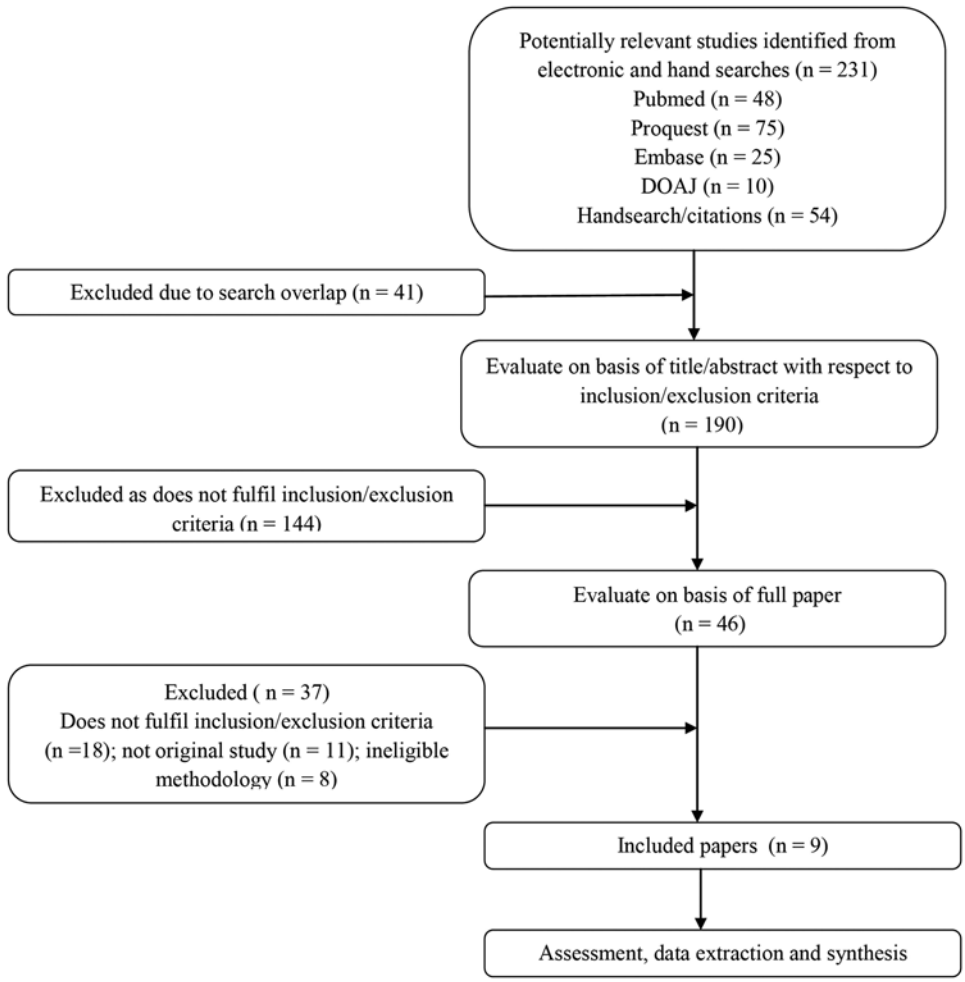



**Figure 1.** Flowchart showing search and retrieval of articles

2-6), and the rationale for this was, in the main, not specified. Where specified, frequency was tailored to study objectives,[19] and it is reasonable to presume that the 2 retrospective studies[16,26] were following hospital protocol for frequency of blood glucose monitoring.

## Study Methodology for Reporting Hypoglycemia

These 9 studies utilized 5 methods for reporting hypoglycemia (see Table 2), and 4 studies[16,17,19,29] reported 2 ways. The most common reporting method (6 studies)[16,19,28-31] involved total number of hypoglycemic events. Study group sample size varied from 1 to 76 and data collection duration, when specified, from 3 to 84 days; thus, reporting of total number of hypoglycemic events equates to a large variation among studies in frequency of hypoglycemic events per patient-day. The second-most utilized reporting method was percentage of patients with hypoglycemic event (2 studies)[19,29] and percentage of total blood glucose levels < 70 mg/dL (3.9 mmol/L) (2 studies).[16,17] One study each reported frequency of hypoglycemia as patient-days with 1 or more hypoglycemic events[17] and percentage of time with blood glucose level < 60 mg/dL (3.3 mmol/L).[26]

## Reported Frequency of Hypoglycemia

Reported frequencies of hypoglycemia are shown on Table 2. The only reporting methods utilized frequently enough to allow interstudy comparison were percentage of patients with hypoglycemic event and percentage of

Table 1

Included studies (n = 9): Design, Outcomes, Hypoglycemia Reporting Mode

| Author | Study Design: EV[a] | Patient Type (No.) | Intervention: Limitations | Study Conclusions |
|---|---|---|---|---|
| Pohl[19] | Randomized double blind control trial: II | Non–critically ill patients with insulin-treated diabetes FPG ≥ 120.6 mg/dL (6.7 mmol/L) receiving ≥ 84 d enteral nutrition (105) | Standard feed and diabetes-specific low-carbohydrate feed: Sample reduced to 55 by study endpoint | Diabetes-specific feed showed significant improvement in total daily insulin dose and FPG.[b] |
| Korytkowski[17] | Prospective randomized open label trial: III-2 | Non–critically ill patients with insulin-treated diabetes with 2 or more BGL > 129.6 mg/dL (7.2 mmol/L) receiving enteral nutrition (50) | Two insulin regimens: Small sample size but no dropout. | No significant difference between groups for glycemic control or triglycerides.[c] |
| Leon-Sanz[29] | Comparative randomized open label trial: III-2 | Non–critically ill patients with insulin-treated diabetes receiving ≥ 14 d continuous enteral nutrition (63) | Two enteral feeds: Small sample size with significant dropout. | No significant difference between feeds for BGL, lipids, or insulin dose.[b] |
| Cortinovis[27] | Prospective nonrandomized control study: III-1 | Non–critically ill patients with insulin-treated diabetes receiving enteral nutrition (38) | Standard versus carbohydrate-based insulin protocol: Nonrandomized, group differences. | Efficacy and safety of tailored insulin protocol demonstrated.[c] |
| Cook[26] | Retrospective cohort study: III-2 | Non–critically ill patients with insulin-treated diabetes receiving continuous enteral nutrition (159) | Three insulin regimens: Retrospective nonrandomized, different study duration per group (NPH insulin groups, 9.5 ± 9.1 d; aspart group, 5.8 ± 4.9 d). | Significant difference in mean BGL between insulin aspart and NPH (4 hourly or 6 hourly) ($P < .001$), no significant difference between NPH groups.[c] |
| Hsia[16] | Retrospective cohort study: III-2 | Non–critically ill patients with insulin-treated diabetes receiving ≥ 3 d continuous enteral nutrition (22) | Three insulin regimens: Retrospective, nonrandomized, and small sample size. | Biphasic insulin produces less hypoglycemia and is a safe regimen in these patients.[c] |
| Oyibo[30] | Observational case series: IV | Non–critically ill patients with insulin-treated diabetes receiving ≥ 14 d enteral nutrition (24) | Nil (observational only): Small sample size, 20 of 24 participants completing. | Twice daily insulin regimen safe for these patients.[d] |
| Fatati[28] | Observational case series: IV | Non–critically ill patients receiving insulin receiving ≥ 7 d enteral nutrition (8 of 25 participants with diabetes) | Nil (observational only): Small sample size | Glargine insulin regimen safe for these patients.[d] |
| Putz[31] | Observational case study: — | Non–critically ill patient with insulin-treated diabetes receiving continuous enteral feeding (1) | Nil (observational only): Case study | Glargine insulin safe for continuous enteral feeding.[c] |

Abbreviations: BGL, blood glucose level; EV, evidence level; FPG, fasting plasma glucose; NPH, neutral protamine Hagedorn.
[a]National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. http://www.nhmrc.gov.au/guidelines/publications/cp69. Accessed January 2014.
[b]Hypoglycemia reported as adverse event.
[c]Hypoglycemia reported as outcome.
[d]Hypoglycemia reported as clinical data.

Table 2

Included Studies (n = 9): Quantitative Data on Hypoglycemia

| Study: Grouping (No.) | Duration of Data Collection | Hypoglycemia, mg/dL (mmol/L) | Reporting Methodologies | | | | | Assess BGL |
|---|---|---|---|---|---|---|---|---|
| | | | Total EVTs | Patients With EVT, % | Patient Days With 1+ EVT, % | Total BGL < 70 mg/dL,[a] % | Time With EVT, % | |
| Pohl[19] | 84 d | < 60 (3.3) | | | | | | 2/d |
| Diabetes feed (34) | | | 1 | 2.1 | | | | |
| Standard feed (21) | | | 5 | 10.2 | | | | |
| Korytkowski[17] | 6 ± 2.2 d | < 70 (3.9) | | | | | | Max 6/day |
| Glargine insulin (25) | | | | | 2.7 | 1.3 | | |
| Sliding scale insulin (25) | | | | | 4.8 | 1.1 | | |
| Leon-Sanz[29] | Mdn, 13 d | < 60 (3.3) | | | | | | 3/d |
| High MFA feed (18) | | | 7 | 3.9 | | | | |
| High CHO feed (14) | | | 5 | 2.9 | | | | |
| Cortinovis[27] | 3 d | < 80 (4.4) | | | | | | 4+/d |
| Standard regimen (19) | | | | | | | | |
| Protocol regimen (19) | | | | | | | | |
| Cook et al[26] | Variable | < 60 (3.3) | | | | | | Not stated |
| Insulin aspart (31) | | | | | | | 0.7 | |
| NPH every 4 h (52) | | | | | | | 1.36 | |
| NPH every 6 h (76) | | | | | | | 0.9 | |
| Hsia[16] | 3 d | < 70 (3.9) | | | | | | 4/d |
| Glargine/lispro (8) | | | 5 | | | 5.4 | | |
| Biphasic insulin 2/d (8) | | | 2 | | | 2.1 | | |
| Biphasic insulin 3/d (6) | | | 1 | | | 1.4 | | |
| Oyibo[30] | | | | | | | | |
| Observational study (24) | Variable | Not defined | 0 | 0 | 0 | 0 | 0 | 5+/d |
| Fatati[28] | | | | | | | | |
| Observational study (8) | 7 d | < 80 (4.4) | 0 | 0 | 0 | 0 | 0 | 6/d (4/7) |
| Putz[31] | | | | | | | | |
| Case study (1) | 3+ mo | Not defined | 0 | 0 | 0 | 0 | 0 | 4/d |

Abbreviations: BGL, blood glucose level; CHO, carbohydrate; EVT, event; MFA, monounsaturated fatty acid; NPH, neutral protamine Hagedorn.
[a]3.9 mmol/L.

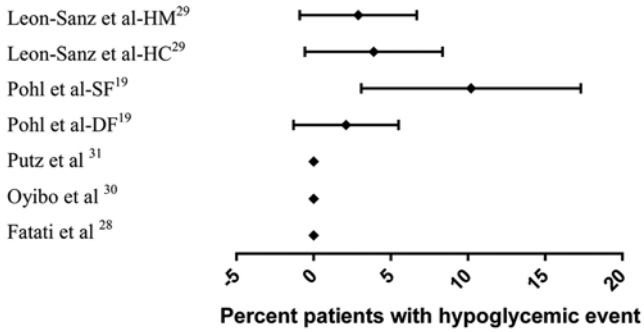



**Figure 2.** Modified forest plot showing percentage of patients with hypoglycemic events as reported in reviewed studies, with 90% confidence intervals calculated from study data. DF, diabetes feed; HC, high carbohydrate; HM, high monounsaturated fatty acid; SF, standard feed.

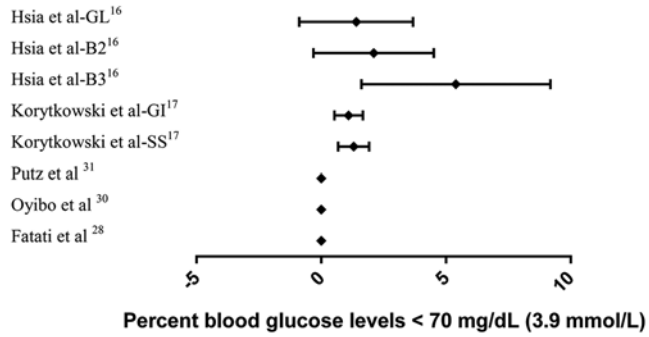



**Figure 3.** Modified forest plot showing percentage of total blood glucose levels < 70 mg/dL (3.9 mmol/L) as reported in reviewed studies, with 90% confidence intervals (calculated from study data). B2, biphasic insulin, 2/d; B3, biphasic insulin, 3/d; GI, glargine insulin; GL, glargine/lispro; SS, sliding scale insulin.

total blood glucose levels < 70 mg/dL (3.9 mmol/L), and these are presented on modified forest plots (Figures 2 and 3). These plots are intended to give only a visual impression of study trends. Confidence intervals were calculated from study data using the point estimate (percentage) and the sample size—that is, group size (Figure 2) and total number of blood glucose values (Figure 3) to calculate standard error. Total number of blood glucose values was estimated by the product of study data collection duration by number of blood glucose assessments per day. Due to small sample sizes, 90% (rather than 95%) confidence intervals were calculated to minimize confidence interval spanning 0. As data are descriptive, data points are not weighted for study effect size, and a combined effect is not displayed. Both plots give the visual impression of moderate variation in hypoglycemic frequency among studies, showing a range of 2.1% to 10.2% of patients with a hypoglycemic event and 1.1% to 5.4% blood glucose level < 70 mg/dL (3.9 mmol/L).

## Discussion

A systematic review of the literature from 1999 onward was carried out to identify and analyze information on the summary statistics of frequency of hypoglycemia in insulin-treated adults on established nasogastric feeding in the general ward. Only 9 acceptable articles were identified, none with the stated primary objective of assessing hypoglycemic frequency in the targeted group. In these studies, biochemical definition and identification and reporting of hypoglycemia—factors crucial to accurate assessment of frequency of hypoglycemia—exhibited great heterogeneity.

### Definition of Hypoglycemia

The variations in biochemical definition of hypoglycemia reflect the lack of consensus in the general literature, with recommendations varying from < 70 mg/dL (3.9 mmol/L)[34,36] to < 63 mg/dL (3.5 mmol/L)[37,38] and < 60 mg/dL (3.3 mmol/L)[39] as levels having greater "clinical" significance. Swinnen et al demonstrated that changing the glucose cutoff values that define hypoglycemia has a major effect on reported frequencies of hypoglycemia[40]; so, valid interstudy comparisons would seem to be precluded pending consensus on a definition. Dual documentation at the 2 most commonly defined levels may be a practical solution: < 63 mg/dL (3.5 mmol/L) and < 70 mg/dL (3.9 mmol/L).

### Reporting of Hypoglycemia

Heterogeneity of reporting methodology in included studies precluded valid comparisons of frequency of hypoglycemia, especially the reporting of total number of hypoglycemic events in studies of markedly differing duration and sample size. Reporting as hypoglycemic events per patient-days and/or percentage blood glucose level < defined hypoglycemic level would facilitate interstudy comparison.

### Identification of Hypoglycemia

The significance of the interstudy variation in frequency of blood glucose monitoring is difficult to assess. Increased frequency of blood glucose monitoring can increase and even overestimate documented inpatient hypoglycemia,[41] but any trend in this direction was

impossible to identify due to definitional and reporting heterogeneity.

### Reported Frequency of Hypoglycemia

Due to the small number and heterogeneity of identified studies, we were unable to calculate a quantitative synthesis of frequency of hypoglycemia but instead present a descriptive summary. In the few studies where comparisons were possible, forest plots give the visual impression of moderate variation in hypoglycemic frequency between studies (2.1%-10.2% of patients with an event; 1.1%-5.4% blood glucose level < 70 mg/dL [3.9 mmol/L]). However, given the limited numbers and secondary calculation of confidence intervals, this should be interpreted with caution.

Both the Endocrine Society[42] and the Society of Hospital Medicine[43] have recommended standardized documentation and reporting of inpatient hypoglycemia, and in this context, it is of concern that there is so little comparable information on the frequency of hypoglycemia in this potentially vulnerable population. There is no reason to suppose that people on established nasogastric feeding are at any less risk of hypoglycemia-associated mortality than the general hospital population,[2,3,5] and, indeed, their risk may well be greater.

### Limitations of Study

The major limitation of this study was the small number and heterogeneity of identified papers and the indirect nature of the data. We were unable to identify any trials designed to directly quantify frequency of hypoglycemia in insulin-treated adults on established nasogastric feeding in the general ward and therefore utilized data generated from trials designed to compare the efficacy of insulin/feed regimens, including 1 case study.

## Implications for Diabetes Educators and Conclusions

This systematic review indicates that hypoglycemia is not uncommon in insulin-treated adults on established nasogastric feeding in the general ward. There is a need for further practical research to accurately quantify this. Standardized documentation and reporting methods incorporating sample size and study duration, such as hypoglycemic events per patient-days, would facilitate interstudy comparisons, as would documentation of hypoglycemia at the 2 most commonly defined levels: < 63 mg/dL (3.5 mmol/L) and < 70 mg/dL (3.9 mmol/L).

### Author Contributions

S.A.V. planned/executed project, researched data, and wrote manuscript; J.L.S. planned project and reviewed articles for inclusion; K.G.S. planned project and reviewed manuscript.

### References

1. Wexler DJ, Meigs JB, Cagliero E, Nathan DM, Grant RW. Prevalence of hyper- and hypoglycemia among inpatients with diabetes: a national survey of 44 US hospitals. *Diabetes Care*. 2007;30:367-369.
2. Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care*. 2009;32:1153-1157.
3. Brodovicz KG, Mehta V, Zhang Q, et al. Association between hypoglycemia and inpatient mortality and length of hospital stay in hospitalized, insulin-treated patients. *Curr Med Res Opin*. 2013;29:101-107.
4. Deepak PJ, Sunitha K, Nagaraj J, Sanjukta A, Bhattacharyya A. Inpatient management of diabetes: survey in a tertiary care centre. *Postgrad Med J*. 2003;79(936):585-587.
5. Nirantharakumar K, Marshall T, Kennedy A, Narendran P, Hemming K, Coleman JJ. Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. *Diabet Med*. 2012;29:e445-e448.
6. Curkendall SM, Natoli JL, Alexander CM, Nathanson BH, Haidar T, Dubois RW. Economic and clinical impact of inpatient diabetic hypoglycemia. *Endocr Pract*. 2009;15:302-12.
7. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012;367:1108-18.
8. Krinsley JS, Schultz MJ, Spronk PE, et al. Mild hypoglycemia is independently associated with increased mortality in the critically ill. *Crit Care*. 2011;15:R173.
9. Sechterberger MK, Bosman RJ, Oudemans-van Straaten HM, et al. The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study. *Crit Care*. 2013;17:R52.
10. Braithwaite SS, Buie MM, Thompson CL, et al. Hospital hypoglycemia: not only treatment but also prevention. *Endocr Pract*. 2004;10(suppl 2):89-99.
11. Ng JM, Cox H, Longbotham D, Kilpatrick ES, Atkin SL, Allan BJ. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward: response to Turchin et al. *Diabetes Care*. 2009;32:e151.
12. Ceriello A, Lansink M, Rouws CH, van Laere KM, Frost GS. Administration of a new diabetes-specific enteral formula results in an improved 24h glucose profile in type 2 diabetic patients. *Diabetes Res Clin Pract*. 2009;84:259-266.
13. del Carmen Crespillo M, Olveira G, de Adana MS, et al. Metabolic effects of an enteral nutrition formula for diabetes: comparison with standard formulas in patients with type 1 diabetes. *Clin Nutr*. 2003;22:483-487.

14. Hofman Z, Lansink M, Rouws C, van Drunen JDE, Kuipers H. Diabetes specific tube feed results in improved glycaemic and triglyceridaemic control during 6h continuous feeding in diabetes patients. *e-SPEN*. 2007;2:44-50.
15. Vanschoonbeek K, Lansink M, van Laere KM, Senden JM, Verdijk LB, van Loon LJ. Slowly digestible carbohydrate sources can be used to attenuate the postprandial glycemic response to the ingestion of diabetes-specific enteral formulas. *Diabetes Educ*. 2009;35:631-640.
16. Hsia E, Seggelke SA, Gibbs J, Rasouli N, Draznin B. Comparison of 70/30 biphasic insulin with glargine/lispro regimen in non-critically ill diabetic patients on continuous enteral nutrition therapy. *Nutr Clin Pract*. 2011;26:714-717.
17. Korytkowski MT, Salata RJ, Koerbel GL, et al. Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. *Diabetes Care*. 2009;32:594-596.
18. Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2005;28:2267-2279.
19. Pohl M, Mayr P, Mertl-Roetzer M, et al. Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: stage II of a randomized, controlled multicenter trial. *JPEN Nutr*. 2009;33:37-49.
20. Pohl M, Mayr P, Mertl-Roetzer M, et al. Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. *Eur J Clin Nutr*. 2005;59:1221-1232.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
22. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement: quality of reporting of meta-analyses. *Lancet*. 1999;354(9193):1896-1900.
23. Moher D, Tricco AC. Issues related to the conduct of systematic reviews: a focus on the nutrition field. *Am J Clin Nutr*. 2008;88:1191-1199.
24. Kucera ML, Graham JP. Insulin lispro, a new insulin analog. *Pharmacotherapy*. 1998;18:526-538.
25. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ*. 2001;323(7308):334-336.
26. Cook A, Burkitt D, McDonald L, Sublett L. Evaluation of glycemic control using NPH insulin sliding scale versus insulin aspart sliding scale in continuously tube-fed patients. *Nutr Clin Pract*. 2009;24:718-722.
27. Cortinovis F, Colombo O, Sileo F. Efficacy of a protocol for blood glucose control in enteral nutrition. *Mediterr J Nutr Metab*. 2011;4:47-52.
28. Fatati G, Mirri E, Tosto S, et al. Use of insulin glargine in patients with hyperglycaemia receiving artificial nutrition. *Acta Diabetologica*. 2005;42:182-186.
29. Leon-Sanz M, Garcia-Luna PP, Sanz-Paris A, et al. Glycemic and lipid control in hospitalized type 2 diabetic patients: evaluation of 2 enteral nutrition formulas (low carbohydrate-high monounsaturated fat vs high carbohydrate). *JPEN*. 2005;29:21-29.
30. Oyibo SO, Sagi SV, Home C. Glycaemic control during enteral tube feeding in patients with diabetes who have had a stroke: a twice-daily insulin regimen. *Practical Diabetes*. 2012;29:135-139.
31. Putz D, Kabadi UM. Insulin glargine in continuous enteric tube feeding. *Diabetes Care*. 2002;25:1889-1890.
32. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA*. 2003;290:2041-2047.
33. DiNardo M, Noschese M, Korytkowski M, Freeman S. The medical emergency team and rapid response system: finding, treating, and preventing hypoglycemia. *Jt Comm J Qual Patient Saf*. 2006;32:591-595.
34. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care*. 2009;32:1119-1131.
35. Hypoglycemic reaction: non-pregnant patient [policy 36.600.2.103]. Nashville, TN: Centennial Medical Center; 2005.
36. Cryer PE. Preventing hypoglycaemia: what is the appropriate glucose alert value? *Diabetologia*. 2009;52:35-37.
37. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in type 2 diabetes. *Diabet Med*. 2008;25:245-254.
38. Frier BM. Defining hypoglycaemia: what level has clinical relevance? *Diabetologia*. 2009;52:31-34.
39. Moghissi E. Hospital management of diabetes: beyond the sliding scale. *Cleve Clin J Med*. 2004;71:801-808.
40. Swinnen SG, Mullins P, Miller M, Hoekstra JB, Holleman F. Changing the glucose cut-off values that define hypoglycaemia has a major effect on reported frequencies of hypoglycaemia. *Diabetologia*. 2009;52:38-41.
41. Weinberg ME, Bacchetti P, Rushakoff RJ. Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *J Diabetes Sci Technol*. 2010;4:577-82.
42. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:16-38.
43. Schnipper JL, Magee M, Larsen K, Inzucchi SE, Maynard G. Society of Hospital Medicine Glycemic Control Task Force summary: practical recommendations for assessing the impact of glycemic control efforts. *J Hosp Med*. 2008;3(S5):66-75.

# CHAPTER 9: GENERAL DISCUSSION AND CONCLUSION

## 9.1 Introduction and significance

Hypoglycaemia in diabetes-related states is well researched, but has tended to focus on mechanisms and prevention of hypoglycaemia, hypoglycaemia-associated autonomic failure and longer-term physical and psychological consequences of hypoglycaemia.

All evidence shows that hypoglycaemia can be a major stressor for those who experience it, with a significant number suffering major anxiety or fear of hypoglycaemia syndrome (Amiel et al., 2008; Anderbro et al., 2010; McCoy et al., 2013; Shiu & Wong, 2002; Shiu & Wong, 2000). There is evidence that anxiety is lessened when individuals have a sense of control over their hypoglycaemia (Wild et al., 2007), and to this end, swift effective treatment of hypoglycaemia is obviously desirable. Dietary treatment of hypoglycaemia, although a crucial element in a swift resolution of a hypoglycaemic event, has been presumed to be a 'given' determined by expert opinion (American Diabetes Association, 2014b) or has relied on findings from older laboratory-based investigations (Brodows et al., 1984; Slama et al., 1990; Wiethop & Cryer, 1993) with results being extrapolated to present regimes in the free-living situation.

To address these gaps in the literature, the overall aim of this thesis, presented as a series of seven published papers, has been to quantitatively and qualitatively investigate dietary practices associated with the treatment of hypoglycaemia with a view to determining efficacious resolution of hypoglycaemia. All investigations have been practically based, and include, where possible the perspective of those experiencing hypoglycaemia. When, as with inpatients on total nasogastric feeding, the person experiencing hypoglycaemia is dependent on carers to identify, treat and document the frequency of their hypoglycaemia, the problems of treatment are compounded. Quantifying methods of identification, reporting methods and frequency of hypoglycaemic events is essential for instigating efficacious treatment without subsequent hypoglycaemic events or hyperglycaemia, and again, there is a dearth of information in this area. All projects aimed to obtain measurable results that would be of potential benefit to those experiencing hypoglycaemia.

The study findings can be found in the included papers, however this chapter provides a brief summary of the study results in relation to the overall research objectives. The overall significance of the study, limitations of the research and recommendations for future research are also discussed.

## 9.2 Summary of study findings

Research objectives are italicized:

*1. To practically establish and verify, in free-living individuals, in various states of glucose dysmetabolism and on current medication regimes, effective dietary treatments of hypoglycaemia or relative hypoglycaemia.*

The first paper of this thesis (paper 1) presents a case report of a woman with NGT and elevated 1-h postload glucose. It examines the relationship between loss of first phase insulin, postprandial hyperglycaemia with a subsequent rapid drop in blood glucose resulting in relative hypoglycaemia, carbohydrate intake, glycaemic index and weight gain and assesses the effect of a low carbohydrate diet and early intervention with short-acting preprandial insulin on glycaemia over 2 h and compares this to treatment with the DPP-4 inhibitor, sitagliptin or no treatment. Results showed a significant difference between the 1-h postload rise for low carbohydrate and insulin-treated meals compared with no treatment or sitagliptin. There was no significant difference between no treatment and sitagliptin. On a regime of either low carbohydrate meals or preprandial insulin, glycaemic variability, symptoms of relative hypoglycaemia and consequent postprandial hunger diminished with loss of 3.6 kg over 4 y. Cubeddu *et al*. showed that 8.3% of those with NGT have 1-h BGL ≥ 8.6 mmol/L, so this condition is not unusual, but treatment of it is (Cubeddu & Hoffmann, 2010). It has been suggested that recognition and management of those with NGT and 1-h glucose ≥ 8.6mmol/L may reduce incidence of diabetes and vascular events (Cubeddu & Hoffmann, 2010; Meisinger et al., 2006). This represents the first published case of identification and treatment of relative hypoglycaemia and glucose variability in an individual with NGT and elevated 1-h postload glucose.

The second paper in this thesis (paper 2) investigated dietary treatment of hypoglycaemia in those with insulin-treated diabetes and aimed to determine if there was a significant difference in the need for repeat treatment of hypoglycaemia

following initial treatment with 15 or 20 g of fast-acting carbohydrate with wait-time to repeat treatment either 5 or 10 min. The effect of carbohydrate quantity and wait-time to repeat treatment on subsequent hyperglycaemia was also investigated. Results showed that 20 g of fast-acting carbohydrate will resolve hypoglycaemia within 10 min in 89.3% of free-living individuals on current insulin regimes compared with 15 g that resulted in 63.2% resolving in 10 min. Decreasing the wait-time to retreatment to 5 min increased those needing repeat treatments with both 15 and 20 g treatments. Hyperglycaemia at 30 min post hypoglycaemia was not significant but numbers were insufficient to relate to quantity of carbohydrate.

Insufficient initial treating quantity of carbohydrate necessitating repeat treatments markedly increases the duration of hypoglycaemia and often uncomfortable hypoglycaemic symptoms that last until clinical hypoglycaemia resolves, and in a third of symptomatic participants in this study, up to 10 min longer. Therefore this study supports an initial treatment of 20 g carbohydrate with a 10 min wait-time to repeat treatment as an optimal recommendation for the conscious insulin-treated individual self-treating hypoglycaemia.

2. *To assess self-reported current practices in dietary treatment of hypoglycaemia and their perceived effectiveness with respect to resolution of initial hypoglycaemia, prevention of repeat hypoglycaemia and generation of subsequent hyperglycaemia. To compare this to verified scientific standards (GI) and currently-used laboratory-generated recommendations for dietary treatment of hypoglycaemia.*

The third paper in this thesis (paper 3) again looks at free-living people with insulin-treated diabetes and investigates self-reported qualitative and quantitative patterns of food selection for self-treatment of hypoglycaemia as compared with international and national guidelines, rate of absorption of carbohydrate, self-reported efficacy of treatment and subsequent hypoglycaemia. Results showed that 78% of responders reported initial treatment with recommended foods, but only 40.8% of these were quick-acting carbohydrate, mainly glucose tablets and jellybeans. Initial treating carbohydrate quantity showed 20.6% of responders used quantities exceeding all guidelines with 46.4% used quantities exceeding Australian recommendations but consistent with the most liberal recommendations (EASD). Only 55.8% reported ingesting follow-up food.

Most study participants reported treating with recommended foods in quantities

exceeding minimum recommendations, possibly attempting to resolve unpleasant symptoms of hypoglycaemia quickly. Non-adherence in itself is not a reason to review recommendations, but in view of the results of paper 2, the relatively low evidence level on which recommendations are based and the variation in world recommendations, it would seem practicable to increase recommended treatment quantities. Failure of many to ingest follow-up food was concerning in view of the perceived risk of repeat hypoglycaemic episodes and was deemed to warrant investigation (see paper 4) as was various foods recommended for treatment but not fitting the criteria of quick-acting carbohydrate (see recommendations, section 9.4 ).

In the fourth paper (paper 4) repeat hypoglycaemia within 2 h of a primary hypoglycaemic event in people with insulin-treated diabetes is investigated in greater depth to ascertain if there was an association between omission or under-treatment with carbohydrate after an initial hypoglycaemic event and increased frequency of repeat hypoglycaemia. A secondary aim was to investigate association between repeat hypoglycaemia and presence or absence of symptoms and duration of action of carbohydrate. Results showed repeat hypoglycaemia within 2-h post primary hypoglycaemic event was reported by 8.2% and consumption of follow-up longer-acting carbohydrate by 58.2% of responders. Method of insulin administration (MDI/ SCII) and consumption of follow-up food were significantly associated with repeat hypoglycaemia but presence or absence of symptoms and duration of action of carbohydrate were not. Hierarchical logistic regression analysis showed omission of follow-up food was not a significant predictor of increased likelihood of repeat hypoglycaemia within 2 h of a primary hypoglycaemic event, irrespective of method of insulin administration. This study supports guidelines that recommend judicious, rather than routine use of follow-up longer-acting carbohydrate post primary hypoglycaemic event.

*3. To assess individual knowledge of self-treatment of hypoglycaemia in a situation of high risk for sustained hypoglycaemia (alcohol ingestion) and compare this to easily available internet-based information.*

The fifth paper (paper 5) looks at the more specialized issue of knowledge of the key aspects of alcohol-induced sustained hypoglycaemia in the presence of insulin in those with type 1 diabetes and how it relates to freely available diabetes association information on the internet. Available information and participant knowledge were assessed according to 6 key criteria. Results showed information on alcohol and

hypoglycaemia addressed by 6 national Diabetes Associations provided general information on alcohol and hypoglycaemia, eating with, and snacking after alcohol and sustained hypoglycaemic effect, but that the specified possible duration of hypoglycaemia varied from unspecified to 16 - 24 h, with only 2 guidelines providing information on reduction of long-acting insulin to minimize sustained hypoglycaemic effect.

When knowledge of people with type 1 diabetes was assessed, most responders (88.2%) identified the hypoglycaemic effect of alcohol but only 32.4% postulated duration of 4+ h post-consumption for this. Standard drink quantity perceived to lower blood glucose level was 1 - 3 (50%) and 4+ (41.2%). Risk reduction (dietary or insulin modification) was not addressed to minimize prejudicing assessment of knowledge of hypoglycaemic effect per se. Knowledge of alcohol and hypoglycaemia was acceptable, except in the important area of duration of alcohol-induced hypoglycaemia. This is congruent with accessed guidelines and may reflect an identified lack of consistency in information given to patients regarding alcohol-induced hypoglycaemia. Additionally not all guidelines provided information on reduction of long-acting insulin, an important strategy to minimize hypoglycaemic risk.

*4. To assess treatment and frequency of hypoglycaemia in inpatients on nasogastric feeding and thus dependent on carers for identification and treatment of hypoglycaemia and therefore at putative high risk from that hypoglycaemia.*

The last two papers investigate the specialized and under-researched area of hypoglycaemia in inpatients with diabetes on nasogastric feeding in the general ward. Paper 6 describes a retrospective review of 50 in-patients treated with insulin and insulin secretagogues on ≥ 3 d nasogastric feeding to determine factors influencing hypoglycaemia. Results show frequency of hypoglycaemia as 10.9% patient-days with ≥1 hypoglycaemic episode and 3.5% total blood glucose values < 3.5mmol/L. There was no association with feed type but there was an association between sulphonylurea treatment and increased and extended hypoglycaemia. As this was a retrospective observational study, duration of nasogastric feeding varied, therefore Kaplan-Meier survival curves were used for time to event analysis of the effect of reduction in medication post-hypoglycaemia on a subsequent hypoglycaemic episode. It showed a significantly longer time to a subsequent hypoglycaemic episode between patients whose treatment was reduced in response to

hypoglycaemia and those whose treatment remained unchanged. There was no association with subsequent hyperglycaemia.

This study supports optimal blood glucose monitoring, insulin treatment and judicious medication reduction post-hypoglycaemia but frequency of hypoglycaemia was not comparable with other studies due to variation in reporting methods (see paper 7).

Paper 7 is a systematic review of the literature that aimed to answer the questions: 1. What are the existing summary statistics of frequency of hypoglycaemia in insulin-treated adults on established nasogastric feeding in the general ward? 2. To what extent does lack of homogeneity in defining, identifying and reporting hypoglycaemia affect these statistics? Results were sourced from 9 studies (from 231 identified) judged suitable according to inclusion/exclusion criteria. None had assessment of hypoglycaemia as their primary objective but rather the assessment of efficacy of insulin/feed regimens in the target population. Studies exhibited major heterogeneity with definitions of hypoglycaemia varying from < 3.3 mmol/L to < 4.4 mmol/L. Five different methods of reporting frequency of hypoglycaemia were utilized, which precluded a pooled analysis, however a descriptive synthesis of results was generated and some comparable results presented on modified forest plots. These showed 2.1 - 10.2% of patients with a hypoglycaemic event and 1.1 - 5.4% blood glucose level < 3.9 mmol/L. The major conclusions were that standardization of documentation, reporting methods incorporating patient-numbers and duration of feeding (hypoglycaemic events per patient-days and/or percentage blood glucose level < defined hypoglycaemic level) and documentation of hypoglycaemia at the two most commonly defined levels: < 3.5 mmol/L and < 3.9 mmol/L are crucial to allow interstudy comparisons.

## 9.3 Limitations

### *9.3.1 Classification of diabetes*

Limitations of studies have been outlined within the individual papers. This section will merely expand on two reoccurring themes.

Several of the studies (papers 2,3,4,6) have investigated insulin-treated subjects, that is, a mixture of those with type 1 diabetes and insulin-treated type 2 diabetes. There are differences between these two groups, which may affect dietary treatment of

hypoglycaemia, although obviously the aetiology of the hypoglycaemia is the same, being a relative insulin excess causing blood glucose to drop below the definitional level for hypoglycaemia. Those with type 1 diabetes have an absolute deficiency of insulin secretion while the mechanism of type 2 diabetes varies, but, in the main, encompasses relative rather than absolute insulin deficiency, progressive over time with β-cell function declining and thus endogenous insulin secretion declining (American Diabetes Association, 2005; Cryer et al., 2003). People with type 2 diabetes who have been treated with insulin > 10 y are therefore more insulin deficient behaving more like those with type 1 diabetes. There is both a higher incidence of mild and severe hypoglycaemia in type 1 compared to type 2 diabetes, except in advanced type 2 diabetes (Donnelly et al., 2005). In insulin-treated type 2 diabetes, there is relative insulin deficiency, therefore both endogenous and exogenous insulin present, and it could be surmised that response to dietary treatment will be different than with total insulin deficiency. Insulin resistance will likely also modify the situation (Miller et al., 2001).

In papers 3 and 4, to maintain anonymity, all data was self-reported and it was considered that self-reported data on diabetes type would be of questionable accuracy. There was no reason to think lack of differentiation of diabetes type would affect the qualitative data on foods consumed but may have had some effect on the quantitative data. Similarly, in paper 6, although information was collected from patient medical notes, type of diabetes was often not documented or was documented with no accompanying medical rationale. Therefore, in this study, mode of treatment of diabetes was recorded, but not diabetes type.

In paper 2, we aimed to make a new recommendation for optimal quantity of quick-acting carbohydrate and wait-time to repeat treatment for hypoglycaemia in diabetes. The aim was for a universal recommendation (as with presently existing recommendations), and therefore differentiation of diabetes type was unnecessary and was not considered a limitation in this paper.

### 9.3.2 *Self-reported data*

The second overall study limitation was the use of indirect self-reported data accessed by data collection via a self-administered questionnaire (papers 3,4,5). Although direct observation of subject food consumption and hypoglycaemic

behaviour would, on the face of it, seem a more accurate method of data collection, it is impractical in the free-living situation, with the presence of an observer having the potential to change the very behaviour being observed. There is a discussion of the strengths and limitations of this type of data collection in section 5.1 of this thesis. Collection of self-reported data was chosen judiciously for these three projects which had, as their aim, that the investigation be from the subjects' perspective. Every effort was made to maximise accuracy of collected data (see section 5.1). Hawkshead *et al* comment that self-reported data can have reduced accuracy due to recall bias and the propensity for the respondent to return socially desirable responses (Hawkshead & Krousel-Wood, 2007). The latter has been covered in detail in section 5.1. Recall bias cannot be eliminated from self-reported retrospective data but has been shown to be less where the retrospective time frame is shorter, where recalled information is of a repeated behaviour, and where the recalled information is in temporal proximity to an event that made an impression on the respondent (Choi & Pak, 2005; Evans & Crawford, 1999), all factors likely pertinent to the recall of the experience and treatment of hypoglycaemia

### 9.4 Recommendations

Some recommendations arising from the study findings are as follows:

- The initial steps in the Australian guidelines for dietary treatment of hypoglycaemia should be amended to recommend initial consumption of 20 g of quick-acting carbohydrate with a 10 minute wait-time to retreatment.
  This is based on Paper 2, Level 4 Evidence (NHMRC, 1999), in the absence of higher level evidence. A higher level of evidence, namely a prospective randomised control trial would give a more definitive result.
- Increased education on the use of quick-acting carbohydrate for initial treatment of hypoglycaemia is recommended, as quick-acting carbohydrate has been shown to have an enhanced glucose response 15 min post-consumption compared to medium-acting carbohydrate (Brand-Miller et al, 2009). ( Based on results reported in Paper 3 that 50.5% of participants used medium-acting carbohydrate for initial self-treatment of their hypoglycaemia).

- The follow-up step in the Australian guidelines for dietary treatment of hypoglycaemia should read: If your next meal is more than 20 minutes away, you may need to eat some longer-acting carbohydrate, rather than the present wording of: 'If your next meal is more than 20 minutes away, eat some longer acting carbohydrate' (Diabetes Australia, 2009). Based on Paper 4 (results from a well-validated questionnaire), in the absence of higher level evidence. A higher level of evidence, namely a prospective randomised control trial would give a more definitive result.
- All guidelines and educational material giving information on alcohol and insulin should highlight the fact that sustained alcohol-induced hypoglycaemia can have a duration of 24 h and include information on reduction of long-acting insulin to minimize hypoglycaemia when the quantity of alcohol consumed is significant.
- Insulin, rather than sulphonylurea agents should be used to treat in-patients with diabetes who are receiving ≥ 70% of their nutrition from nasogastric feeding, as the use of sulphonylureas in this situation is significantly associated with increased hypoglycaemia and extended hypoglycaemia. (Based on observational evidence only).
- There should be increased education for medical and ward staff involved in caring for insulin-treated in-patients with diabetes on nasogastric feeding regarding the very real possibility of hypoglycaemia in these patients.
- Research, quality assurance etc assessing hypoglycaemia in insulin-treated in-patients with diabetes on nasogastric feeding should use standardized documentation and reporting methods incorporating sample size and study duration, such as hypoglycaemic events per patient-days and report hypoglycaemia at the two levels of < 3.5 mmol/L and < 3.9 mmol/L.

### 9.5 Suggestions for future research

Suggested areas for further research that arise from the study findings are:

- It has been suggested that recognition and management of those with NGT and 1-h glucose ≥ 8.6mmol/L may reduce incidence of diabetes and vascular events. The case study in paper 1 in this thesis demonstrates a practical

intervention in a woman with NGT and 1-h glucose ≥ 8.6mmol/L effective over 4 years. A case series is now needed to further investigate this.

- The findings from paper 2 in this thesis have shown that 20 g of fast-acting carbohydrate will resolve hypoglycaemia within 10 min in 89.3% of free-living individuals on current insulin regimes compared with 15 g that resulted in 63.2% resolving in 10 min. Hyperglycaemia at 30 min post-hypoglycaemia was not significant but numbers were insufficient to relate to quantity of treating carbohydrate. In view of the fact that the findings from paper 3 showed that 46.4% of those surveyed self-treat their hypoglycaemia with between 15 and 30 g of quick-acting carbohydrate, investigation with a cross-over study of the effect on resolution of hypoglycaemia and subsequent hyperglycaemia of 20, 25 and 30 g of quick acting carbohydrate is warranted.
- Arising from the findings of paper 4, a further study of follow-up food and repeat hypoglycaemia with a sample size large enough to differentiate more accurately the relationship between duration of follow-up carbohydrate action and frequency of hypoglycaemia.
- Findings from paper 6 indicated that frequency of hypoglycaemia appeared to rise with increasing duration of nasogastric feeding in insulin-treated individuals obtaining > 70% of nutrition from nasogastric feeding in the general ward. A follow-up case control study confirming this would add to the knowledge of distribution of hypoglycaemic events in these vulnerable patients.

### 9.6 Conclusion

Findings from the series of studies presented in this thesis make a significant contribution to existing knowledge in the area of dietary practices and treatment of hypoglycaemia, with an emphasis on practically-based investigations grounded in current dietary practices and treatment regimens. Where possible, studies have been based on information collected from, and from the perspective of, those experiencing hypoglycaemia or relative hypoglycaemia.

Study findings are presented in seven published journal articles included within this thesis, with expanded information on significance, methods and results preceding these where considered necessary. The study findings have allowed

recommendations to be made on amendments to the Australian guidelines for treatment of hypoglycaemia in the area of optimal quantity of treating carbohydrate, wait-time to retreatment and appropriate food selection. They have delineated dietary practices in treatment of hypoglycaemia and relative hypoglycaemia and their relationship to blood glucose levels, duration of action of carbohydrate and repeat episodes of hypoglycaemia, and also highlighted deficits in knowledge and available information regarding alcohol-induced sustained hypoglycaemia. In the area of hypoglycaemia and nasogastric feeding, findings from an observational study have highlighted factors affecting severity, duration and frequency of hypoglycaemia, with a follow-up systematic review which identifies the need for specific changes in reporting methods and documentation of hypoglycaemia, and for further research in this area. Findings from all studies will hopefully benefit those who experience hypoglycaemia as a reality in their everyday lives.

## REFERENCES

Abdul-Ghani, M. A., Abdul-Ghani, T., Ali, N., & DeFronzo, R. A. (2008). One-Hour Plasma Glucose Concentration and the Metabolic Syndrome Identify Subjects at High Risk for Future Type 2 Diabetes. *Diabetes Care, 31*(8), 1650-1655. doi: 10.2337/dc08-0225

Abdul-Ghani, M. A., & DeFronzo, R. A. (2009). Pathophysiology of prediabetes. *Current Diabetes Reports, 9*(3), 193-199.

Ahmed, A. T., Karter, A. J., Warton, E. M., Doan, J. U., & Weisner, C. M. (2008). The relationship between alcohol consumption and glycemic control among patients with diabetes: the Kaiser Permanente Northern California Diabetes Registry. *Journal of General Internal Medicine, 23*(3), 275-282. doi: 10.1007/s11606-007-0502-z

Alish, C. J., Garvey, W. T., Hegazi, R. A., Hustead, D. S., Maki, K. C., Mustad, V. A., & Sacks, G. S. (2010). A diabetes-specific enteral formula improves glycemic variability in patients with type 2 diabetes. *Diabetes Technology & Therapeutics, 12*(6), 419+.

Alvarez-Guisasola, F., Yin, D. D., Nocea, G., Qiu, Y., & Mavros, P. (2010). Association of hypoglycemic symptoms with patients' rating of their health-related quality of life state: a cross sectional study. *Health And Quality Of Life Outcomes, 8*, 86. doi: 10.1186/1477-7525-8-86

American Diabetes Association. (2005). Defining and Reporting Hypoglycemia in Diabetes. *Diabetes Care, 28*(5), 1245-1249. doi: 10.2337/diacare.28.5.1245

American Diabetes Association. (2008b). Nutrition Recommendations and Interventions for Diabetes. *Diabetes Care, 31*(Supplement 1), S61-S78. doi: 10.2337/dc08-S061

American Diabetes Association. (2013a). Diabetes and Driving. *Diabetes Care, 36*(Supplement 1), S80-S85. doi: 10.2337/dc13-S080

American Diabetes Association. (2013b). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care, 36*(Supplement 1), S67-S74. doi: 10.2337/dc13-S067

American Diabetes Association. (2013c). Standards of Medical Care in Diabetes—2013. *Diabetes Care, 36*(Supplement 1), S11-S66. doi: 10.2337/dc13-S011

American Diabetes Association. (2014a). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 37 Suppl 1,* S81-90. doi: 10.2337/dc14-S081

American Diabetes Association. (2014b). Standards of Medical Care in Diabetes—2014. *Diabetes Care, 37*(Supplement 1), S14-S80. doi: 10.2337/dc14-S014

American Diabetes Association, E. A. f. t. S. o. D., International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. (2007). Consensus statement on the worldwide standardisation of the HbA1c measurement. *Diabetologia, 50*(10), 2042-2043. doi: 10.1007/s00125-007-0789-7

Amiel, S. A., Dixon, T., Mann, R., & Jameson, K. (2008). Hypoglycaemia in Type 2 diabetes. *Diabetic Medicine, 25*(3), 245-254. doi: DME2341 [pii] 10.1111/j.1464-5491.2007.02341.x [doi]

Amiel, S. A. M. D. F. (2009). Hypoglycemia: From the Laboratory to the Clinic. *Diabetes Care, 32*(8), 1364-1371.

Anderbro, T., Amsberg, S., Adamson, U., Bolinder, J., Lins, P. E., Wredling, R., . . . Johansson, U. B. (2010). Fear of hypoglycaemia in adults with Type 1 diabetes. *Diabetic Medicine, 27*(10), 1151-1158. doi: 10.1111/j.1464-5491.2010.03078.x [doi]

Angelopoulos, T. P., & Doupis, J. (2014). Sodium-Glucose linked transporter 2 (SGLT2) inhibitors--fighting diabetes from a new perspective. *Advances in Therapy, 31*(6), 579-591. doi: 10.1007/s12325-014-0127-7

Anthony, M. (2007). Treatment of hypoglycemia in hospitalized adults: a descriptive study. *The Diabetes Educator, 33*(4), 709-715. doi: 33/4/709 [pii] 10.1177/0145721707303806 [doi]

Asian-Pacific Type 2 Diabetes Policy Group. (2002). Type 2 Diabetes Practical Targets and Treatments Retrieved from International Diabetes Federation. www.idf.org/idfwpr-type-2-diabetes-pratical-targets-and-treatments website.

Atkinson, F. S., Foster-Powell, K., & Brand-Miller, J. C. (2008). International Tables of Glycemic Index and Glycemic Load Values: 2008. *Diabetes Care, 31*(12), 2281-2283. doi: 10.2337/dc08-1239

Aung, P. P., Strachan, M. W., Frier, B. M., Butcher, I., Deary, I. J., & Price, J. F. (2012). Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetic Medicine, 29*(3), 328-336. doi: 10.1111/j.1464-5491.2011.03505.x

Australian Institute of Health and Welfare. (2013). Prevalence of diabetes (AIHW) https://www.aihw.gov.au/diabetes-indicators/prevalence/

Australian Bureau of Statistics. (2011a). Adult Literacy in Western Australia. (November 2013). Retrieved from http://www.abs.gov.au/ ausstats/

Australian Bureau of Statistics. (2011b). The Australian Health Survey. Retrieved from http://www.abs.gov.au/ausstats/

Australian Bureau of Statistics. (2012). *Alcohol consumption* 4364.0.55.001 - Australian Health Survey: First Results, 2011-12

Australian Institute of Health and Welfare. (2012). AIHW analysis of National Mortality Database (NMD). https://www.aihw.gov.au/diabetes-indicators/deaths/

Australian Institute of Health and Welfare. (2013). Diabetes Complications. Retrieved from https://www.aihw.gov.au/diabetes/complications/

Avery, L., Flynn, D., van Wersch, A., Sniehotta, F. F., & Trenell, M. I. (2012). Changing Physical Activity Behavior in Type 2 Diabetes: A systematic review and meta-analysis of behavioral interventions. *Diabetes Care, 35*(12), 2681-2689. doi: 10.2337/dc11-2452

Bahar, A., Makhlough, A., Yousefi, A., Kashi, Z., & Abediankenari, S. (2013). Correlation between prediabetes conditions and microalbuminuria. *Nephro-urology Monthly, 5*(2), 741-744. doi: 10.5812/numonthly.7646

Bantle, J. P., Wylie-Rosett, J., Albright, A. L., Apovian, C. M., Clark, N. G., Franz, M. J., Wheeler, M. L. (2008). Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care, 31 Suppl 1*, S61-78. doi: 31/Supplement_1/S61 [pii] 10.2337/dc08-S061 [doi]

Barnard, K., Sinclair, J. M. A., Lawton, J., Young, A. J., & Holt, R. I. G. (2012). Alcohol-associated risks for young adults with Type 1 diabetes: a narrative review. *Diabetic Medicine, 29*(4), 434-440. doi: 10.1111/j.1464-5491.2012.03579.x

Barnett, A. H., Cradock, S., Fisher, M., Hall, G., Hughes, E., & Middleton, A. (2010). Key considerations around the risks and consequences of hypoglycaemia in people with type 2 diabetes. *International Journal of Clinical Practice, 64*(8), 1121-1129. doi: 10.1111/j.1742-1241.2009.02332.x

Barrou, Z., Lemaire, A., Boddaert, J., & Verny, M. (2008). [Diabetes mellitus and cognition: is there a link?]. *Psychologie & Neuropsychiatrie du Vieillissement, 6*(3), 189-198. doi: 10.1684/pnv.2008.0136

Baruch, Y., & Holtom, B. C. (2008). Survey response rate levels and trends in organizational research. *Human Relations, 61*(8), 1139-1160.

Beck, F., & Peretti-Watel, P. (2002). The Impact of Data Collection Methodology on the Reporting of Illicit Drug Use by Adolescents. *Population-E, 57*(3), 571 - 592.

Bergenstal, R. M., Klonoff, D. C., Garg, S. K., Bode, B. W., Meredith, M., Slover, R. H., . . . Kaufman, F. R. (2013). Threshold-based insulin-pump interruption for reduction of hypoglycemia. *New England Journal of Medicine, 369*(3), 224-232. doi: 10.1056/NEJMoa1303576

Bergman, M. (2013). Pathophysiology of prediabetes and treatment implications for the prevention of type 2 diabetes mellitus. *Endocrine, 43*(3), 504-513. doi: 10.1007/s12020-012-9830-9

Bianchi, C., Miccoli, R., Trombetta, M., Giorgino, F., Frontoni, S., Faloia, E., . . . Del Prato, S. (2013). Elevated 1-hour postload plasma glucose levels identify subjects with normal glucose tolerance but impaired beta-cell function, insulin resistance, and worse cardiovascular risk profile: the GENFIEV study. *Journal of Clinical Endocrinology and Metabolism, 98*(5), 2100-2105. doi: 10.1210/jc.2012-3971

Bloomfield, H. E., Greer, N., Newman, D., MacDonald, R., Carlyle, M., Fitzgerald, P., . . . Wilt, T. J. (2012). *Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes - A Systematic Review of the Evidence*. Washington DC.

Bohme, P., Bertin, E., Cosson, E., & Chevalier, N. (2013). Fear of hypoglycaemia in patients with type 1 diabetes: do patients and diabetologists feel the same way? *Diabetes and Metabolism, 39*(1), 63-70. doi: 10.1016/j.diabet.2012.10.006

Bolli, G. B., & Fanelli, C. G. (1999). Physiology of glucose counterregulation to hypoglycemia. *Endocrinology and Metabolism Clinics of North America, 28*(3), 467-493, v.

Bolli, G. B. (2001). Physiological insulin replacement in type 1 diabetes mellitus. *Experimental and Clinical Endocrinology and Diabetes, 109 Suppl 2*, S317-332. doi: 10.1055/s-2001-18591

Bonds, D. E., Miller, M. E., Bergenstal, R. M., Buse, J. B., Byington, R. P., Cutler, J. A., . . . Sweeney, M. E. (2010). The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *British Medical Journal, 340*, b4909.

Boren, S. A., & Clarke, W. L. (2010). Analytical and clinical performance of blood glucose monitors. *Journal of Diabetes Science & Technology, 4*(1), 84-97.

Boucai, L., Southern, W. N., & Zonszein, J. (2011). Hypoglycemia-associated Mortality Is Not Drug-associated but Linked to Comorbidities. *The American Journal of Medicine, 124*(11), 1028-1035. doi: 10.1016/j.amjmed.2011.07.011

Bowling, A. (2005). Mode of questionnaire administration can have serious effects on data quality. *Journal of Public Health (Oxf), 27*(3), 281-291. doi: 10.1093/pubmed/fdi031

Boyle, P. J., & Zrebiec, J. (2007). Management of diabetes-related hypoglycemia. *Southern Medical Journal, 100*(2), 183-194.

Braithwaite, S. S., Buie, M. M., Thompson, C. L., Baldwin, D. F., Oertel, M. D., Robertson, B. A., & Mehrotra, H. P. (2004). Hospital hypoglycemia: not only treatment but also prevention. *Endocrine Practice, 10 Suppl 2*, 89-99. doi: yhaganyxu61fp4g1 [pii]

Brand-Miller, J. C., Stockmann, K., Atkinson, F., Petocz, P., & Denyer, G. (2009). Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: analysis of a database of more than 1000 foods. *The American Journal of Clinical Nutrition, 89*(1), 97-105. doi: 10.3945/ajcn.2008.26354

Briscoe, V. J., & Davis, S. N. (2006). Hypoglycemia in Type 1 and Type 2 Diabetes: Physiology, Pathophysiology, and Management. *Clinical Diabetes, 24*(3), 115-121. doi: 10.2337/diaclin.24.3.115

Briscoe, V. J., Tate, D. B., & Davis, S. N. (2007). Type 1 diabetes: exercise and hypoglycemia. *Appl Physiol Nutr Metab, 32*(3), 576-582. doi: 10.1139/h07-025

Brodovicz, K. G., Mehta, V., Zhang, Q., Zhao, C., Davies, M. J., Chen, J., . . . Engel, S. S. (2013). Association between hypoglycemia and inpatient mortality and length of hospital stay in hospitalized, insulin-treated patients. *Current Medical Research and Opinion, 29*(2), 101-107. doi: 10.1185/03007995.2012.754744

Brodows, R. G., Williams, C., & Amatruda, J. M. (1984). Treatment of insulin reactions in diabetics. *Journal of the American Medical Association, 252*(24), 3378-3381.

Bruce, D. G., Chisholm, D. J., Storlien, L. H., & Kraegen, E. W. (1988). Physiological importance of deficiency in early prandial insulin secretion in non-insulin-dependent diabetes. *Diabetes, 37*(6), 736-744. doi: 10.2337/diabetes.37.6.736

Cain, E., Ackroyd-Stolarz, S., Alexiadis, P., & Murray, D. (2003). Prehospital hypoglycemia: the safety of not transporting treated patients. *Prehospital Emergency Care, 7*(4), 458-465. doi: S1090312703002193 [pii]

Campbell, M. D., Walker, M., Trenell, M. I., Jakovljevic, D. G., Stevenson, E. J., Bracken, R. M., . . . West, D. J. (2013). Large pre- and postexercise rapid-acting insulin reductions preserve glycemia and prevent early- but not late-onset hypoglycemia in patients with type 1 diabetes. *Diabetes Care, 36*(8), 2217-2224. doi: 10.2337/dc12-2467

Canadian Diabetes Association. (2012). Hypoglycemia. *2012*. Retrieved from http://www.diabetes.ca/ website:

Carroll, M. F., Burge, M. R., & Schade, D. S. (2003). Severe hypoglycemia in adults. *Reviews in Endocrine and Metabolic Disorders, 4*(2), 149-157.

Caumo, A., & Luzi, L. (2004). First-phase insulin secretion: does it exist in real life? Considerations on shape and function. *American Journal Physiology and Endocrine Metabolism, 287*(3), E371-385. doi: 10.1152/ajpendo.00139.2003

Cengiz, E., & Tamborlane, W. V. (2009). A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technology Therapeutics, 11 Suppl 1*, S11-16. doi: 10.1089/dia.2009.0002

Ceriello, A., & Colagiuri, S. (2008). International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. *Diabetic Medicine, 25*(10), 1151-1156. doi: 10.1111/j.1464-5491.2008.02565.x

Ceriello, A., Lansink, M., Rouws, C. H., van Laere, K. M., & Frost, G. S. (2009). Administration of a new diabetes-specific enteral formula results in an improved 24h glucose profile in type 2 diabetic patients. *Diabetes Research and Clinical Practice, 84*(3), 259-266. doi: S0168-8227(09)00073-4 [pii] 10.1016/j.diabres.2009.02.013 [doi]

Chen, T., Xu, F., Su, J. B., Wang, X. Q., Chen, J. F., Wu, G., . . . Wang, X. H. (2013). Glycemic variability in relation to oral disposition index in the subjects with different stages of glucose tolerance. *Diabetology Metabolic Syndrome, 5*(1), 38. doi: 10.1186/1758-5996-5-38

Chimen, M., Kennedy, A., Nirantharakumar, K., Pang, T. T., Andrews, R., & Narendran, P. (2012). What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia, 55*(3), 542-551. doi: 10.1007/s00125-011-2403-2

Cheyne, E. H., Sherwin, R. S., Lunt, M. J., Cavan, D. A., Thomas, P. W., & Kerr, D. (2004). Influence of alcohol on cognitive performance during mild hypoglycaemia; implications for Type 1 diabetes. *Diabetic Medicine, 21*(3), 230-237.

Choi, B. C., & Pak, A. W. (2005). Peer reviewed: A Catalog of Biases in Questionnaires. *Preventing Chronic Disease [electronic resource]*. *2*(1).

Choudhary, P., & Amiel, S. A. (2011). Hypoglycaemia: current management and controversies. *Postgraduate Medical Journal, 87*(1026), 298-306. doi: pgmj.2008.068197 [pii] 10.1136/pgmj.2008.068197 [doi]

Christiansen, M., Bailey, T., Watkins, E., Liljenquist, D., Price, D., Nakamura, K., . . . Peyser, T. (2013). A new-generation continuous glucose monitoring system: improved accuracy and reliability compared with a previous-generation system. *Diabetes Technology Therapy, 15*(10), 881-888. doi: 10.1089/dia.2013.0077

Clarke, S. F., & Foster, J. R. (2012). A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *British Journal of Biomedical Science, 69*(2), 83-93.

Clauson, K. A., Zeng-Treitler, Q., & Kandula, S. (2010). Readability of patient and health care professional targeted dietary supplement leaflets used for diabetes and chronic fatigue syndrome. *Journal of Alternative and Complementary Medicine, 16*(1), 119-124. doi: 10.1089/acm.2008.0611 [doi]

Colagiuri, S., Sandbaek, A., Carstensen, B., Christensen, J., Glumer, C., Lauritzen, T., & Borch-Johnsen, K. (2003). Comparability of venous and capillary glucose measurements in blood. *Diabetic Medicine, 20*(11), 953-956. doi: 1048 [pii]

Colak, A., Akinci, B., Diniz, G., Turkon, H., Ergonen, F., Yalcin, H., & Coker, I. (2013). Postload hyperglycemia is associated with increased subclinical inflammation in patients with prediabetes. *Scandinavian Journal of Clinical and Laboratory Investigation, 73*(5), 422-427. doi: 10.3109/00365513.2013.798870

Consoli, A., & Di Fulvio, P. (2013). Anti-diabetes agents and hypoglycemia. *Italian Journal Cardiology (Rome), 14*(12), 9-14. doi: 10.1714/1375.15276

Cook, C. B., Wellik, K. E., Kongable, G. L., & Shu, J. (2012). Assessing inpatient glycemic control: what are the next steps? *Journal Diabetes Science Technology, 6*(2), 421-427.

Corathers, S. D., Peavie, S., & Salehi, M. (2013). Complications of diabetes therapy. *Endocrinology and Metabolism Clinics of North America, 42*(4), 947-970. doi: 10.1016/j.ecl.2013.06.005

Cowie, C. C., Rust, K. F., Ford, E. S., Eberhardt, M. S., Byrd-Holt, D. D., Li, C., . . . Geiss, L. S. (2009). Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care, 32*(2), 287-294. doi: 10.2337/dc08-1296

Cox, D. J., Irvine, A., Gonder-Frederick, L., Nowacek, G., & Butterfield, J. (1987). Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care, 10*(5), 617-621.

Cox, D. J., Penberthy, J. K., Zrebiec, J., Weinger, K., Aikens, J. E., Frier, B., . . . Clarke, W. (2003). Diabetes and Driving Mishaps: Frequency and correlations from a multinational survey. *Diabetes Care, 26*(8), 2329-2334. doi: 10.2337/diacare.26.8.2329

Craig, M., Twigg, S., Donaghue, K., Cheung, N., Cameron, F., Conn, J., . . . Silink, M. (2011). National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults. *Canberra: Australian Government Department of Health and Ageing*.

Cryer, P. E. (1999). Symptoms of hypoglycemia, thresholds for their occurrence, and hypoglycemia unawareness. *Endocrinology and Metabolism Clinics of North America, 28*(3), 495-500, v-vi.

Cryer, P. E. (2009). Preventing hypoglycaemia: what is the appropriate glucose alert value? *Diabetologia, 52*(1), 35-37. doi: 10.1007/s00125-008-1205-7 [doi]

Cryer, P. E. (2010). Hypoglycemia in type 1 diabetes mellitus. *Endocrinology and Metabolism Clinics of North America, 39*(3), 641-654. doi: S0889-8529(10)00034-4 [pii]
10.1016/j.ecl.2010.05.003 [doi]

Cryer, P. E. (2011). Elimination of Hypoglycemia From the Lives of People Affected by Diabetes. *Diabetes, 60*(1), 24-27. doi: 10.2337/db10-1359

Cryer, P. E. (2012). Severe Hypoglycemia Predicts Mortality in Diabetes. *Diabetes Care, 35*(9), 1814-1816. doi: 10.2337/dc12-0749

Cryer, P. E. (2013). Hypoglycemia-associated autonomic failure in diabetes. *Handbook of Clinical Neurology, 117*, 295-307. doi: 10.1016/b978-0-444-53491-0.00023-7

Cryer, P. E., Axelrod, L., Grossman, A. B., Heller, S. R., Montori, V. M., Seaquist, E. R., & Service, F. J. (2009). Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism, 94*(3), 709-728. doi: 10.1210/jc.2008-1410

Cryer, P. E., Davis, S. N., & Shamoon, H. (2003). Hypoglycemia in Diabetes. *Diabetes Care, 26*(6), 1902-1912. doi: 10.2337/diacare.26.6.1902

Cryer, P. E., Fisher, J. N., & Shamoon, H. (1994). Hypoglycemia. *Diabetes Care, 17*(7), 734-755. doi: 10.2337/diacare.17.7.734

Cubeddu, L. X., & Hoffmann, I. S. (2010). One-hour postload plasma glucose levels, a predictor of additional risk for diabetes: prevalence, mechanisms, and associated cardiovascular and metabolic risk factors in Hispanics. *Metabolic Syndrome and Related Disorders, 8*(5), 395-402. doi: 10.1089/met.2010.0010 [doi]

Cummings, S. M., Savitz, L. A., & Konrad, T. R. (2001). Reported response rates to mailed physician questionnaires. *Health Services Research, 35*(6), 1347-1355.

Cummins, E., Royle, P., Snaith, A., Greene, A., Robertson, L., McIntyre, L., & Waugh, N. (2010). Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technology Assessment, 14*(11), iii-iv, xi-xvi, 1-181. doi: 10.3310/hta14110

d'Emden, M. C., Shaw, J. E., Colman, P. G., Colagiuri, S., Twigg, S. M., Jones, G. R., . . . Cheung, N. W. (2012). The role of HbA1c in the diagnosis of diabetes mellitus in Australia. *Medical Journal of Australia, 197*(4), 220-221.

Davis, R. E., Couper, M. P., Janz, N. K., Caldwell, C. H., & Resnicow, K. (2010). Interviewer effects in public health surveys. *Health Education Research, 25*(1), 14-26. doi: 10.1093/her/cyp046

Davis, T. C., Michielutte, R., Askov, E. N., Williams, M. V., & Weiss, B. D. (1998). Practical Assessment of Adult Literacy in Health Care. *Health Education and Behavior, 25*(5), 613-624. doi: 10.1177/109019819802500508

Davis, W. A., Bruce, D. G., & Davis, T. M. E. (2006). Is Self-Monitoring of Blood Glucose Appropriate for All Type 2 Diabetic Patients?: The Fremantle Diabetes Study. *Diabetes Care, 29*(8), 1764-1770. doi: 10.2337/dc06-0268

DCCT Research Group. (1990). Diabetes Control and Complications Trial (DCCT): Update. *Diabetes Care, 13*(4), 427-433. doi: 10.2337/diacare.13.4.427

de Galan, B. E., Schouwenberg, B. J., Tack, C. J., & Smits, P. (2006). Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *Netherlands Journal of Medicine, 64*(8), 269-279.

Deedwania, P., Patel, K., Fonarow, G. C., Desai, R. V., Zhang, Y., Feller, M. A., . . . Ahmed, A. (2013). Prediabetes is not an independent risk factor for incident heart failure, other cardiovascular events or mortality in older adults: Findings from a population-based cohort study. *International Journal of Cardiology*. doi: 10.1016/j.ijcard.2013.05.038

Del Prato, S., & Tiengo, A. (2001). The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus. *Diabetes/Metabolism Research and Reviews, 17*(3), 164-174. doi: 10.1002/dmrr.198 [pii]

Deusenberry, C. M., Coley, K. C., Korytkowski, M. T., & Donihi, A. C. (2012). Hypoglycemia in Hospitalized Patients Treated with Sulfonylureas.

*Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, n/a-n/a. doi: 10.1002/j.1875-9114.2011.01088.x

Devaraj, S., Hirany, S. V., Burk, R. F., & Jialal, I. (2001). Divergence between LDL oxidative susceptibility and urinary F(2)-isoprostanes as measures of oxidative stress in type 2 diabetes. *Clinical Chemistry, 47*(11), 1974-1979.

Diabetes Australia. (2009). *Treating Hypoglycemia.* www.diabetesaustralia.au

Diabetes Co UK, F. (2013). Is my blood sugar too low? Retrieved from http://www.diabetes.co.uk/forum/threads/type-2-blood-glucose-readings.38474/

Diabetes Education Study Group of the European Association for the Study of Diabetes. (1998). Teaching Letter 2, Hypoglycemia. www.desg.org/

Diabetes New Zealand. (2008). http://www.diabetes.org.nz/living_with_diabetes/

Dobson, K., & Scott, A. (2007). Review of ICU nutrition support practices: implementing the nurse-led enteral feeding algorithm. *Nursing in Critical Care, 12*(3), 114-123. doi: 10.1111/j.1478-5153.2007.00222.x

Donnelly, L. A., Morris, A. D., Frier, B. M., Ellis, J. D., Donnan, P. T., Durrant, R., . . . Leese, G. P. (2005). Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabetic Medicine, 22*(6), 749-755. doi: DME1501 [pii] 10.1111/j.1464-5491.2005.01501.x [doi]

Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P. D., . . . Huang, G. D. (2009). Glucose control and vascular complications in veterans with type 2 diabetes. *New England Journal of Medicine, 360*(2), 129-139. doi: 10.1056/NEJMoa0808431

Edwards, P., Roberts, I., Clarke, M., DiGuiseppi, C., Pratap, S., Wentz, R., & Kwan, I. (2002). Increasing response rates to postal questionnaires: systematic review. *British Medical Journal, 324*(7347), 1183.

Eiland, L., Goldner, W., Drincic, A., & Desouza, C. (2014). Inpatient hypoglycemia: a challenge that must be addressed. *Current Diabetes Reports, 14*(1), 445. doi: 10.1007/s11892-013-0445-1

Elia, M., Ceriello, A., Laube, H., Sinclair, A. J., Engfer, M., & Stratton, R. J. (2005). Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. *Diabetes Care, 28*(9), 2267-2279. doi: 28/9/2267 [pii]

Elliott, J. A., Abdulhadi, N. N., Al-Maniri, A. A., Al-Shafaee, M. A., & Wahlstrom, R. (2013). Diabetes self-management and education of people living with diabetes: a survey in primary health care in Muscat Oman. *PLoS One, 8*(2), e57400. doi: 10.1371/journal.pone.0057400

Elliott, J., Jacques, R. M., Kruger, J., Campbell, M. J., Amiel, S. A., Mansell, P., . . . Heller, S. R. (2014). Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with Type 1 diabetes. *Diabetic Medicine, 31*(7), 847-853. doi: 10.1111/dme.12441

Elliott, M. B., Schafers, S. J., McGill, J. B., & Tobin, G. S. (2012). Prediction and prevention of treatment-related inpatient hypoglycemia. *Journal of Diabetes Science & Technology, 6*(2), 302-309.

Endocrinology Expert Group. (2009). *Endocrinology, Therapeutic Guidelines Ltd*. Melbourne, Victoria, Australia.

Engler, P., Ramsey, S., & Smith, R. (2013). Alcohol use of diabetes patients: the need for assessment and intervention. *Acta Diabetologica, 50*(2), 93-99. doi: 10.1007/s00592-010-0200-x

Evans, C., & Crawford, B. (1999). Patient self-reports in pharmacoeconomic studies. Their use and impact on study validity. *Pharmacoeconomics, 15*(3), 241-256.

Evans, K. M., Kerr, D., & Flanagan, D. E. (2006). Diabetes and alcohol: time for realistic advice based on the evidence. *Practical Diabetes International, 23*(6), 267-272. doi: 10.1002/pdi.974

Fan, H., Pan, Q., Zhang, P., Liu, J., Xu, Y., & Yang, X. (2013). Influence of islet function on typing and prognosis of new-onset diabetes after intensive insulin therapy. *Medical Science Monitor, 19*, 787-793. doi: 10.12659/msm.889099

Fanelli, C. G., Pampanelli, S., Porcellati, F., Bartocci, L., Scionti, L., Rossetti, P., & Bolli, G. B. (2003). Rate of fall of blood glucose and physiological responses of counterregulatory hormones, clinical symptoms and cognitive function to hypoglycaemia in Type I diabetes mellitus in the postprandial state. *Diabetologia, 46*(1), 53-64. doi: 10.1007/s00125-002-0948-9

Feinkohl, I., Aung, P. P., Keller, M., Robertson, C. M., Morling, J. R., McLachlan, S., . . . Price, J. F. (2014). Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the edinburgh type 2 diabetes study. *Diabetes Care, 37*(2), 507-515. doi: 10.2337/dc13-1384

Ferrannini, E., Nannipieri, M., Williams, K., Gonzales, C., Haffner, S. M., & Stern, M. P. (2004). Mode of Onset of Type 2 Diabetes from Normal or Impaired Glucose Tolerance. *Diabetes, 53*(1), 160-165. doi: 10.2337/diabetes.53.1.160

Fleming, M., Brown, R., & Brown, D. (2004). The efficacy of a brief alcohol intervention combined with %CDT feedback in patients being treated for type 2 diabetes and/or hypertension. *Journal of Studies on Alcohol, 65*(5), 631-637.

Ford, E. S., Zhao, G., & Li, C. (2010). Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *Journal of the American College of Cardiology, 55*(13), 1310-1317. doi: 10.1016/j.jacc.2009.10.060

Franz, M. J., Bantle, J. P., Beebe, C. A., Brunzell, J. D., Chiasson, J. L., Garg, A., . . . Wheeler, M. (2003). Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care, 26 Suppl 1*, S51-61.

Friedman, D. B., & Hoffman-Goetz, L. (2006). A systematic review of readability and comprehension instruments used for print and web-based cancer information. *Health Education and Behavior, 33*(3), 352-373. doi: 33/3/352 [pii] 10.1177/1090198105277329 [doi]

Frier, B. M. (2009). Defining hypoglycaemia: what level has clinical relevance? *Diabetologia, 52*(1), 31-34. doi: 10.1007/s00125-008-1209-3 [doi]

Galassetti, P., Tate, D., Neill, R. A., Richardson, A., Leu, S. Y., & Davis, S. N. (2006). Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. *Am J Physiol Endocrinol Metab, 290*(6), E1109-1117. doi: 10.1152/ajpendo.00244.2005

Garber, A. J., Ligthelm, R., Christiansen, J. S., & Liebl, A. (2007). Premixed insulin treatment for type 2 diabetes: analogue or human? *Diabetes Obesity & Metabolism, 9*(5), 630-639. doi: 10.1111/j.1463-1326.2006.00654.x

Garg, S. K., Brazg, R. L., Bailey, T. S., Buckingham, B. A., Slover, R. H., Klonoff, D. C., . . . Kaufman, F. R. (2014). Hypoglycemia Begets Hypoglycemia: The Order Effect in the ASPIRE In-Clinic Study. *Diabetes Technology & Therapeutics*. doi: 10.1089/dia.2013.0219

Gaston, S. F. (1992). Outcomes of hypoglycemia treated by standardized protocol in a community hospital. *Diabetes Educator, 18*(6), 491-494.

Geddes, J., Schopman, J. E., Zammitt, N. N., & Frier, B. M. (2008). Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. *Diabetic Medicine, 25*(4), 501-504. doi: DME2413 [pii] 10.1111/j.1464-5491.2008.02413.x [doi]

Genuth, S. (2008). The UKPDS and its global impact. *Diabetic Medicine, 25 Suppl 2*, 57-62. doi: 10.1111/j.1464-5491.2008.02504.x

Gerstein, H. C., Santaguida, P., Raina, P., Morrison, K. M., Balion, C., Hunt, D., . . . Booker, L. (2007). Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: A systematic overview and meta-analysis of prospective studies. *Diabetes Research and Clinical Practice, 78*(3), 305-312. doi: http://dx.doi.org/10.1016/j.diabres.2007.05.004

Gill, G. V., Woodward, A., Casson, I. F., & Weston, P. J. (2009). Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes--the 'dead in bed' syndrome revisited. *Diabetologia, 52*(1), 42-45. doi: 10.1007/s00125-008-1177-7

Glasgow, A. M., Tynan, D., Schwartz, R., Hicks, J. M., Turek, J., Driscol, C., . . . Getson, P. R. (1991). Alcohol and drug use in teenagers with diabetes mellitus. *Journal of Adolescent Health, 12*(1), 11-14.

Goldstein, D. E., Little, R. R., Lorenz, R. A., Malone, J. I., Nathan, D. M., & Peterson, C. M. (2004). Tests of glycemia in diabetes. *Diabetes Care, 27 Suppl 1*, S91-93.

Gonder-Frederick, L. A., Vajda, K. A., Schmidt, K. M., Cox, D. J., Devries, J. H., Erol, O., . . . Snoek, F. J. (2013). Examining the Behaviour subscale of the Hypoglycaemia Fear Survey: an international study. *Diabetic Medicine, 30*(5), 603-609. doi: 10.1111/dme.12129

Goodall, I. (2005). HbA1c standardisation destination--global IFCC Standardisation. How, why, where and when--a tortuous pathway from kit manufacturers, via inter-laboratory lyophilized and whole blood comparisons to designated national comparison schemes. *Clinical Biochemical Reviews, 26*(1), 5-19.

Guelfi, K. J., Jones, T. W., & Fournier, P. A. (2007). New insights into managing the risk of hypoglycaemia associated with intermittent high-intensity exercise in individuals with type 1 diabetes mellitus: implications for existing guidelines. *Sports Medicine, 37*(11), 937-946.

Guelfi, K. J., Ratnam, N., Smythe, G. A., Jones, T. W., & Fournier, P. A. (2007). Effect of intermittent high-intensity compared with continuous moderate

exercise on glucose production and utilization in individuals with type 1 diabetes. *Am J Physiol Endocrinol Metab, 292*(3), E865-870. doi: 10.1152/ajpendo.00533.2006

Guettier, J. M., & Gorden, P. (2006). Hypoglycemia. *Endocrinology and Metabolism Clinics of North America, 35*(4), 753-766, viii-ix. doi: 10.1016/j.ecl.2006.09.005

Gunning, R. R., & Garber, A. J. (1978). Bioactivity of instant glucose. Failure of absorption through oral mucosa. *Journalof the American Medical Association, 240*(15), 1611-1612.

Haffner, S. M., Mykkanen, L., Festa, A., Burke, J. P., & Stern, M. P. (2000). Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation, 101*(9), 975-980.

Hagelberg, A., Ivert, T., Efendic, S., Ohrvik, J., & Anderson, R. E. (2008). Insulin glargine improves glycaemic control after coronary surgery in patients with diabetes or pre-diabetes. *Scandinavian Cardiovascular Journal, 42*(1), 71-76. doi: 10.1080/14017430701721756

Halimi, S. (2010). Acute consequences of hypoglycaemia in diabetic patients. *Diabetes and Metabolism, 36 Suppl 3*, S75-83. doi: 10.1016/s1262-3636(10)70471-7

Hanas, R., & John, G. (2010). 2010 consensus statement on the worldwide standardization of the hemoglobin A(1c) measurement. *Diabetes Research and Clinical Practice, 90*(2), 228-230. doi: 10.1016/j.diabres.2010.05.011

Hanefeld, M., & Bramlage, P. (2013). Insulin use early in the course of type 2 diabetes mellitus: the ORIGIN trial. *Current Diabetes Reports, 13*(3), 342-349. doi: 10.1007/s11892-013-0366-z

Hanley, A. J., Wagenknecht, L. E., Norris, J. M., Bryer-Ash, M., Chen, Y. I., Anderson, A. M., . . . Haffner, S. M. (2009). Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family study. *Diabetologia, 52*(10), 2079-2086. doi: 10.1007/s00125-009-1464-y

Harada, N., Fukushima, M., Toyoda, K., Mitsui, R., Izuka, T., Taniguchi, A., . . . Inagaki, N. (2008). Factors responsible for elevation of 1-h postchallenge

plasma glucose levels in Japanese men. *Diabetes Research and Clinical Practice, 81*(3), 284-289. doi: 10.1016/j.diabres.2008.04.011

Harjutsalo V, Forsblom C, & P, G. (2011). Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *British Medical Journal, 343*. doi: 10.1136/bmj.d5364

Harper, J. (2007). Glucose control in the intensive care unit: how it is done. *Proceedings of the Nutrition Society, 66*(3), 362-366. doi: 10.1017/s0029665107005629

Haus, J. M., Solomon, T. P. J., Marchetti, C. M., Edmison, J. M., González, F., & Kirwan, J. P. (2010). Free Fatty Acid-Induced Hepatic Insulin Resistance is Attenuated Following Lifestyle Intervention in Obese Individuals with Impaired Glucose Tolerance. *Journal of Clinical Endocrinology & Metabolism, 95*(1), 323-327. doi: 10.1210/jc.2009-1101

Hawkshead, J., & Krousel-Wood, M. A. (2007). Techniques for measuring medication adherence in hypertensive patients in outpatient settings. *Disease Management & Health Outcomes, 15*(2), 109-118.

Hejlesen, O. K., Andreassen, S., Cavan, D. A., & Hovorka, R. (1996). Analysing the hypoglycaemic counter-regulation: a clinically relevant phenomenon? *Computer Methods and Programs in Biomedicine, 50*(3), 231-240.

Heller, S. (2002). Reducing hypoglycaemia with insulin analogues. *International Journal of Obesity and Related Metabolic Disorders, 26 Suppl 3*, S31-36. doi: 10.1038/sj.ijo.0802175

Heller, S. R., Amiel, S. A., & Mansell, P. (1999). Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. U.K. Lispro Study Group. *Diabetes Care, 22*(10), 1607-1611.

Hermanns, N., Plate, M., Kulzer, B., Fischer, B., Linn, T., Bretzel, R., & Haak, T. (2008). Effect of experimentally induced hypoglycemia and different insulin levels on feelings of hunger in type 1 diabetic patients. *Experimental and Clinical Endocrinology and Diabetes, 116*(5), 255-261. doi: 10.1055/s-2007-993143

Hermanns, N., Kulzer, B., Kubiak, T., Krichbaum, M., & Haak, T. (2007). The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients with type 1 diabetes. *Diabetes/Metabolism Research and Reviews, 23*(7), 528-538. doi: 10.1002/dmrr.710

Hermanns, N., Kulzer, B., Krichbaum, M., Kubiak, T., & Haak, T. (2010). Long-term effect of an education program (HyPOS) on the incidence of severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care, 33*(3), e36. doi: 10.2337/dc09-1656

Hermansen, K., Fontaine, P., Kukolja, K. K., Peterkova, V., Leth, G., & Gall, M. A. (2004). Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia, 47*(4), 622-629. doi: 10.1007/s00125-004-1365-z

Hirsch, I. B. (2005). Insulin analogues. *New England Journal of Medicine, 352*(2), 174-183. doi: 10.1056/NEJMra040832

Hofman, Z., Lansink, M., Rouws, C., van Drunen, J. D. E., & Kuipers, H. (2007). Diabetes specific tube feed results in improved glycaemic and triglyceridaemic control during 6 h continuous feeding in diabetes patients. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, 2*(2), 44-50. doi: http://dx.doi.org/10.1016/j.eclnm.2007.02.001

Hong, J., Zhang, Y. F., Gu, W. Q., Zhang, Y. W., Su, Y. X., Chi, Z. N., . . . Ning, G. (2008). Insulin sensitivity and first-phase insulin secretion in obese Chinese with hyperglycemia in 30 and/or 60 min during glucose tolerance tests. *Endocrine, 34*(1-3), 75-80. doi: 10.1007/s12020-008-9106-6 [doi]

Hopper, I., Billah, B., Skiba, M., & Krum, H. (2011). Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials. *Eur J Cardiovascular Prevention and Rehabilitation, 18*(6), 813-823. doi: 10.1177/1741826711421687

Hsieh, A., & Twigg, S. M. (2014). The enigma of the dead-in-bed syndrome: Challenges in predicting and preventing this devastating complication of type 1 diabetes. *Journal of Diabetes and Its Complications*. doi: 10.1016/j.jdiacomp.2014.04.005

Iacovidou, A., & Hakim, N. (2013). Recent advances in pancreatic transplantation. *Experimental and Clinical Transplantation, 11*(6), 471-474.

Idris, I., Pillai, A., Fernando, D. J., Thomson, G., & Tate, H. (2013). Responders to insulin therapy at 18 months in adults with newly diagnosed diabetes: which insulin regimen? *Diabetic Medicine, 30*(3), e95-100. doi: 10.1111/dme.12096

International Diabetes Federation. (2013). IDF Diabetes Atlas 6th edition. Retrieved from http://www.idf.org/sites/default/files/5E_IDFAtlasPoster_2012_EN.pdf

Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., . . . Matthews, D. R. (2012). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care, 35*(6), 1364-1379. doi: 10.2337/dc12-0413

Iscoe, K. E., & Riddell, M. C. (2011). Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. *Diabetic Medicine, 28*(7), 824-832. doi: 10.1111/j.1464-5491.2011.03274.

Jaser, S. S., Yates, H., Dumser, S., & Whittemore, R. (2011). Risky business: risk behaviors in adolescents with type 1 diabetes. *The Diabetes Educator, 37*(6), 756-764. doi: 10.1177/0145721711422610

Jayawardena, R., Ranasinghe, P., Byrne, N. M., Soares, M. J., Katulanda, P., & Hills, A. P. (2012). Prevalence and trends of the diabetes epidemic in South Asia: a systematic review and meta-analysis. *BMC Public Health, 12*, 380. doi: 10.1186/1471-2458-12-380

Jensen, V. F., Bogh, I. B., & Lykkesfeldt, J. (2014). Effect of insulin-induced hypoglycaemia on the CNS: Evidence from experimental studies. *Journal of Neuroendocrinology*. doi: 10.1111/jne.12133

Jones, E., Sinclair, J. M., Holt, R. I., & Barnard, K. D. (2013). Social networking and understanding alcohol-associated risk for people with type 1 diabetes: friend or foe? *Diabetes Technology & Therapeutics, 15*(4), 308-314. doi: 10.1089/dia.2012.0327

Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature, 444*(7121), 840-846.

Kang, Y., Lu, J. M., Sun, J. F., Li, C. L., Wang, X. L., Zhang, X. Q., . . . Mu, Y. M. (2009). [Characteristics of glycemic excursion in different subtypes of impaired glucose intolerance]. *Zhonghua Yi Xue Za Zhi, 89*(10), 669-672.

Karter, A. J., Parker, M. M., Moffet, H. H., Spence, M. M., Chan, J., Ettner, S. L., & Selby, J. V. (2006). Longitudinal Study of New and Prevalent Use of Self-Monitoring of Blood Glucose. *Diabetes Care, 29*(8), 1757-1763. doi: 10.2337/dc06-2073

Kedia, N. (2011). Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach. *Diabetes, Metabolic Syndrome And Obesity: Targets And Therapy, 4*, 337.

Kelley, K., Clark, B., Brown, V., & Sitzia, J. (2003). Good practice in the conduct and reporting of survey research. *International Journal for Quality in Health Care, 15*(3), 261-266. doi: 10.1093/intqhc/mzg031

Kerry, C., Mitchell, S., Sharma, S., Scott, A., & Rayman, G. (2013). Diurnal temporal patterns of hypoglycaemia in hospitalized people with diabetes may reveal potentially correctable factors. *Diabetic Medicine, 30*(12), 1403-1406. doi: 10.1111/dme.12256

Kim, J. Y., Goran, M. I., Toledo-Corral, C. M., Weigensberg, M. J., Choi, M., & Shaibi, G. Q. (2013). One-hour glucose during an oral glucose challenge prospectively predicts beta-cell deterioration and prediabetes in obese Hispanic youth. *Diabetes Care, 36*(6), 1681-1686. doi: 10.2337/dc12-1861

Kim, Y., Rajan, K. B., Sims, S. A., Wroblewski, K. E., & Reutrakul, S. (2014). Impact of glycemic variability and hypoglycemia on adverse hospital outcomes in non-critically ill patients. *Diabetes Research and Clinical Practice*. doi: 10.1016/j.diabres.2013.11.026

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., & Nathan, D. M. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine, 346*(6), 393-403. doi: 10.1056/NEJMoa012512

Krinsley, J. S., & Grover, A. (2007). Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Critical Care Medicine, 35*(10), 2262-2267. doi: 10.1097/01.ccm.0000282073.98414.4b

Krnacova, V., Kubena, A., Macek, K., Bezdek, M., Smahelova, A., & Vlcek, J. (2012). Severe hypoglycaemia requiring the assistance of emergency medical services--frequency, causes and symptoms. *Biomedical papers of the Medical Faculty of the University Palacky, 156*(3), 271-277. doi: 10.5507/bp.2012.037

Kucera, M. L., & Graham, J. P. (1998). Insulin lispro, a new insulin analog. *Pharmacotherapy, 18*(3), 526-538.

Kuzuya, T., Nakagawa, S., Satoh, J., Kanazawa, Y., Iwamoto, Y., Kobayashi, M., . . . Kadowaki, T. (2002). Report of the Committee on the classification and

diagnostic criteria of diabetes mellitus. *Diabetes Research and Clinical Practice, 55*(1), 65-85.

Langendam, M., Luijf, Y. M., Hooft, L., Devries, J. H., Mudde, A. H., & Scholten, R. J. (2012). Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews, 1*, CD008101. doi: 10.1002/14651858.CD008101.pub2

Lawton, J., Rankin, D., Cooke, D. D., Elliott, J., Amiel, S., & Heller, S. (2013). Self-treating hypoglycaemia: a longitudinal qualitative investigation of the experiences and views of people with Type 1 diabetes. *Diabetic Medicine, 30*(2), 209-215. doi: 10.1111/dme.12007

Leckie, A. M., Graham, M. K., Grant, J. B., Ritchie, P. J., & Frier, B. M. (2005). Frequency, Severity, and Morbidity of Hypoglycemia Occurring in the Workplace in People With Insulin-Treated Diabetes. *Diabetes Care, 28*(6), 1333-1338. doi: 10.2337/diacare.28.6.1333

Leiter L, Y. J., Chiasson J, Harris S, Kleinstiver P, Sauriol L (2005). Assessment of the Impact of Fear of Hypoglycemic Episodes on Glycemic and Hypoglycemia Management *Canadian Journal Of Diabetes, 29*(3), 186 - 192.

Levitzky, Y. S., Pencina, M. J., D'Agostino, R. B., Meigs, J. B., Murabito, J. M., Vasan, R. S., & Fox, C. S. (2008). Impact of Impaired Fasting Glucose on Cardiovascular Disease: The Framingham Heart Study. *Journal of the American College of Cardiology, 51*(3), 264-270. doi: http://dx.doi.org/10.1016/j.jacc.2007.09.038

Ley, P., & Florio, T. (1996). The use of readability formulas in health care. *Psychology, Health & Medicine, 1*(1), 7-28.

Lleva, R. R., & Inzucchi, S. E. (2011). Hospital management of hyperglycemia. *Current Opinion in Endocrinology, Diabetes, and Obesity, 18*(2), 110-118. doi: 10.1097/MED.0b013e3283447a6d

Lloyd, D. A., & Powell-Tuck, J. (2004). Artificial nutrition: principles and practice of enteral feeding. *Clinics in Colon and Rectal Surgery, 17*(2), 107-118. doi: 10.1055/s-2004-828657

Lu, J., Zang, J., & Li, H. (2013). Impact of Three Oral Antidiabetic Drugs on Markers of beta-Cell Function in Patients with Type 2 Diabetes: A Meta-Analysis. *PLoS One, 8*(10), e76713. doi: 10.1371/journal.pone.0076713

Luo, P., Cheng, Q., Chen, B., Li, Y., Wu, J., Zhang, X., . . . Lv, X. (2013). Hypoglycemia and Blood Glucose Fluctuations in the Application of a Sensor-Augmented Insulin Pump. *Diabetes Technology & Therapeutics,* doi: 10.1089/dia.2013.0078

Ly, T. T., Nicholas, J. A., Retterath, A., Lim, E. M., Davis, E. A., & Jones, T. W. (2013). Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *Journal of the American Medical Association, 310*(12), 1240-1247. doi: 10.1001/jama.2013.277818

McIntyre, H. D., Knight, B. A., Harvey, D. M., Noud, M. N., Hagger, V. L., & Gilshenan, K. S. (2010). Dose adjustment for normal eating (DAFNE) - an audit of outcomes in Australia. *Medical Journal of Australia, 192*(11), 637-640.

MacLeod, S. F., Terada, T., Chahal, B. S., & Boule, N. G. (2013). Exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes: a meta-analysis of studies using continuous glucose monitoring. *Diabetes/Metabolism Research and Reviews, 29*(8), 593-603. doi: 10.1002/dmrr.2461

Madhu, S. V., Muduli, S. K., & Avasthi, R. (2013). Abnormal glycemic profiles by CGMS in obese first-degree relatives of type 2 diabetes mellitus patients. *Diabetes Technology & Therapeutics, 15*(6), 461-465. doi: 10.1089/dia.2012.0333

Magee, M. C. (2012). Improving IV insulin administration in a community hospital. *Journal of Visualized Experiments,* (64), e3705. doi: 10.3791/3705

Magrys, S. A., & Olmstead, M. C. (2014). Alcohol intoxication alters cognitive skills mediated by frontal and temporal brain regions. *Brain and Cognition, 85C,* 271-276. doi: 10.1016/j.bandc.2013.12.010

Mandel, A. L., & Breslin, P. A. (2012). High endogenous salivary amylase activity is associated with improved glycemic homeostasis following starch ingestion in adults. *Journal of Nutrition, 142*(5), 853-858. doi: 10.3945/jn.111.156984

Mann, J. I., De Leeuw, I., Hermansen, K., Karamanos, B., Karlstrom, B., Katsilambros, N., . . . Vessby, B. (2004). Evidence-based nutritional

approaches to the treatment and prevention of diabetes mellitus. *Nutrition, Metabolism, And Cardiovascular Diseases, 14*(6), 373-394.

Manterola, C., Munoz, S., Grande, L., & Bustos, L. (2002). Initial validation of a questionnaire for detecting gastroesophageal reflux disease in epidemiological settings. *Journal of Clinical Epidemiology, 55*(10), 1041-1045. doi: S0895435602004547 [pii]

Marbury, T. C., Schwartz, S., Rosenberg, M. A., Jariwala, N., Becker, R. H., & Johnston, P. S. (2008). A pilot study to examine the feasibility of insulin glargine in subjects with impaired fasting glucose, impaired glucose tolerance or new-onset type 2 diabetes. *Experimental and Clinical Endocrinology and Diabetes, 116*(5), 282-288. doi: 10.1055/s-2007-1022521

Marchesini, G., Veronese, G., Forlani, G., Forlani, G., Ricciardi, L. M., & Fabbri, A. (2014). The management of severe hypoglycemia by the emergency system: The HYPOTHESIS study. *Nutr Metab Cardiovasc Dis*. doi: 10.1016/j.numecd.2014.05.012

Martínez-Aguayo, A., Araneda, J. C., Fernandez, D., Gleisner, A., Perez, V., & Codner, E. (2007). Tobacco, alcohol, and illicit drug use in adolescents with diabetes mellitus*. *Pediatric Diabetes, 8*(5), 265-271. doi: 10.1111/j.1399-5448.2007.00307.x

Mason, C. C., Hanson, R. L., & Knowler, W. C. (2007). Progression to type 2 diabetes characterized by moderate then rapid glucose increases. *Diabetes, 56*(8), 2054-2061. doi: 10.2337/db07-0053

Maynard, G. A., Huynh, M. P., & Renvall, M. (2008). Iatrogenic Inpatient Hypoglycemia: Risk Factors, Treatment, and Prevention. *Diabetes Spectrum, 21*(4), 241-247. doi: 10.2337/diaspect.21.4.241

Mazer, M., & Chen, E. (2009). Is subcutaneous administration of rapid-acting insulin as effective as intravenous insulin for treating diabetic ketoacidosis? *Annals of Emergency Medicine, 53*(2), 259-263.

McAndrew, L., Schneider, S. H., Burns, E., & Leventhal, H. (2007). Does patient blood glucose monitoring improve diabetes control? A systematic review of the literature. *The Diabetes Educator, 33*(6), 991-1010.

McCall, A. L., & Farhy, L. S. (2013). Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. *Minerva Endocrinologica, 38*(2), 145-163.

McCormack, P. L. (2014). Exenatide Twice Daily: A Review of Its Use in the Management of Patients with Type 2 Diabetes Mellitus. *Drugs*. doi: 10.1007/s40265-013-0172-6

McCoy, R. G., Van Houten, H. K., Ziegenfuss, J. Y., Shah, N. D., Wermers, R. A., & Smith, S. A. (2013). Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. *Endocrine Practice*, *19*(5), 792-799. doi: 10.4158/ep12382.or

McCrimmon, R. (2009). Glucose sensing during hypoglycemia: lessons from the lab. *Diabetes Care*, *32*(8), 1357-1363. doi: 10.2337/dc09-0123

McCrimmon, R. J., Shaw, M., Fan, X., Cheng, H., Ding, Y., Vella, M. C., . . . Sherwin, R. S. (2008). Key role for AMP-activated protein kinase in the ventromedial hypothalamus in regulating counterregulatory hormone responses to acute hypoglycemia. *Diabetes*, *57*(2), 444-450. doi: 10.2337/db07-0837

McKeage, K., & Goa, K. L. (2001). Insulin glargine: a review of its therapeutic use as a long-acting agent for the management of type 1 and 2 diabetes mellitus. *Drugs*, *61*(11), 1599-1624.

Medical Update Co. UK. (2013). Hypoglycemia. Retrieved from http://medicalupdate.co.uk/files/2013_Feb_DiabetesClapham-Web_download.pdf website:

Meisinger, C., Wölke, G., Brasche, S., Strube, G., & Heinrich, J. (2006). Postload Plasma Glucose and 30-Year Mortality Among Nondiabetic Middle-Aged Men From the General Population: The ERFORT Study. *Annals of Epidemiology*, *16*(7), 534-539. doi: 10.1016/j.annepidem.2005.10.008

Melanson, K. J., Westerterp-Plantenga, M. S., Saris, W. H., Smith, F. J., & Campfield, L. A. (1999). Blood glucose patterns and appetite in time-blinded humans: carbohydrate versus fat. *American Journal of Physiology*, *277*(2 Pt 2), R337-345.

Mellbin, L. G., Ryden, L., Riddle, M. C., Probstfield, J., Rosenstock, J., Diaz, R., . . . Gerstein, H. C. (2013). Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *European Heart Journal*, *34*(40), 3137-3144. doi: 10.1093/eurheartj/eht332

Mendez, C. E., Mok, K. T., Ata, A., Tanenberg, R. J., Calles-Escandon, J., & Umpierrez, G. E. (2013). Increased glycemic variability is independently

associated with length of stay and mortality in noncritically ill hospitalized patients. *Diabetes Care, 36*(12), 4091-4097. doi: 10.2337/dc12-2430

Mike, H (2012). One guy's perspectives on portable glucose options. Life with diabetes. Retrieved from www.diabetesmine.com website.

Miller-Hagan, R. S., & Janas, B. G. (2002). Drinking Perceptions and Management Strategies of College Students With Diabetes. *The Diabetes Educator, 28*(2), 233-244. doi: 10.1177/014572170202800209

Miller, C. D., Phillips, L. S., Ziemer, D. C., Gallina, D. L., Cook, C. B., & El-Kebbi, I. M. (2001). Hypoglycemia in patients with type 2 diabetes mellitus. *Archives of Internal Medicine, 161*(13), 1653-1659.

Milman, S., & Crandall, J. P. (2011). Mechanisms of vascular complications in prediabetes. *Medical Clinics of North America, 95*(2), 309-325, vii. doi: 10.1016/j.mcna.2010.11.004

Minges, K. E., Zimmet, P., Magliano, D. J., Dunstan, D. W., Brown, A., & Shaw, J. E. (2011). Diabetes prevalence and determinants in Indigenous Australian populations: A systematic review. *Diabetes Research and Clinical Practice, 93*(2), 139-149. doi: 10.1016/j.diabres.2011.06.012

Moghissi, E. S., Korytkowski, M. T., DiNardo, M., Einhorn, D., Hellman, R., Hirsch, I. B., . . . Umpierrez, G. E. (2009). American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. *Diabetes Care, 32*(6), 1119-1131. doi: 10.2337/dc09-9029

Mori, Y., Ohta, T., Tanaka, T., Morohoshi, Y., Matsuura, K., Yokoyama, J., & Utsunomiya, K. (2011). Effects of a low-carbohydrate diabetes-specific formula in type 2 diabetic patients during tube feeding evaluated by continuous glucose monitoring. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, 6*(2), e68-e73. doi: http://dx.doi.org/10.1016/j.eclnm.2011.01.010

Myers, V., Boyer, B., Herbert, J., Barakat, L., & Scheiner, G. (2007). Fear of Hypoglycemia and Self Reported Posttraumatic Stress in Adults with Type I Diabetes Treated by Intensive Regimens. *Journal of Clinical Psychology in Medical Settings, 14*(1), 11-21. doi: 10.1007/s10880-007-9051-1

Nair, K. M., Levine, M., Lohfeld, L. H., & Gerstein, H. C. (2007). I take what I think works for me": a qualitative study to explore patient perception of diabetes

treatment benefits and risks. *The Canadian Journal of Clinical Pharmacology, 14*(2), e251-e259.

Nathan, D. M. (2014). The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care, 37*(1), 9-16. doi: 10.2337/dc13-2112

Nathan, D. M., Davidson, M. B., DeFronzo, R. A., Heine, R. J., Henry, R. R., Pratley, R., & Zinman, B. (2007). Impaired Fasting Glucose and Impaired Glucose Tolerance. *Diabetes Care, 30*(3), 753-759. doi: 10.2337/dc07-9920

National Health and Medical Research Council. (2008). *Alcohol and Health in Australia*. http://www.nhmrc.gov.au/your-health/alcohol-guidelines/alcohol-and-health-australia.

Ng, J. M., Cox, H., Longbotham, D., Kilpatrick, E. S., Atkin, S. L., & Allan, B. J. (2009). Hypoglycemia and Clinical Outcomes in Patients With Diabetes Hospitalized in the General Ward. *Diabetes Care, 32*(12), e151. doi: 10.2337/dc09-1341

O'Toole, B. I., Catts, S. V., Outram, S., Pierse, K. R., & Cockburn, J. (2009). The Physical and Mental Health of Australian Vietnam Veterans 3 Decades After the War and Its Relation to Military Service, Combat, and Post-Traumatic Stress Disorder. *American Journal of Epidemiology, 170*(3), 318-330. doi: 10.1093/aje/kwp146

Official Statistics of Finland (OSF). (2012). *Causes of death [e-publication]*. http://www.stat.fi/til/ksyyt/2011/ksyyt_2011_2012-12-21_tie_001_en.html.

Okamoto, K., Ohsuka, K., Shiraishi, T., Hukazawa, E., Wakasugi, S., & Furuta, K. (2002). Comparability of epidemiological information between self- and interviewer-administered questionnaires. *Journal of Clinical Epidemiology, 55*(5), 505-511.

Papargyri, P., Ojeda Rodriguez, S., Corrales Hernandez, J. J., Mories Alvarez, M. T., Recio Cordova, J. M., Delgado Gomez, M., . . . Miralles Garcia, J. M. (2013). An observational 7-year study of continuous subcutaneous insulin infusion for the treatment of type 1 diabetes mellitus. *Endocrinología y Nutrición,* doi: 10.1016/j.endonu.2013.09.003

Paranjape, S. A., Chan, O., Zhu, W., Horblitt, A. M., McNay, E. C., Cresswell, J. A., . . . Sherwin, R. S. (2010). Influence of insulin in the ventromedial

hypothalamus on pancreatic glucagon secretion in vivo. *Diabetes, 59*(6), 1521-1527. doi: 10.2337/db10-0014

Parfitt, V. J., & Bhake, R. (2012). An analysis of all cases of severe hypoglycaemia presenting to a major teaching hospital over one year. *Diabetic Medicine, 29*, 131.

Park, Y. W., Chang, Y., Sung, K. C., Ryu, S., Sung, E., & Kim, W. S. (2006). The sequential changes in the fasting plasma glucose levels within normoglycemic range predict type 2 diabetes in healthy, young men. *Diabetes Research and Clinical Practice, 73*(3), 329-335. doi: 10.1016/j.diabres.2006.02.006

Patterson, C. C., Dahlquist, G., Harjutsalo, V., Joner, G., Feltbower, R. G., Svensson, J., . . . Soltesz, G. (2007). Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. *Diabetologia, 50*(12), 2439-2442. doi: 10.1007/s00125-007-0824-8

Pedersen-Bjergaard, U., Reubsaet, J. L., Nielsen, S. L., Pedersen-Bjergaard, S., Perrild, H., Pramming, S., & Thorsteinsson, B. (2005). Psychoactive drugs, alcohol, and severe hypoglycemia in insulin-treated diabetes: analysis of 141 cases. *American Journal of Medicine, 118*(3), 307-310. doi: 10.1016/j.amjmed.2004.07.054

Perry, L., & McConney, A. (2010). Does the SES of the school matter? An examination of socioeconomic status and student achievement using PISA 2003. *The Teachers College Record, 112*(4), 7-8.

Persenius, M. W., Hall-Lord, M. L., Baath, C., & Larsson, B. W. (2008). Assessment and documentation of patients' nutritional status: perceptions of registered nurses and their chief nurses. *Journal of Clinical Nursing, 17*(16), 2125-2136. doi: 10.1111/j.1365-2702.2007.02202.x

Pietraszek, A., Gregersen, S., & Hermansen, K. (2010). Alcohol and type 2 diabetes. A review. *Nutrition, Metabolism, and Cardiovascular Diseases, 20*(5), 366-375.

Plosker, G. L. (2014). Sitagliptin: A Review of Its Use in Patients with Type 2 Diabetes Mellitus. *Drugs*. doi: 10.1007/s40265-013-0169-1

Plougmann, S., Hejlesen, O., Turner, B., Kerr, D., & Cavan, D. (2003). The effect of alcohol on blood glucose in Type 1 diabetes--metabolic modelling and

integration in a decision support system. *International Journal of Medical Informatics, 70*(2-3), 337-344.

Ramchandani, N., Cantey-Kiser, J. M., Alter, C. A., Brink, S. J., Yeager, S. D., Tamborlane, W. V., & Chipkin, S. R. (2000). Self-Reported Factors That Affect Glycemic Control in College Students With Type 1 Diabetes. *The Diabetes Educator, 26*(4), 656-666. doi: 10.1177/014572170002600413

Rana, O. A., Byrne, C. D., & Greaves, K. (2014). Intensive glucose control and hypoglycaemia: a new cardiovascular risk factor? *Heart, 100*(1), 21-27. doi: 10.1136/heartjnl-2013-303871

Rasmussen, B. M., Orskov, L., Schmitz, O., & Hermansen, K. (2001). Alcohol and glucose counterregulation during acute insulin-induced hypoglycemia in type 2 diabetic subjects. *Metabolism: Clinical and Experimental, 50*(4), 451-457. doi: 10.1053/meta.2001.21697

Rattray, J., & Jones, M. C. (2007). Essential elements of questionnaire design and development. *Journal of Clinical Nursing, 16*(2), 234-243.

Richardson, T., Weiss, M., Thomas, P., & Kerr, D. (2005). Day After the Night Before: Influence of evening alcohol on risk of hypoglycemia in patients with type 1 diabetes. *Diabetes Care, 28*(7), 1801-1802.

Riddle, M. C., Rosenstock, J., Vlajnic, A., & Gao, L. (2013). Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes, Obesity & Metabolism,* doi: 10.1111/dom.12225

Roberts, C. (2008). Modelling patterns of agreement for nominal scales. *Statistics in Medicine, 27*(6), 810-830. doi: 10.1002/sim.2945

Roberts, K., & Smith, A. (2003). Outcome of diabetic patients treated in the prehospital arena after a hypoglycaemic episode, and an exploration of treat and release protocols: a review of the literature. *Emergency Medicine Journal, 20*(3), 274-276.

Rodin, J., Wack, J., Ferrannini, E., & DeFronzo, R. A. (1985). Effect of insulin and glucose on feeding behavior. *Metabolism: Clinical and Experimental, 34*(9), 826-831.

Rotella, C., Pala, L., & Mannucci, E. (2013). Role of Insulin in the Type 2 Diabetes Therapy: Past, Present and Future. *International Journal of Endocrinology* and *Metabolism, 11*(3), 137-144. doi: 10.5812/ijem.7551

Rubin, R. R., & Peyrot, M. (2001). Psychological issues and treatments for people with diabetes. *Journal of Clinical Psychology, 57*(4), 457-478.

Rusavy, Z., Lacigova, S., & Kvapil, M. (2013). [What has the largest study in the history of diabetology brought us?]. *Vnitrni Lekarstvi, 59*(3), 160-164.

Saloranta, C., Guitard, C., Pecher, E., de Pablos-Velasco, P., Lahti, K., Brunel, P., & Groop, L. (2002). Nateglinide Improves Early Insulin Secretion and Controls Postprandial Glucose Excursions in a Prediabetic Population. *Diabetes Care, 25*(12), 2141-2146. doi: 10.2337/diacare.25.12.2141

Saw, S. M., & Ng, T. P. (2001). The design and assessment of questionnaires in clinical research. *Singapore Medical Journal, 42*(3), 131-135.

Scaramuzza, A., De Palma, A., Mameli, C., Spiri, D., Santoro, L., & Zuccotti, G. V. (2010). Adolescents with type 1 diabetes and risky behaviour. *Acta Paediatrica, 99*(8), 1237-1241. doi: 10.1111/j.1651-2227.2010.01813.x

Schalm, R. L., & Kelloway, E. K. (2001). The relationship between response rate and effect size in occupational health psychology research. *Journal of Occupational Health Psychology, 6*(2), 160-163.

Scheen, A. J., & Lefebvre, P. J. (2004). [Reactive hypoglycaemia, a mysterious, insidious but non dangerous critical phenomenon]. Revue Medicale de Liege, 59(4), 237-242.

Schmid, S. M., Jauch-Chara, K., Hallschmid, M., Oltmanns, K. M., Born, J., & Schultes, B. (2008). Short-term nocturnal hypoglycaemia increases morning food intake in healthy humans. *Diabetic Medicine, 25*(2), 232-235. doi: 10.1111/j.1464-5491.2007.02347.x

Scholtes, V. A., Terwee, C. B., & Poolman, R. W. (2011). What makes a measurement instrument valid and reliable? *Injury, 42*(3), 236-240. doi: 10.1016/j.injury.2010.11.042

Schopman, J. E., Simon, A. C., Hoefnagel, S. J., Hoekstra, J. B., Scholten, R. J., & Holleman, F. (2014). The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews, 30*(1), 11-22. doi: 10.1002/dmrr.2470

Seaquist, E. R., Anderson, J., Childs, B., Cryer, P., Dagogo-Jack, S., Fish, L., . . . Vigersky, R. (2013). Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care, 36*(5), 1384-1395. doi: 10.2337/dc12-2480

Sheetz, M. J., & King, G. L. (2002). Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *Journal of the Americal Medical Association, 288*(20), 2579-2588.

Shiu, A. T., & Wong, R. Y. (2002). Fears and worries associated with hypoglycaemia and diabetes complications: perceptions and experience of Hong Kong Chinese clients. *Journal of Advanced Nursing, 39*(2), 155-163.

Shiu, A. T. Y., & Wong, R. Y. M. (2000). Fear of hypoglycaemia among insulin-treated Hong Kong Chinese patients: implications for diabetes patient education. *Patient Education and Counseling, 41*(3), 251-261.

Sigal, R. J., Kenny, G. P., Wasserman, D. H., Castaneda-Sceppa, C., & White, R. D. (2006). Physical activity/exercise and Type 2 diabetes A consensus statement from the American Diabetes Association. *Diabetes Care, 29*(6), 1433-1438.

Siler, S. Q., Neese, R. A., Christiansen, M. P., & Hellerstein, M. K. (1998). The inhibition of gluconeogenesis following alcohol in humans. *American Journal of Physiology-Endocrinology And Metabolism, 275*(5), E897-E907.

Singapore Diabetes Society. (2010). Diabetes and Hypoglycemia. *www.diabetes.org.sg.*

Sitzia, J., & Wood, N. (1998). Response rate in patient satisfaction research: an analysis of 210 published studies. *International Journal for Quality in Health Care, 10*(4), 311-317.

Skrivarhaug, T., Bangstad, H. J., Stene, L. C., Sandvik, L., Hanssen, K. F., & Joner, G. (2006). Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia, 49*(2), 298-305. doi: 10.1007/s00125-005-0082-6

Skyler, J. S., Bergenstal, R., Bonow, R. O., Buse, J., Deedwania, P., Gale, E. A., . . . Sherwin, R. S. (2009). Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation

and the American Heart Association. *Journal of the American College of Cardiology, 53*(3), 298-304. doi: 10.1016/j.jacc.2008.10.008

Slama, G., Traynard, P.-Y., Desplanque, N., Pudar, H., Dhunputh, I., Letanoux, M., . . . Tchobroutsky, G. (1990). The Search for an Optimized Treatment of Hypoglycemia: Carbohydrates in Tablets, Solution, or Gel for the Correction of Insulin Reactions. *Archives of Internal Medicine, 150*(3), 589-593. doi: 10.1001/archinte.1990.00390150083016

Socransky, S. J., Pirrallo, R. G., & Rubin, J. M. (1998). Out-of-hospital treatment of hypoglycemia: refusal of transport and patient outcome. *Academic Emergency Medicine, 5*(11), 1080-1085.

Somerset, A., Coffey, R., Jones, L., & Murphy, C. V. (2014). The impact of prediabetes on glycemic control and clinical outcomes postburn injury. *J Journal of burn care & research, 35*(1), 5-10. doi: 10.1097/BCR.0b013e3182a2adea

Sommerfield, A. J., Ewing, F. M. E., Strachan, M. W. J., Deary, I. J., Aitken, G., & Frier, B. M. (2003). Self-treatment of mild symptomatic hypoglycaemia by people with insulin-treated diabetes. *Diabetic Medicine, 20*(8), 686-687. doi: 10.1046/j.1464-5491.2003.09281.x

Sorensen, M., & Johansen, O. E. (2010). Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. *Scandinavian Journal of Clinical and Laboratory Investigation, 70*(6), 385-391. doi: 10.3109/00365513.2010.491869

Stagnaro-Green, A., Barton, M. K., Linekin, P. L., Corkery, E., deBeer, K., & Roman, S. H. (1995). Mortality in hospitalized patients with hypoglycemia and severe hyperglycemia. *Mount Sinai Journal of Medicine, 62*(6), 422-426.

Stahn, A., Pistrosch, F., Ganz, X., Teige, M., Koehler, C., Bornstein, S., & Hanefeld, M. (2014). Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: silent hypoglycemias and silent arrhythmias. *Diabetes Care, 37*(2), 516-520. doi: 10.2337/dc13-0600

Stefanova, S. D., Cox, C., & Hill, M. (2013). Hypoglycaemia: causes, risk factors and pathophysiology. *Nursing Standard, 27*(42), 42-48.

Stein, C., Devore, R., & Wojcik, B. (2005). *Calculation of the Kappa Statistic for Inter-Rater Reliability: The Case Where Raters Can Select Multiple*

*Responses from a Large Number of Categories*. Paper presented at the SUGI 30 Proceedings, Philadelphia, Pennsylvania

Stockwell, T., Donath, S., Cooper-Stanbury, M., Chikritzhs, T., Catalano, P., & Mateo, C. (2004). Under-reporting of alcohol consumption in household surveys: a comparison of quantity–frequency, graduated–frequency and recent recall. *Addiction, 99*(8), 1024-1033. doi: 10.1111/j.1360-0443.2004.00815.x

Strote, J., Simons, R., & Eisenberg, M. (2008). Emergency medical technician treatment of hypoglycemia without transport. *The American Journal of Emergency Medicine, 26*(3), 291-295. doi: http://dx.doi.org/10.1016/j.ajem.2007.05.030

Su, G., Mi, S., Tao, H., Li, Z., Yang, H., Zheng, H., . . . Ma, C. (2011). Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. *Cardiovascular Diabetology, 10,* 19. doi: 10.1186/1475-2840-10-19

Su, J. B., Chen, T., Xu, F., Wang, X. Q., Chen, J. F., Wu, G., . . . Wang, X. H. (2013). Glycemic variability in normal glucose regulation subjects with elevated 1-h postload plasma glucose levels. *Endocrine*. doi: 10.1007/s12020-013-0047-3

Subar, A. F., Ziegler, R. G., Thompson, F. E., Johnson, C. C., Weissfeld, J. L., Reding, D., . . . Hayes, R. B. (2001). Is shorter always better? Relative importance of questionnaire length and cognitive ease on response rates and data quality for two dietary questionnaires. *American Journal of Epidemiology, 153*(4), 404-409.

Succurro, E., Marini, M. A., Arturi, F., Grembiale, A., Lugarà, M., Andreozzi, F., . . . Sesti, G. (2009). Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. *Atherosclerosis, 207*(1), 245-249. doi: 10.1016/j.atherosclerosis.2009.04.006

Sumner, J., Baber, C., & Williams, V. (2000). What do patients with type 1 diabetes know about hypoglycaemia? *Practical Diabetes International, 17*(6), 187-190. doi: 10.1002/1528-252x(200009)17:6<187::aid-pdi74>3.0.co;2-i

Swinnen, S. G., Hoekstra, J. B., & DeVries, J. H. (2009). Insulin Therapy for Type 2 Diabetes. *Diabetes Care, 32*(suppl 2), S253-S259. doi: 10.2337/dc09-S318

Swinnen, S. G., Mullins, P., Miller, M., Hoekstra, J. B., & Holleman, F. (2009). Changing the glucose cut-off values that define hypoglycaemia has a major effect on reported frequencies of hypoglycaemia. *Diabetologia, 52*(1), 38-41. doi: 10.1007/s00125-008-1147-0 [doi]

Tabak, A. G., Herder, C., Rathmann, W., Brunner, E. J., & Kivimaki, M. (2012). Prediabetes: a high-risk state for diabetes development. *Lancet, 379*(9833), 2279-2290. doi: 10.1016/s0140-6736(12)60283-9

Taheri, N., Iraj, B., Amini, M., Amini, P., & Aminorroaya, A. (2010). Cardiovascular risk factors in relatives of type 2 diabetics with normal glucose tolerance test and elevated one-hour plasma glucose. *Endokrynologia Polska, 61*(4), 359-363.

Tan, P., Chen, H. C., Taylor, B., & Hegney, D. (2012). Experience of hypoglycaemia and strategies used for its management by community-dwelling adults with diabetes mellitus: a systematic review. The *International Journal of Evidence-Based Healthcare, 10*(3), 169-180. doi: 10.1111/j.1744-1609.2012.00276.x

Temelkova-Kurktschiev, T. S., Koehler, C., Henkel, E., Leonhardt, W., Fuecker, K., & Hanefeld, M. (2000). Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care, 23*(12), 1830-1834.

Testa, M. A., Gill, J., Su, M., Turner, R. R., Blonde, L., & Simonson, D. C. (2012). Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. *Journal of Clinical Endocrinology and Metabolism, 97*(10), 3504-3514. doi: 10.1210/jc.2012-1763

Thomas, R. M., Francis Gerstel, P. A., Williams, E. C., Sun, H., Bryson, C. L., Au, D. H., & Bradley, K. A. (2012). Association between alcohol screening scores and diabetic self-care behaviors. *Family Medicine, 44*(8), 555-563.

Thunander, M., Petersson, C., Jonzon, K., Fornander, J., Ossiansson, B., Torn, C., . . . Landin-Olsson, M. (2008). Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. *Diabetes Research and Clinical Practice, 82*(2), 247-255. doi: 10.1016/j.diabres.2008.07.022

Tirimacco, R., Koumantakis, G., Erasmus, R., Mosca, A., Sandberg, S., Watson, I. D., . . . Gillery, P. (2013). Glucose meters - fit for clinical purpose. *Clinical Chemistry and Laboratory Medicine, 51*(5), 943-952. doi: 10.1515/cclm-2013-0011

Tirosh, A., Shai, I., Tekes-Manova, D., Israeli, E., Pereg, D., Shochat, T., . . . Rudich, A. (2005). Normal fasting plasma glucose levels and type 2 diabetes in young men. *New England Journal of Medicine, 353*(14), 1454-1462. doi: 10.1056/NEJMoa050080

Tong, Q., Ye, C., McCrimmon, R. J., Dhillon, H., Choi, B., Kramer, M. D., . . . Lowell, B. B. (2007). Synaptic glutamate release by ventromedial hypothalamic neurons is part of the neurocircuitry that prevents hypoglycemia. *Cell Metab, 5*(5), 383-393. doi: 10.1016/j.cmet.2007.04.001

Tonyushkina, K., & Nichols, J. H. (2009). Glucose meters: a review of technical challenges to obtaining accurate results. *Journal of Diabetes Science and Technology, 3*(4), 971-980.

Torimoto, K., Okada, Y., Mori, H., & Tanaka, Y. (2013). Relationship between fluctuations in glucose levels measured by continuous glucose monitoring and vascular endothelial dysfunction in type 2 diabetes mellitus. *Cardiovascular Diabetology, 12,* 1. doi: 10.1186/1475-2840-12-1

Tourangeau, R., & Yan, T. (2007). Sensitive questions in surveys. *Psychological Bulletin, 133*(5), 859-883. doi: 2007-12463-007 [pii] 10.1037/0033-2909.133.5.859 [doi]

Turchin, A., Matheny, M. E., Shubina, M., Scanlon, J. V., Greenwood, B., & Pendergrass, M. L. (2009). Hypoglycemia and Clinical Outcomes in Patients With Diabetes Hospitalized in the General Ward. *Diabetes Care, 32*(7), 1153-1157. doi: 10.2337/dc08-2127

Turner, B. C., Jenkins, E., Kerr, D., Sherwin, R. S., & Cavan, D. A. (2001). The Effect of Evening Alcohol Consumption on Next-Morning Glucose Control in Type 1 Diabetes. *Diabetes Care, 24*(11), 1888-1893. doi: 10.2337/diacare.24.11.1888

Twigg, S. M., Kamp, M. C., Davis, T. M., Neylon, E. K., & Flack, J. R. (2007). Prediabetes: a position statement from the Australian Diabetes Society and

Australian Diabetes Educators Association. *Medical Journal of Australia, 186*(9), 461-465. doi: twi11006_fm [pii]

UK Hypoglycaemia Study Group. (2007). Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia, 50*(6), 1140-1147. doi: 10.1007/s00125-007-0599-y [doi]

UKPDS Group. (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet, 352*(9131), 837-853.

Umpierrez, G. E., Hor, T., Smiley, D., Temponi, A., Umpierrez, D., Ceron, M., . . . Baldwin, D. (2009). Comparison of inpatient insulin regimens with detemir plus aspart versus neutral protamine hagedorn plus regular in medical patients with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism, 94*(2), 564-569. doi: 10.1210/jc.2008-1441

Umpierrez, G. E., Smiley, D., Jacobs, S., Peng, L., Temponi, A., Mulligan, P., . . . Rizzo, M. (2011). Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care, 34*(2), 256-261. doi: 10.2337/dc10-1407

Unwin, N., Shaw, J., Zimmet, P., & Alberti, K. G. (2002a). Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetic Medicine, 19*(9), 708-723.

Unwin, N., Shaw, J., Zimmet, P., & Alberti, K. G. (2002b). Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetic Medicine, 19*(9), 708-723. doi: 835 [pii]

Vaisman, N., Lansink, M., Rouws, C. H., van Laere, K. M., Segal, R., Niv, E., . . . Morley, J. E. (2009). Tube feeding with a diabetes-specific feed for 12 weeks improves glycaemic control in type 2 diabetes patients. *Clinical Nutrition, 28*(5), 549-555. doi: http://dx.doi.org/10.1016/j.clnu.2009.05.004

van de Wiel, A. (2004). Diabetes mellitus and alcohol. *Diabetes/Metabolism Research and Reviews, 20*(4), 263-267. doi: 10.1002/dmrr.492

Vagn Korsgaard, T., & Colding-Jorgensen, M. (2006). Time-dependent mechanisms in beta-cell glucose sensing. *J Biol Phys, 32*(3-4), 289-306. doi: 10.1007/s10867-006-9017-9

Vanschoonbeek, K., Lansink, M., van Laere, K. M., Senden, J. M., Verdijk, L. B., & van Loon, L. J. (2009). Slowly digestible carbohydrate sources can be used to attenuate the postprandial glycemic response to the ingestion of diabetes-specific enteral formulas. *The Diabetes Educator, 35*(4), 631-640. doi: 0145721709335466 [pii] 10.1177/0145721709335466 [doi]

Varghese, P., Gleason, V., Sorokin, R., Senholzi, C., Jabbour, S., & Gottlieb, J. E. (2007). Hypoglycemia in hospitalized patients treated with antihyperglycemic agents. *J Hosp Med, 2*(4), 234-240. doi: 10.1002/jhm.212 [doi]

Verlohren, H. J. (1981). [Diabetes and alcohol]. *Zeitschrift fur Die Gesamte Innere Medizin und Ihre Grenzgebiete, 36*(16), 547-551.

Vetter, M. L., Amaro, A., & Volger, S. (2014). Nutritional management of type 2 diabetes mellitus and obesity and pharmacologic therapies to facilitate weight loss. *Postgraduate Medicine, 126*(1), 139-152. doi: 10.3810/pgm.2014.01.2734

Viera, A. J., & Garrett, J. M. (2005). Understanding interobserver agreement: the kappa statistic. *Family Medicine, 37*(5), 360-363.

Vignesh, J. P., & Mohan, V. (2004). Hypoglycaemia unawareness. *Journal of the Association of Physicians of India, 52*, 727-732.

Voss, A. C., Maki, K. C., Garvey, W. T., Hustead, D. S., Alish, C., Fix, B., & Mustad, V. A. (2008). Effect of two carbohydrate-modified tube-feeding formulas on metabolic responses in patients with type 2 diabetes. *Nutrition, 24*(10), 990-997. doi: S0899-9007(08)00281-5 [pii] 10.1016/j.nut.2008.06.009 [doi]

Wang, C., Lv, L., Yang, Y., Chen, D., Liu, G., Chen, L., . . . Ran, X. (2012). Glucose fluctuations in subjects with normal glucose tolerance, impaired glucose regulation and newly diagnosed type 2 diabetes mellitus. *Clinical Endocrinology, 76*(6), 810-815. doi: 10.1111/j.1365-2265.2011.04205.x

Wang, Y., Rimm, E. B., Stampfer, M. J., Willett, W. C., & Hu, F. B. (2005). Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *The American Journal of Clinical Nutrition, 81*(3), 555-563.

Wentholt, I. M., Maran, A., Masurel, N., Heine, R. J., Hoekstra, J. B., & DeVries, J. H. (2007). Nocturnal hypoglycaemia in Type 1 diabetic patients, assessed

with continuous glucose monitoring: frequency, duration and associations. *Diabetic Medicine, 24*(5), 527-532. doi: 10.1111/j.1464-5491.2007.02107.x

Weykamp, C., John, W. G., & Mosca, A. (2009). A review of the challenge in measuring hemoglobin A1c. *Journal of Diabetes Science* and *Technology, 3*(3), 439-445.

WHO/IDF. (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF Consultation.*

Wiethop, B. V., & Cryer, P. E. (1993). Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care, 16*(8), 1131-1136. doi: 10.2337/diacare.16.8.1131

Wiggers, J. H., Sanson-Fisher, R. W., & Halpin, S. J. (1995). Prevalence and frequency of health service use: associations with occupational prestige and educational attainment. *Australian Journal of Public Health, 19*(5), 512-519.

Wild, D., von Maltzahn, R., Brohan, E., Christensen, T., Clauson, P., & Gonder-Frederick, L. (2007). A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Education and Counseling, 68*(1), 10-15. doi: S0738-3991(07)00176-0 [pii]
10.1016/j.pec.2007.05.003 [doi]

Wilmot, E. G., Edwardson, C. L., Biddle, S. J., Gorely, T., Henson, J., Khunti, K., . . . Davies, M. J. (2013). Prevalence of diabetes and impaired glucose metabolism in younger 'at risk' UK adults: insights from the STAND programme of research. *Diabetic Medicine, 30*(6), 671-675. doi: 10.1111/dme.12173

Wolever, T. M., Gibbs, A. L., Mehling, C., Chiasson, J. L., Connelly, P. W., Josse, R. G., . . . Ryan, E. A. (2008). The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. *American Journal of Clinical Nutrition, 87*(1), 114-125.

World Health Organisation/International Diabetes Federation. (2006.). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Retrieved from

http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf

Yardley, J. E., Iscoe, K. E., Sigal, R. J., Kenny, G. P., Perkins, B. A., & Riddell, M. C. (2013). Insulin pump therapy is associated with less post-exercise hyperglycemia than multiple daily injections: an observational study of physically active type 1 diabetes patients. *Diabetes Technol Ther, 15*(1), 84-88. doi: 10.1089/dia.2012.0168

Yeh, H. C., Brown, T. T., Maruthur, N., Ranasinghe, P., Berger, Z., Suh, Y. D., . . . Golden, S. H. (2012). Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Annals of Internal Medicine, 157*(5), 336-347. doi: 10.7326/0003-4819-157-5-201209040-00508

Yen, T., Williams, P., & Twigg, M. (2008). *Isolated 1 hour glucose spikers' on the 75gram oral glucose tolerance test (OGTT) show features of relative insulin deficiency and are more likely to develop IGT.* Paper presented at the Australian Diabetes Society and Australian Diabetes Educators Association Annual Scientific Meeting, Melbourne, Australia.

Zaki, R., Bulgiba, A., Nordin, N., & Azina Ismail, N. (2013). A systematic review of statistical methods used to test for reliability of medical instruments measuring continuous variables. *Iranian Journal of Basic* Medical Sciences, *16*(6), 803-807.

Zhang, Y. H., Ma, W. J., Thomas, G. N., Xu, Y. J., Lao, X. Q., Xu, X. J., . . . Yu, I. T. (2012). Diabetes and pre-diabetes as determined by glycated haemoglobin A1c and glucose levels in a developing southern Chinese population. *PLoS One, 7*(5), e37260. doi: 10.1371/journal.pone.0037260

Zhao, Y., Campbell, C. R., Fonseca, V., & Shi, L. (2012). Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care, 35*(5), 1126-1132. doi: 10.2337/dc11-2048

Zheng, F., Lu, W., Jia, C., Li, H., Wang, Z., & Jia, W. (2010). Relationships between glucose excursion and the activation of oxidative stress in patients with newly diagnosed type 2 diabetes or impaired glucose regulation. *Endocrine, 37*(1), 201-208. doi: 10.1007/s12020-009-9296-6

Zhou, J., Li, H., Ran, X., Yang, W., Li, Q., Peng, Y., . . . Jia, W. (2011). Establishment

of normal reference ranges for glycemic variability in Chinese subjects using continuous glucose monitoring. *Medical Science Monitor, 17*(1), CR9-13.

Zhou, J., Lv, X., Mu, Y., Wang, X., Li, J., Zhang, X., . . . Jia, W. (2012). The accuracy and efficacy of real-time continuous glucose monitoring sensor in Chinese diabetes patients: a multicenter study. *Diabetes Technology & Therapeutics, 14*(8), 710-718. doi: 10.1089/dia.2012.0014

Zhou, L., Podolsky, N., Sang, Z., Ding, Y., Fan, X., Tong, Q., . . . McCrimmon, R. J. (2010). The medial amygdalar nucleus: a novel glucose-sensing region that modulates the counterregulatory response to hypoglycemia. *Diabetes, 59*(10), 2646-2652. doi: 10.2337/db09-0995

Zhu, W., Czyzyk, D., Paranjape, S. A., Zhou, L., Horblitt, A., Szabo, G., . . . Chan, O. (2010). Glucose prevents the fall in ventromedial hypothalamic GABA that is required for full activation of glucose counterregulatory responses during hypoglycemia. *American Journal of Physiology. Endocrinology and Metabolism, 298*(5), E971-977. doi: 10.1152/ajpendo.00749.2009

Zoungas, S., Patel, A., Chalmers, J., de Galan, B. E., Li, Q., Billot, L., . . . Heller, S. (2010). Severe hypoglycemia and risks of vascular events and death. *New England Journal of Medicine, 363*(15), 1410-1418. doi: 10.1056/NEJMoa1003795

## APPENDICES

**Appendix 1:** Statements of contribution by co-authors

**Appendix 2:** Permission statements from publishers

**Appendix 3:** Forms: data collection and information

**Appendix 4:** Hypoglycaemia and alcohol - recommendations

# APPENDIX 1

## STATEMENTS OF CONTRIBUTION BY CO-AUTHORS

**School of Public Health**
Curtin Health Innovation Research Institute,
Curtin University,
GPO Box U1987
Perth, Western Australia, 6845

**To Whom It May Concern,**

1. I, Sally Vindedzis was the lead author and major contributor to the following paper, which is based on data collected for my PhD. I had prime responsibility for its origination, implementation, drafting and proof reading.

   Vindedzis S, Marsh B, Sherriff J, Dhaliwal S, Stanton K. Dietary treatment of hypoglycaemia: should the Australian recommendation be increased? Internal Medicine Journal. 2012;42(7):830-3.

   S. V

   Sally Vindedzis

   I, as a co-author of the above paper, endorse the level of contribution to this paper by Sally Vindedzis as stated above.

   Beryl Marsh _____

   Dr Jill Sherriff _____

   Dr Satvinder Dhaliwal _____

   Dr Kim Stanton _____

2. I, Sally Vindedzis was the lead author and major contributor to the following paper, which is based on data collected for my PhD. I had prime responsibility for its origination, implementation, drafting and proof reading.

   Vindedzis SA, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Food selection for treatment of hypoglycaemia in insulin-treated diabetes: what happens in real life? Practical Diabetes. 2012;29(7):271-4.

   S. V

   Sally Vindedzis

   I, as a co-author of the above paper, endorse the level of contribution to this paper by Sally Vindedzis as stated above.

   Beryl Marsh _____

   Dr Jill Sherriff _____

   Dr Satvinder Dhaliwal _____

   Dr Kim Stanton _____

**School of Public Health**
Curtin Health Innovation Research Institute,
Curtin University,
GPO Box U1987
Perth, Western Australia, 6845

**To Whom It May Concern,**

1. I, Sally Vindedzis was the lead author and major contributor to the following paper, which is based on data collected for my PhD. I had prime responsibility for its origination, implementation, drafting and proof reading.

   Vindedzis SA, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Low carbohydrate meals or a small dose of insulin normalises one-hour blood glucose in a woman with normal glucose tolerance and elevated one-hour postload glucose: a case report. The British Journal of Diabetes & Vascular Disease. 2013;13(2):103-5.

   S. V

   Sally Vindedzis

   I, as a co-author of the above paper, endorse the level of contribution to this paper by Sally Vindedzis as stated above.

   Beryl Marsh _____

   Dr Jill Sherriff _____

   Dr Satvinder Dhaliwal _____

   X Dr Kim Stanton _____

2. I, Sally Vindedzis was the lead author and major contributor to the following paper, which is based on data collected for my PhD. I had prime responsibility for its origination, implementation, drafting and proof reading.

   Vindedzis S, Marsh B, Sherriff J, Dhaliwal S, Stanton K. Omitting follow-up food after initial hypoglycaemic treatment does not increase the likelihood of repeat hypoglycaemia. Diabetes Therapy. 2013;4(1):67-75.

   S V

   Sally Vindedzis

   I, as a co-author of the above paper, endorse the level of contribution to this paper by Sally Vindedzis as stated above.

   Beryl Marsh _____

   Dr Jill Sherriff _____

   Dr Satvinder Dhaliwal _____

   X Dr Kim Stanton _____

**School of Public Health**
Curtin Health Innovation Research Institute,
Curtin University,
GPO Box U1987
Perth, Western Australia, 6845

**To Whom It May Concern,**

1. I, Sally Vindedzis was the lead author and major contributor to the following paper, which is based on data collected for my PhD. I had prime responsibility for its origination, implementation, drafting and proof reading.

   Vindedzis SA, Marsh B, Sherriff JL, Stanton KG. Alcohol and type 1 diabetes: Patient knowledge of alcohol-induced sustained hypoglycaemia. Diabetes Res Clin Pract. 2013 Nov;102(2):e19-20. doi: 10.1016/j.diabres.2013.08.010. Epub 2013 Sep 26.

   S. V

   Sally Vindedzis

   I, as a co-author of the above paper, endorse the level of contribution to this paper by Sally Vindedzis as stated above.

   Beryl Marsh _____

   Dr Jill Sherriff _____

   Dr Kim Stanton _____

2. I, Sally Vindedzis was the lead author and major contributor to the following paper, which is based on data collected for my PhD. I had prime responsibility for its origination, implementation, drafting and proof reading.

   Vindedzis SA, Marsh B, Sherriff JL, Stanton KG. Hypoglycaemia in inpatients with diabetes on nasogastric feeding. Practical Diabetes. 2014; 31(1):29-31. DOI:10.1002/pdi.1824.

   S. V

   Sally Vindedzis

   I, as a co-author of the above paper, endorse the level of contribution to this paper by Sally Vindedzis as stated above.

   Beryl Marsh _____

   Dr Jill Sherriff _____

   Dr Kim Stanton _____

**School of Public Health**
Curtin Health Innovation Research Institute,
Curtin University,
GPO Box U1987
Perth, Western Australia, 6845

**To Whom It May Concern,**

1. I, Sally Vindedzis was the lead author and major contributor to the following paper, which is based on data collected for my PhD. I had prime responsibility for its origination, implementation, drafting and proof reading.

   Vindedzis SA, Sherriff JL, Stanton KG. Hypoglycemia in Insulin-Treated Adults on Established Nasogastric Feeding in the General Ward: A Systematic Review. Diabetes Educ. 2014. DOI: 10.1177/0145721714523510

   S. V

   Sally Vindedzis

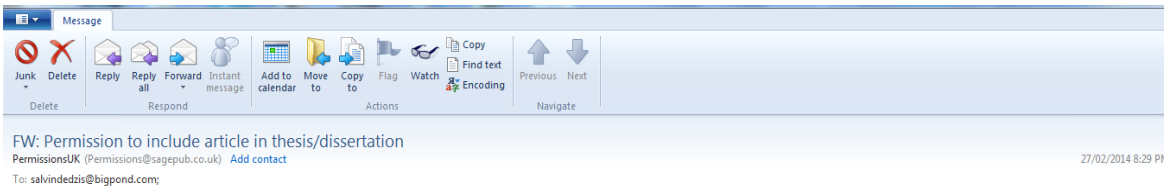
   I, as a co-author of the above paper, endorse the level of contribution to this paper by Sally Vindedzis as stated above.

   Dr Jill Sherriff _____

   Dr Kim Stanton _____

**APPENDIX 2**

**PERMISSION STATEMENTS FROM PUBLISHERS**




Dear Sally,
Thank you for your email.

Please consider this email as written permission to include your article 'Low carbohydrate meals or a small dose of insulin normalises one-hour blood glucose in a woman with normal glucose tolerance and elevated one-hour postload glucose: a case report' from our publication *The British Journal of Diabetes & Vascular Disease* as part of your thesis/ dissertation.

Please ensure you inform your co-authors of this reuse and include a full reference to the original Sage published material.
Best Wishes,

Leah Griffiths
Permissions Assistant
SAGE Publications Ltd
1 Oliver's Yard, 55 City Road
London, EC1Y 1SP
UK
www.sagepub.co.uk
SAGE Publications Ltd, Registered in England No.1017514
Los Angeles | London | New Delhi
Singapore | Washington DC


From: Binur, Michelle On Behalf Of permissions (US)
Sent: 20 February 2014 17:10
To: Sally Vindedzis
Cc: PermissionsUK
Subject: RE: Permission to include article in thesis/dissertation

Dear Sally,

Thank you for your request. The title, The British Journal of Diabetes & Vascular Disease, is published by our U.K. office. I'm copying the U.K. permissions team on this e-mail, who can assist you with your request.

Best regards,
Michelle Binur
Rights Assistant
SAGE Publications Inc.
Michelle.Binur@sagepub.com

www.sagepub.com
Los Angeles | London | New Delhi

Singapore | Washington DC
The natural home for authors, editors & societies

From: Sally Vindedzis [mailto:salvindedzis@bigpond.com]
Sent: Thursday, February 20, 2014 1:38 AM
To: permissions (US)
Subject: Fw: Permission to include article in thesis/dissertation

Subject: Permission to include article in thesis/dissertation....I cannot work out what to do from website info (apologies)

Dear Sir/Madam,

I request permission to include the article:

Vindedzis SA, Marsh B, Sherriff JL, Dhaliwal SS, Stanton KG. Low carbohydrate meals or a small dose of insulin normalises one-hour blood glucose in a woman with normal glucose tolerance and elevated one-hour postload glucose: a case report.. 2013;13(2):103-5.

in a dissertation/thesis entitled:

Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes

a thesis of ~ 200 words due to be finished in ~ June 2014.

Kind regards,
Sally Vindedzis

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS
Feb 19, 2014

---

This is a License Agreement between Sally Vindedzis ("You") and John Wiley and Sons ("John Wiley and Sons") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by John Wiley and Sons, and the payment terms and conditions.

**All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**

| | |
|---|---|
| License Number | 3332841186290 |
| License date | Feb 19, 2014 |
| Licensed content publisher | John Wiley and Sons |
| Licensed content publication | Internal Medicine Journal |
| Licensed content title | Dietary treatment of hypoglycaemia: should the Australian recommendation be increased? |
| Licensed copyright line | © 2012 The Authors. Internal Medicine Journal © 2012 Royal Australasian College of Physicians |
| Licensed content author | S. Vindedzis,B. Marsh,J. Sherriff,S. Dhaliwal,K. Stanton |
| Licensed content date | Jul 18, 2012 |
| Start page | 830 |
| End page | 833 |
| Type of use | Dissertation/Thesis |
| Requestor type | Author of this Wiley article |
| Format | Print and electronic |
| Portion | Full article |
| Will you be translating? | No |
| Title of your thesis / dissertation | Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes |
| Expected completion date | Jun 2014 |
| Expected size (number of pages) | 200 |
| Total | 0.00 USD |
| Terms and Conditions | |

**TERMS AND CONDITIONS**

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a "Wiley Company") or a society for whom a Wiley Company has exclusive publishing rights in relation to a particular journal (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

**Terms and Conditions**

1. The materials you have requested permission to reproduce (the "Materials") are protected by copyright.

2.You are hereby granted a personal, non-exclusive, non-sublicensable, non-transferable, worldwide, limited license to reproduce the Materials for the purpose specified in the licensing process. This license is for a one-time use only with a maximum distribution equal to the number that you identified in the licensing process. Any form of republication granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before may be distributed thereafter). The Materials shall not be used in any other manner or for any other purpose. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Material. Any third party material is expressly excluded from this permission.

3. With respect to the Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Materials without the prior permission of the respective copyright owner. You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Materials, or any of the rights

granted to you hereunder to any other person.

4. The Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc or one of its related companies (WILEY) or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto.

5. NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

6. WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

7. You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

8. IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

9. Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

10. The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

11. This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

12. Any fee required for this permission shall be non-refundable after thirty (30) days from receipt

13. These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

14. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

15. WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

16. This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

17. This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such

court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

**Wiley Open Access Terms and Conditions**

Wiley publishes Open Access articles in both its Wiley Open Access Journals program [http://www.wileyopenaccess.com/view/index.html] and as Online Open articles in its subscription journals. The majority of Wiley Open Access Journals have adopted the Creative Commons Attribution License (CC BY) which permits the unrestricted use, distribution, reproduction, adaptation and commercial exploitation of the article in any medium. No permission is required to use the article in this way provided that the article is properly cited and other license terms are observed. A small number of Wiley Open Access journals have retained the Creative Commons Attribution Non Commercial License (CC BY-NC), which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Online Open articles - Authors selecting Online Open are, unless particular exceptions apply, offered a choice of Creative Commons licenses. They may therefore select from the CC BY, the CC BY-NC and the Attribution-NoDerivatives (CC BY-NC-ND). The CC BY-NC-ND is more restrictive than the CC BY-NC as it does not permit adaptations or modifications without rights holder consent.

Wiley Open Access articles are protected by copyright and are posted to repositories and websites in accordance with the terms of the applicable Creative Commons license referenced on the article. At the time of deposit, Wiley Open Access articles include all changes made during peer review, copyediting, and publishing. Repositories and websites that host the article are responsible for incorporating any publisher-supplied amendments or retractions issued subsequently.
Wiley Open Access articles are also available without charge on Wiley's publishing platform, **Wiley Online Library** or any successor sites.

Conditions applicable to all Wiley Open Access articles:

- The authors' moral rights must not be compromised. These rights include the right of "paternity" (also known as "attribution" - the right for the author to be identified as such) and "integrity" (the right for the author not to have the work altered in such a way that the author's reputation or integrity may be damaged).

- Where content in the article is identified as belonging to a third party, it is the obligation of the user to ensure that any reuse complies with the copyright policies of the owner of that content.

- If article content is copied, downloaded or otherwise reused for research and other purposes as permitted, a link to the appropriate bibliographic citation (authors, journal, article title, volume, issue, page numbers, DOI and the link to the definitive published version on Wiley Online Library) should be maintained. Copyright notices and disclaimers must not be deleted.
    - Creative Commons licenses are copyright licenses and do not confer any other rights, including but not limited to trademark or patent rights.

- Any translations, for which a prior translation agreement with Wiley has not been agreed, must prominently display the statement: "This is an unofficial translation of an article that appeared in a Wiley publication. The publisher has not endorsed this translation."

  **Conditions applicable to non-commercial licenses (CC BY-NC and CC BY-NC-ND)**

  For non-commercial and non-promotional purposes individual non-commercial users may access, download, copy, display and redistribute to colleagues Wiley Open Access articles. In addition, articles adopting the CC BY-NC may be adapted, translated, and text- and data-mined subject to the conditions above.

  **Use by commercial "for-profit" organizations**

  Use of non-commercial Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee. Commercial purposes include:

    - Copying or downloading of articles, or linking to such articles for further redistribution, sale or licensing;

    - Copying, downloading or posting by a site or service that incorporates advertising with such content;

    - The inclusion or incorporation of article content in other works or services (other than normal quotations with an appropriate citation) that is then available for sale or licensing, for a fee (for example, a compilation produced for marketing purposes, inclusion in a sales pack)

    - Use of article content (other than normal quotations with appropriate citation) by for-profit organizations for

promotional purposes

- Linking to article content in e-mails redistributed for promotional, marketing or educational purposes;
- Use for the purposes of monetary reward by means of sale, resale, license, loan, transfer or other form of commercial exploitation such as marketing products
- Print reprints of Wiley Open Access articles can be purchased from: corporatesales@wiley.com

The modification or adaptation for any purpose of an article referencing the CC BY-NC-ND License requires consent which can be requested from RightsLink@wiley.com .

Other Terms and Conditions:

BY CLICKING ON THE "I AGREE..." BOX, YOU ACKNOWLEDGE THAT YOU HAVE READ AND FULLY UNDERSTAND EACH OF THE SECTIONS OF AND PROVISIONS SET FORTH IN THIS AGREEMENT AND THAT YOU ARE IN AGREEMENT WITH AND ARE WILLING TO ACCEPT ALL OF YOUR OBLIGATIONS AS SET FORTH IN THIS AGREEMENT.

**v1.8**

**If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501231163.**
**Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.**

**Make Payment To:**
**Copyright Clearance Center**
**Dept 001**
**P.O. Box 843006**
**Boston, MA 02284-3006**

**For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.**

**Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.**

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS
Feb 20, 2014

---

This is a License Agreement between Sally Vindedzis ("You") and John Wiley and Sons ("John Wiley and Sons") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by John Wiley and Sons, and the payment terms and conditions.

**All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**

| | |
|---|---|
| License Number | 3332940466081 |
| License date | Feb 20, 2014 |
| Licensed content publisher | John Wiley and Sons |
| Licensed content publication | Practical Diabetes International |
| Licensed content title | Food selection for treatment of hypoglycaemia in insulin-treated diabetes: what happens in real life? |
| Licensed copyright line | Copyright © 2012 John Wiley & Sons, Ltd. |
| Licensed content author | Sally A Vindedzis,Beryl Marsh,Jill L Sherriff,Satvinder S Dhaliwal,Kim G Stanton |
| Licensed content date | Sep 7, 2012 |
| Start page | 271 |
| End page | 274 |
| Type of use | Dissertation/Thesis |
| Requestor type | Author of this Wiley article |
| Format | Print and electronic |
| Portion | Full article |
| Will you be translating? | No |
| Title of your thesis / dissertation | Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes |
| Expected completion date | Jun 2014 |
| Expected size (number of pages) | 200 |
| Total | 0.00 USD |
| Terms and Conditions | |

**TERMS AND CONDITIONS**

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a "Wiley Company") or a society for whom a Wiley

Company has exclusive publishing rights in relation to a particular journal (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

**Terms and Conditions**

1. The materials you have requested permission to reproduce (the "Materials") are protected by copyright.

2.You are hereby granted a personal, non-exclusive, non-sublicensable, non-transferable, worldwide, limited license to reproduce the Materials for the purpose specified in the licensing process. This license is for a one-time use only with a maximum distribution equal to the number that you identified in the licensing process. Any form of republication granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before may be distributed thereafter). The Materials shall not be used in any other manner or for any other purpose. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Material. Any third party material is expressly excluded from this permission.

3. With respect to the Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Materials without the prior permission of the respective copyright owner. You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Materials, or any of the rights granted to you hereunder to any other person.

4. The Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc or one of its related companies (WILEY) or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto.

5. NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS,

IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

6. WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

7. You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

8. IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

9. Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

10. The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

11. This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

12. Any fee required for this permission shall be non-refundable after thirty (30) days from receipt

13. These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

14. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

15. WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

16. This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

17. This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

**Wiley Open Access Terms and Conditions**

Wiley publishes Open Access articles in both its Wiley Open Access Journals program [http://www.wileyopenaccess.com/view/index.html] and as Online Open articles in its subscription journals. The majority of Wiley Open Access Journals have adopted the Creative Commons Attribution License (CC BY) which permits the unrestricted use, distribution, reproduction, adaptation and commercial exploitation of the article in any medium. No permission is required to use the article in this way provided that the article is properly cited and other license terms are observed. A small number of Wiley Open Access journals have retained the Creative Commons Attribution Non Commercial License (CC BY-NC), which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Online Open articles - Authors selecting Online Open are, unless particular exceptions apply, offered a choice of Creative Commons licenses. They may therefore select from the CC BY, the CC BY-NC and the Attribution-NoDerivatives (CC BY-NC-ND). The CC BY-NC-ND is more restrictive than the CC BY-NC as it does not permit adaptations or modifications without rights holder consent.

Wiley Open Access articles are protected by copyright and are posted to repositories and websites in accordance with the terms of the applicable Creative Commons license referenced on the article. At the time of deposit, Wiley Open Access articles include all

changes made during peer review, copyediting, and publishing. Repositories and websites that host the article are responsible for incorporating any publisher-supplied amendments or retractions issued subsequently.
Wiley Open Access articles are also available without charge on Wiley's publishing platform, **Wiley Online Library** or any successor sites.

Conditions applicable to all Wiley Open Access articles:

- The authors' moral rights must not be compromised. These rights include the right of "paternity" (also known as "attribution" - the right for the author to be identified as such) and "integrity" (the right for the author not to have the work altered in such a way that the author's reputation or integrity may be damaged).

- Where content in the article is identified as belonging to a third party, it is the obligation of the user to ensure that any reuse complies with the copyright policies of the owner of that content.

- If article content is copied, downloaded or otherwise reused for research and other purposes as permitted, a link to the appropriate bibliographic citation (authors, journal, article title, volume, issue, page numbers, DOI and the link to the definitive published version on Wiley Online Library) should be maintained. Copyright notices and disclaimers must not be deleted.
    - Creative Commons licenses are copyright licenses and do not confer any other rights, including but not limited to trademark or patent rights.

- Any translations, for which a prior translation agreement with Wiley has not been agreed, must prominently display the statement: "This is an unofficial translation of an article that appeared in a Wiley publication. The publisher has not endorsed this translation."

  **Conditions applicable to non-commercial licenses (CC BY-NC and CC BY-NC-ND)**

  For non-commercial and non-promotional purposes individual non-commercial users may access, download, copy, display and redistribute to colleagues Wiley Open Access articles. In addition, articles adopting the CC BY-NC may be adapted, translated, and text- and data-mined subject to the conditions above.

  **Use by commercial "for-profit" organizations**

  Use of non-commercial Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee. Commercial purposes include:

    - Copying or downloading of articles, or linking to such articles for further redistribution, sale or licensing;

    - Copying, downloading or posting by a site or service that incorporates

advertising with such content;

- The inclusion or incorporation of article content in other works or services (other than normal quotations with an appropriate citation) that is then available for sale or licensing, for a fee (for example, a compilation produced for marketing purposes, inclusion in a sales pack)

- Use of article content (other than normal quotations with appropriate citation) by for-profit organizations for promotional purposes

- Linking to article content in e-mails redistributed for promotional, marketing or educational purposes;

- Use for the purposes of monetary reward by means of sale, resale, license, loan, transfer or other form of commercial exploitation such as marketing products

- Print reprints of Wiley Open Access articles can be purchased from: corporatesales@wiley.com

  The modification or adaptation for any purpose of an article referencing the CC BY-NC-ND License requires consent which can be requested from RightsLink@wiley.com .

Other Terms and Conditions:

BY CLICKING ON THE "I AGREE..." BOX, YOU ACKNOWLEDGE THAT YOU HAVE READ AND FULLY UNDERSTAND EACH OF THE SECTIONS OF AND PROVISIONS SET FORTH IN THIS AGREEMENT AND THAT YOU ARE IN AGREEMENT WITH AND ARE WILLING TO ACCEPT ALL OF YOUR OBLIGATIONS AS SET FORTH IN THIS AGREEMENT.

**v1.8**

**If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501231287.**
**Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.**

**Make Payment To:**
**Copyright Clearance Center**
**Dept 001**
**P.O. Box 843006**
**Boston, MA 02284-3006**

SPRINGER LICENSE
TERMS AND CONDITIONS
Feb 20, 2014

---

This is a License Agreement between Sally Vindedzis ("You") and Springer ("Springer") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Springer, and the payment terms and conditions.

**All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**

| | |
|---|---|
| License Number | 3332950986252 |
| License date | Feb 20, 2014 |
| Licensed content publisher | Springer |
| Licensed content publication | DIABETES THERAPY |
| Licensed content title | Omitting Follow-up Food After Initial Hypoglycaemic Treatment Does not Increase the Likelihood of Repeat Hypoglycaemia |
| Licensed content author | Sally Vindedzis |
| Licensed content date | Jan 1, 2013 |
| Volume number | 4 |
| Issue number | 1 |
| Type of Use | Thesis/Dissertation |
| Portion | Full text |
| Number of copies | 5 |
| Author of this Springer article | Yes and you are the sole author of the new work |
| Order reference number | |
| Title of your thesis / dissertation | Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes |
| Expected completion date | Jun 2014 |
| Estimated size(pages) | 200 |
| Total | 0.00 EUR |
| Terms and Conditions | |

Introduction

The publisher for this copyrighted material is Springer Science + Business Media. By

clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at http://myaccount.copyright.com).

Limited License
With reference to your request to reprint in your thesis material on which Springer Science and Business Media control the copyright, permission is granted, free of charge, for the use indicated in your enquiry.

Licenses are for one-time use only with a maximum distribution equal to the number that you identified in the licensing process.

This License includes use in an electronic form, provided its password protected or on the university's intranet or repository, including UMI (according to the definition at the Sherpa website: http://www.sherpa.ac.uk/romeo/). For any other electronic use, please contact Springer at (permissions.dordrecht@springer.com or permissions.heidelberg@springer.com).

The material can only be used for the purpose of defending your thesis, and with a maximum of 100 extra copies in paper.

Although Springer holds copyright to the material and is entitled to negotiate on rights, this license is only valid, subject to a courtesy information to the author (address is given with the article/chapter) and provided it concerns original material which does not carry references to other sources (if material in question appears with credit to another source, authorization from that source is required as well).

Permission free of charge on this occasion does not prejudice any rights we might have to charge for reproduction of our copyrighted material in the future.

Altering/Modifying Material: Not Permitted
You may not alter or modify the material in any manner. Abbreviations, additions, deletions and/or any other alterations shall be made only with prior written authorization of the author(s) and/or Springer Science + Business Media. (Please contact Springer at (permissions.dordrecht@springer.com or permissions.heidelberg@springer.com)

Reservation of Rights
Springer Science + Business Media reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

Copyright Notice:Disclaimer
You must include the following copyright and permission notice in connection with any reproduction of the licensed material: "Springer and the original publisher /journal title, volume, year of publication, page, chapter/article title, name(s) of author(s), figure number(s), original copyright notice) is given to the publication in which the material was originally published, by adding; with kind permission from Springer Science and Business

Media"

Warranties: None

Example 1: Springer Science + Business Media makes no representations or warranties with respect to the licensed material.

Example 2: Springer Science + Business Media makes no representations or warranties with respect to the licensed material and adopts on its own behalf the limitations and disclaimers established by CCC on its behalf in its Billing and Payment terms and conditions for this licensing transaction.

Indemnity
You hereby indemnify and agree to hold harmless Springer Science + Business Media and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

No Transfer of License
This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without Springer Science + Business Media's written permission.

No Amendment Except in Writing
This license may not be amended except in a writing signed by both parties (or, in the case of Springer Science + Business Media, by CCC on Springer Science + Business Media's behalf).

Objection to Contrary Terms
Springer Science + Business Media hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and Springer Science + Business Media (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

Jurisdiction
All disputes that may arise in connection with this present License, or the breach thereof, shall be settled exclusively by arbitration, to be held in The Netherlands, in accordance with Dutch law, and to be conducted under the Rules of the 'Netherlands Arbitrage Instituut' (Netherlands Institute of Arbitration).***OR:***

**All disputes that may arise in connection with this present License, or the breach thereof, shall be settled exclusively by arbitration, to be held in the Federal Republic of Germany, in accordance with German law.**

**Other terms and conditions:**

**v1.3**

**If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501231307.**
**Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.**

**Make Payment To:**
**Copyright Clearance Center**
**Dept 001**
**P.O. Box 843006**
**Boston, MA 02284-3006**

**For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.**

**Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.**

ELSEVIER LICENSE
TERMS AND CONDITIONS
Feb 20, 2014

---

This is a License Agreement between Sally Vindedzis ("You") and Elsevier ("Elsevier") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

**All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**

| | |
|---|---|
| Supplier | Elsevier Limited<br>The Boulevard,Langford Lane<br>Kidlington,Oxford,OX5 1GB,UK |
| Registered Company Number | 1982084 |
| Customer name | Sally Vindedzis |
| Customer address | 27 York Tce<br>Mosman Park, WA 6012 |
| License number | 3333011048736 |
| License date | Feb 20, 2014 |
| Licensed content publisher | Elsevier |
| Licensed content publication | Diabetes Research and Clinical Practice |
| Licensed content title | Alcohol and type 1 diabetes: Patient knowledge of alcohol-induced sustained hypoglycaemia |
| Licensed content author | Sally A. Vindedzis,Beryl Marsh,Jill L. Sherriff,Kim G. Stanton |
| Licensed content date | November 2013 |
| Licensed content volume number | 102 |
| Licensed content issue number | 2 |
| Number of pages | 2 |
| Start Page | e19 |
| End Page | e20 |
| Type of Use | reuse in a thesis/dissertation |
| Intended publisher of new work | other |
| Portion | full article |
| Format | both print and electronic |
| Are you the author of this Elsevier article? | Yes |
| Will you be translating? | No |

| | |
|---|---|
| Title of your thesis/dissertation | Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes |
| Expected completion date | Jun 2014 |
| Estimated size (number of pages) | 200 |
| Elsevier VAT number | GB 494 6272 12 |
| Permissions price | 0.00 EUR |
| VAT/Local Sales Tax | 0.00 EUR / 0.00 GBP |
| Total | 0.00 EUR |
| Terms and Conditions | |

## INTRODUCTION

1. The publisher for this copyrighted material is Elsevier. Byclicking "accept" in connection with completing this licensingtransaction, you agree that the following terms and conditions apply to thistransaction (along with the Billing and Payment terms and conditionsestablished by Copyright Clearance Center, Inc. ("CCC"), at the timethat you opened your Rightslink account and that are available at any time at http://myaccount.copyright.com).

Licensing material from an Elsevier book: A hyper-text link must be includedto the Elsevier homepage at http://www.elsevier.com . Allcontent posted to the web site must maintain the copyright information line onthe bottom of each image.

**Posting licensed content on Electronic reserve**: In addition to the above the following clausesare applicable: The web site must be password-protected and made available onlyto bona fide students registered on a relevant course. This permission isgranted for 1 year only. You may obtain a new license for future websiteposting.

**For journal authors:** the following clauses are applicable inaddition to the above: Permission granted is limited to the author acceptedmanuscript version* of your paper.

***Accepted Author Manuscript (AAM) Definition:** An accepted authormanuscript (AAM) is the author's version of the manuscript of an article thathas been accepted for publication and which may include any author-incorporatedchanges suggested through the processes of submission processing, peer review,and editor-author communications. AAMs do not include other publishervalue-added contributions such as copy-editing, formatting, technicalenhancements and (if relevant) pagination.

21. **Other Conditions**:

v1.7

**If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you**

**will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501231409.**
**Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.**

**Make Payment To:**
**Copyright Clearance Center**
**Dept 001**
**P.O. Box 843006**
**Boston, MA 02284-3006**

**For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.**

**Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.**

---

---

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS
Feb 20, 2014

---

---

This is a License Agreement between Sally Vindedzis ("You") and John Wiley and Sons ("John Wiley and Sons") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by John Wiley and Sons, and the payment terms and conditions.

**All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**

| | |
|---|---|
| License Number | 3333020038531 |
| License date | Feb 20, 2014 |
| Licensed content publisher | John Wiley and Sons |
| Licensed content publication | Practical Diabetes International |
| Licensed content title | Hypoglycaemia in inpatients with diabetes on nasogastric feeding |
| Licensed copyright line | Copyright © 2014 John Wiley & Sons, Ltd. |
| Licensed content author | Sally A Vindedzis,Beryl Marsh,Jill L Sherriff,Kim G Stanton |
| Licensed content date | Jan 28, 2014 |
| Start page | 29 |
| End page | 31 |
| Type of use | Dissertation/Thesis |
| Requestor type | Author of this Wiley article |
| Format | Print and electronic |
| Portion | Full article |
| Will you be translating? | No |
| Title of your thesis / dissertation | Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes |
| Expected completion date | Jun 2014 |
| Expected size (number of pages) | 200 |
| Total | 0.00 USD |
| Terms and Conditions | |

## TERMS AND CONDITIONS

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a "Wiley Company") or a society for whom a Wiley Company has exclusive publishing rights in relation to a particular journal (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center

Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

**Terms and Conditions**

1. The materials you have requested permission to reproduce (the "Materials") are protected by copyright.

2.You are hereby granted a personal, non-exclusive, non-sublicensable, non-transferable, worldwide, limited license to reproduce the Materials for the purpose specified in the licensing process. This license is for a one-time use only with a maximum distribution equal to the number that you identified in the licensing process. Any form of republication granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before may be distributed thereafter). The Materials shall not be used in any other manner or for any other purpose. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Material. Any third party material is expressly excluded from this permission.

3. With respect to the Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Materials without the prior permission of the respective copyright owner. You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Materials, or any of the rights granted to you hereunder to any other person.

4. The Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc or one of its related companies (WILEY) or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto.

5. NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A

PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

6. WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

7. You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

8. IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

9. Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

10. The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

11. This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

12. Any fee required for this permission shall be non-refundable after thirty (30) days from receipt

13. These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not

be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

14. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

15. WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

16. This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

17. This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

**Wiley Open Access Terms and Conditions**

Wiley publishes Open Access articles in both its Wiley Open Access Journals program [http://www.wileyopenaccess.com/view/index.html] and as Online Open articles in its subscription journals. The majority of Wiley Open Access Journals have adopted the Creative Commons Attribution License (CC BY) which permits the unrestricted use, distribution, reproduction, adaptation and commercial exploitation of the article in any medium. No permission is required to use the article in this way provided that the article is properly cited and other license terms are observed. A small number of Wiley Open Access journals have retained the Creative Commons Attribution Non Commercial License (CC BY-NC), which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Online Open articles - Authors selecting Online Open are, unless particular exceptions apply, offered a choice of Creative Commons licenses. They may therefore select from the CC BY, the CC BY-NC and the Attribution-NoDerivatives (CC BY-NC-ND). The CC BY-NC-ND is more restrictive than the CC BY-NC as it does not permit adaptations or modifications without rights holder consent.

Wiley Open Access articles are protected by copyright and are posted to repositories and websites in accordance with the terms of the applicable Creative Commons license referenced on the article. At the time of deposit, Wiley Open Access articles include all changes made during peer review, copyediting, and publishing. Repositories and websites that host the article are responsible for incorporating any publisher-supplied amendments or retractions issued subsequently.
Wiley Open Access articles are also available without charge on Wiley's publishing

platform, **Wiley Online Library** or any successor sites.

Conditions applicable to all Wiley Open Access articles:

- The authors' moral rights must not be compromised. These rights include the right of "paternity" (also known as "attribution" - the right for the author to be identified as such) and "integrity" (the right for the author not to have the work altered in such a way that the author's reputation or integrity may be damaged).

- Where content in the article is identified as belonging to a third party, it is the obligation of the user to ensure that any reuse complies with the copyright policies of the owner of that content.

- If article content is copied, downloaded or otherwise reused for research and other purposes as permitted, a link to the appropriate bibliographic citation (authors, journal, article title, volume, issue, page numbers, DOI and the link to the definitive published version on Wiley Online Library) should be maintained. Copyright notices and disclaimers must not be deleted.
    - Creative Commons licenses are copyright licenses and do not confer any other rights, including but not limited to trademark or patent rights.

- Any translations, for which a prior translation agreement with Wiley has not been agreed, must prominently display the statement: "This is an unofficial translation of an article that appeared in a Wiley publication. The publisher has not endorsed this translation."

  **Conditions applicable to non-commercial licenses (CC BY-NC and CC BY-NC-ND)**

  For non-commercial and non-promotional purposes individual non-commercial users may access, download, copy, display and redistribute to colleagues Wiley Open Access articles. In addition, articles adopting the CC BY-NC may be adapted, translated, and text- and data-mined subject to the conditions above.

  **Use by commercial "for-profit" organizations**

  Use of non-commercial Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee. Commercial purposes include:

    - Copying or downloading of articles, or linking to such articles for further redistribution, sale or licensing;

    - Copying, downloading or posting by a site or service that incorporates advertising with such content;

    - The inclusion or incorporation of article content in other works or services (other than normal quotations with an appropriate citation) that is then

available for sale or licensing, for a fee (for example, a compilation produced for marketing purposes, inclusion in a sales pack)

- Use of article content (other than normal quotations with appropriate citation) by for-profit organizations for promotional purposes
- Linking to article content in e-mails redistributed for promotional, marketing or educational purposes;
- Use for the purposes of monetary reward by means of sale, resale, license, loan, transfer or other form of commercial exploitation such as marketing products
- Print reprints of Wiley Open Access articles can be purchased from: corporatesales@wiley.com

  The modification or adaptation for any purpose of an article referencing the CC BY-NC-ND License requires consent which can be requested from RightsLink@wiley.com .

Other Terms and Conditions:

BY CLICKING ON THE "I AGREE..." BOX, YOU ACKNOWLEDGE THAT YOU HAVE READ AND FULLY UNDERSTAND EACH OF THE SECTIONS OF AND PROVISIONS SET FORTH IN THIS AGREEMENT AND THAT YOU ARE IN AGREEMENT WITH AND ARE WILLING TO ACCEPT ALL OF YOUR OBLIGATIONS AS SET FORTH IN THIS AGREEMENT.

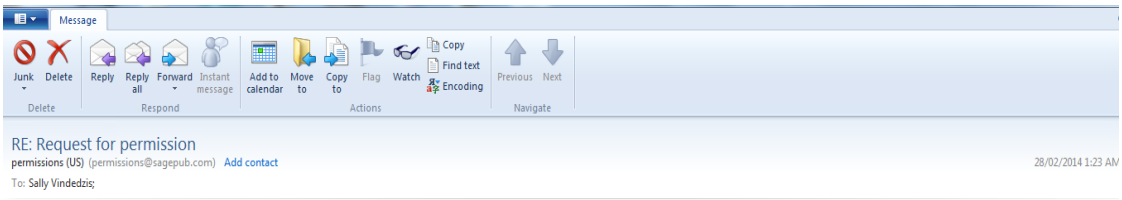
**v1.8**

**If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501231418.**
**Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.**

**Make Payment To:**
**Copyright Clearance Center**
**Dept 001**
**P.O. Box 843006**
**Boston, MA 02284-3006**

**For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.**

**Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.**




Dear Sally,

Thank you for your request. You can consider this email as permission to use the material as detailed below in your upcoming thesis. Please note that this permission does not cover any 3rd party material that may be found within the work. We do ask that you properly credit the original source, The Diabetes Educator. Please contact us for any further usage of the material.

Best regards,
Michelle Binur

Rights Assistant
SAGE Publications Inc.
Michelle.Binur@sagepub.com

www.sagepub.com
Los Angeles | London | New Delhi
Singapore | Washington DC
The natural home for authors, editors & societies

---

**From:** Sally Vindedzis [mailto:salvindedzis@bigpond.com]
**Sent:** Wednesday, February 26, 2014 8:14 PM
**To:** permissions (US)
**Subject:** Request for permission

Dear Sir/ Madam,

As the author of the article:

. **Vindedzis SA, Sherriff JL, Stanton KG. Hypoglycemia in Insulin-Treated Adults on Established Nasogastric Feeding in the General Ward: A Systematic Review. Diabetes Educ. 2014. DOI: 10.1177/0145721714523510**

I request permission to use in a thesis/dissertation (digital and print) of about 200 pages to be completed in June 2014 entitled:

**Dietary Practices In Treatment Of Hypoglycaemia In Elevated One-Hour Postload Glucose And Diabetes**

Many thanks,
Sally Vindedzis

**APPENDIX 3**

**FORMS: DATA COLLECTION AND INFORMATION**

- Information and consent form – case study
- Instructions to diabetes educators conducting assessment of carbohydrate quantity and wait-time
- Sample participant information assessment of carbohydrate quantity and wait-time
- Sample collection sheet A assessment of carbohydrate quantity and wait-time
- Sample collection sheet B (30 min +) assessment of carbohydrate quantity and wait-time
- Home testing collection sheet assessment of carbohydrate quantity and wait-time
- Questionnaire backing/information sheets
- Food selection questionnaire
- Repeat hypoglycaemia questionnaire
- Alcohol and insulin questionnaire
- Data collection forms nasogastric study

## Participant Information and Informed Consent

**Title**: Low carbohydrate meals or a minidose of insulin normalises one-hour postload blood glucose in a one hour glucose spiker. A case report

**Name of Investigators:** Sally Vindedzis, Beryl Marsh, Dr Kim Stanton, Associate Professor Satvinder Dhaliwhal, Associate Professor Jill Sherriff

**General Purpose, Methods and Demands:**

You are being asked to consider allowing the above investigators to use information about treatment of your blood glucose levels to write a case report. A case report is written to share information experienced by one patient during their clinical care that may be useful to other members of the health care profession. This may be published or presented at a conference. The purpose of this case report is to inform other members of the health care profession how the rise in your blood glucose one hour after a meal is affected by low carbohydrate meals, a small dose of insulin before the meal, and a medication called sitagliptin. Your information being used for this case report includes results of your self blood glucose monitoring, body weight and levels of fat in your blood which will be obtained from your private practice medical notes, pathology reports and the memory of your blood glucose monitor, which we will ask you to download for us at your regular doctors appointment.

***Participation is completely voluntary and you may withdraw at any time for any reason without explanation. All data will be kept strictly confidential,*** such that only research staff will have access to the information. The results from this study will be reported in a written research report and you will be provided with a copy of this. Information about the project will not be made public in any way that identifies you.

**Possible risks, inconvenience and discomforts:**

There are no substantial risks with this study. However, you must be prepared to allow access to your medical notes and reports and download the results of your blood glucose meter when you attend the doctor.

**Consent to Participate:**

After considering this information, if you have decided to participate in this study, please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without discrimination, judgment or penalty. Your identity will not be disclosed in any published or written material resulting from the study and you will be offered the opportunity to view the results and or any material produced from this study, before it is submitted. You will not directly benefit from participating in this study. The information that can be shared with other health care professionals, however, may improve the care that is received by others in the future. Allowing your information to be used in this case report will not involve any additional costs to you. You will not receive any compensation.

**Confidentiality:**

All information provided by you will be completely anonymous and no personal details will be collected.

**Further Information:**

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number SPH-55-2012). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au. If you request any further information, or have any queries you wish to be answered, please don't hesitate to contact Sally Vindedzis on 64775213 or sally.vindedzis@postgrad.curtin.edu.au. Please direct any ethical complaints to the Human Research Ethics Committee (Secretary) on phone: 9266 2784 or hrec@curtin.edu.au or in writing C/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth WA 6845.

**Thank you very much for your involvement in this research, your participation is greatly appreciated.**

**CONSENT FORM**

I have read the information on the attached letter. Any questions I have asked have been answered to my satisfaction. I agree to participate in this research but understand that I can change my mind or stop at any time. I understand that all information provided is treated as confidential. I agree that research gathered for this study may be published provided names or any other Information that may identify me is not used.

- I understand the purpose and procedures of the study.
- I have been provided with the participant information sheet.
- I understand that the procedure itself may not benefit me.
- I understand that my involvement is voluntary and I can withdraw at any time without problem.
- I understand that no personal identifying information like my name and address will be used and that all information will be securely stored for 5 years before being destroyed.
- I have been given the opportunity to ask questions.
- I agree to participate in the study outlined to me.

I have read and agree to the terms above

_____ _____

Participant Date

_____ _____

Investigator Date

# Hypo Audit – Instructions to Diabetes Educators

## Procedure:

When a patient has a blood glucose (sugar) less than 3.5 mmol/L on routine testing please follow the following procedure:

1. Blood test immediately and record on **Blood test form A.**
2. Give __ mls carbotest.
3. Record patients symptoms on checklist provided.
4. Blood test again after __ minutes and record. If blood sugar is less than 3.5 mmol/L repeat steps 1, 2, 3 and 4 and record until blood sugar is above 3.5 mmol/L, then go to step 5.
5. Obtain verbal consent for further blood testing. If consent, go to step 6, if no consent offer complex carbohydrate and usual information.
6. Blood test every 30 minutes while patient is in clinic and record on **Blood test form B**.
7. Give patient **Home blood test form C** and stamped self addressed envelope. Ask patient to blood test every 30 minutes to 4 hours post hypo on their own blood glucose meter at home, record on form C and post form back to clinic in provided stamped addressed envelope.

## STUDY INFORMATION

**Study Title:** Audit of Hypoglycaemia in a Tertiary Centre Diabetic Clinic

## STUDY SUMMARY

You are being asked to participate in this study because you have insulin treated diabetes and you have had a routine clinic blood test that is below the normal range (less than 3.5mmol/L), that is you are suffering from hypoglycemia, or are having a 'hypo'. Your participation in this study is voluntary.

Hypoglycemia ('hypos') or low blood glucose (sugar) in insulin treated diabetes is the result of the insulin you have injected being too much for your needs at a particular time. As you will have noticed, a hypo is often followed by rebound hyperglycemia, or high blood sugars. The present current recommended treatment for hypoglycemia is 15g carbohydrate in Australia, and 20 g glucose in the USA. This is repeated 5 or 10 minutes later if low blood sugars persist. In this study we will treat your hypoglycemia with:

60 mls of carbotest (which provides 15 g glucose) repeated at 10 minute intervals until blood testing shows your blood glucose is normal.

To enable us to assess how effective this treatment is we will ask you to blood glucose/sugar test on your own meter every 30 minutes over the next 4 hours, record on the provided sheet and send it back to us in the provided stamped envelopes. This information will be compared with similar results from other people with insulin treated diabetes. If you do not wish to do further blood testing you will be offered a snack and information on hypoglycemia.

There will be no other involvement by you, and no cost.

## DO I HAVE TO TAKE PART?

You do not have to take part in this study if you do not want to.

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 86/2010). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin

University, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au. If you request any further information, or have any queries you wish to be answered, please don't hesitate to contact Sally Vindedzis on 64775213 or email sally.vindedzis@postgrad.curtin.edu.au. Please direct any ethical complaints to the Human Research Ethics Committee (Secretary) on phone: 9266 2784 or hrec@curtin.edu.au or in writing C/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth WA 6845 or Royal Perth Hospital: A/Prof F M Bockxmeer, Chairman of the Ethics Committee, phone 92242244.

**HOW THE INFORMATION WILL BE HANDLED.**

All identifying data will be deleted once your results have been compared. Your name will not appear on any document or publication.

## FURTHER INFORMATION

If you have any further questions, you can contact the dietitian or educator in Diabetic Clinic **on 64775213.**

## Hypo Audit – Diabetic clinic blood test  Form A10 (10 min testing)

| Time | Blood sugar | Symptoms (please tick) |
|---|---|---|
| Blood sugar less than 3.5<br><br>**Treat (60 mls carbotest)** | | ☐ Sweating<br>☐ Hunger<br>☐ Shaking , weakness<br>☐ Irritability<br>☐ Light headedness/Headache<br>☐ Lack of concentration/behaviour change.<br>☐ Numbness around the lips and fingers<br>☐ Other _____<br>☐ None<br>☐ Comment_____ |
| **10** mins after | | Change of symptoms yes/no |

**If blood sugar greater than 3.5 go to Form B**

**OR If blood sugar less than 3.5 treat again and record**

| Time | Blood sugar | Symptoms (please tick) |
|---|---|---|
| Blood sugar less than 3.5<br><br>**Treat (60 mls carbotest)** | FROM ABOVE | ☐ Sweating<br>☐ Hunger<br>☐ Shaking , weakness<br>☐ Irritability<br>☐ Light headedness/Headache<br>☐ Lack of concentration/behaviour change.<br>☐ Numbness around the lips and fingers<br>☐ Other _____ |
| **10** mins after | | Change of symptoms yes/no |

**If blood sugar below 3.5 treat again and record (use another form A)**

***OR***

**If blood sugar greater than 3.5 go to Diabetic clinic blood test form B**

**Signature_____**

**Diabetic clinic blood test** **Form B**

| **Time after hypo** | **Blood sugar** | **Comments** |
|---|---|---|
| 30 mins | | |
| I hour | | |
| 1 hour 30 mins | | |
| 2 hours | | |
| 2 hour 30 mins | | |
| 3 hours | | |
| 3 hour 30 mins | | |
| 4 hours | | |

**Home blood test Form C**

| Time after hypo | Blood sugar | Comments |
|---|---|---|
| 30 mins | | |
| I hour | | |
| 1 hour 30 mins | | |
| 2 hours | | |
| 2 hour 30 mins | | |
| 3 hours | | |
| 3 hour 30 mins | | |
| 4 hours | | |


This questionnaire forms part of the research being conducted by Sally Vindedzis for her PhD project. Your completed questionnaire indicates your consent to participate and as it is anonymous, your answers can't be identified.

This study forms part of an audit at Royal Perth Hospital and has been approved by the Curtin Human Ethics Committee (number HR 86/2010).

If you have any questions about the research, please contact Sally on (64775213) or her supervisor at Curtin, Assoc Prof Jill Sherriff (92667948).

Curtin University

This questionnaire forms part of the research being conducted by Sally Vindedzis for her PhD project. Your completed questionnaire indicates your consent to participate and as it is anonymous, your answers can't be identified.

This study forms part of an audit at Royal Perth Hospital and has been approved by the Curtin Human Ethics Committee (number HR 86/2010).

If you have any questions about the research, please contact Sally on (64775213) or her supervisor at Curtin, Assoc Prof Jill Sherriff (92667948).

# Questionnaire on Hypoglycaemia ('hypos') or low blood sugar

Most people with insulin treated diabetes will, at some time have hypoglycaemia (or 'hypos'). The symptoms of hypos are different for different people, as is the way people treat their hypos. The questionnaire below is designed to ask you about your experience of hypos; and is anonymous. We thank you for filling in the questionnaire and ask you to place your completed questionnaire in the box marked 'questionnaire' next to reception.

1. How many years have you had diabetes? (please circle)

   0 – 5, 6 – 10, 11 – 20, 21 – 30, more than 30

2. Is your diabetes treated with: insulin injection/insulin pump. (please circle)
3. Are you: Male/female (please circle)
4. Please circle your age range:

   15 – 25, 26 – 35, 36 – 45, 46 – 55, 56 – 65, over 66

5. How many hypos would you have a week? (please circle)

   None, 0 -1, 1 – 2, 2 – 3, 3 – 4, 4 – 5, more than 5

6. Please tick which symptoms you have with a hypo.

- ☐ None
- ☐ Sweating
- ☐ Hunger
- ☐ Shaking , weakness
- ☐ Irritability
- ☐ Light headedness/Headache
- ☐ Lack of concentration/behaviour change.
- ☐ Numbness around the lips and fingers
- ☐ Other (please specify) _____

7. What do you first eat or drink to treat a hypo? -

   _____

8. How much of this do you generally need?

   _____

9. Do you follow up with anything else? yes/no (please circle)
10. If yes, what? _____

Thank you for your participation.

# Questionnaire on Hypoglycemia ('hypos') or low blood sugar

Most people with insulin treated diabetes will, at some time have hypoglycemia (or 'hypos'). The symptoms of hypos are different for different people, as is the way people treat their hypos. The questionnaire below is designed to ask you about your experience of hypos; and is anonymous. We thank you for filling in the questionnaire and ask you to place your completed questionnaire in the box marked 'questionnaire' next to reception.

11. How many years have you had diabetes?

☐ *0 – 5,* ☐*6 – 10,* ☐*11 – 15,* ☐*16 – 20,* ☐*21 – 30,* ☐ *more than 30* (please tick)

2. Is your diabetes treated with:

☐ *insulin injection* ☐*insulin pump* (please tick)

3. Your gender:

☐ *male* ☐*female* (please tick)

4. Please indicate your age range:

☐*15 – 25,* ☐ *26 – 35,* ☐*36 – 45,* ☐*46 – 55,* ☐*56 – 65,* ☐*over 66* (please tick)

5. How many hypos would you have a week?

☐*0 -1,* ☐*1 – 2,* ☐*2 – 3,* ☐*3 – 4,* ☐ *4 – 5,* ☐ *more than 5* (please tick)

6. Do you ever have a repeat hypo within 1 – 2 hours of the first one?

☐*yes* ☐*no* (please tick)

7. If yes, how often would this happen?

☐ *every time,* ☐*often,* ☐ *sometimes,* ☐ *rarely,* ☐*never* (please tick)

8. Do you get warning signs that you are about to have a hypo?

☐ *every time,* ☐ *often,* ☐*sometimes,* ☐*rarely,* ☐ *never* (please tick)

9. What do you first eat or drink to treat a hypo? _____

10. How much of this do you generally need? _____

11. Do you follow up with anything else?

☐ *yes* ☐*no* (please tick)

12. If yes, what? _____

Thank you for your participation.

**Questionnaire On Alcohol For People With Type 1 Diabetes**

We are asking people on insulin to fill in this short survey to help us assess if we are giving out information on alcohol and insulin appropriately. The questionnaire below is anonymous. We thank you for filling in the questionnaire and ask you to place your completed questionnaire in the box marked 'questionnaire' next to reception.

1. How long have you had diabetes?

   _____ years

2. What types of insulins do you take and how often do you take them?

   Insulin name: _____ Taken _____ times a day

   Insulin name: _____ Taken _____ times a day

   Insulin name: _____ Taken _____ times a day

3. Is it possible for drinks containing alcohol to **raise** your blood glucose level?

   □ Yes □ No

4. If yes, when would you expect this to happen?

   _____

5. Is it possible for drinks containing alcohol to **lower** your blood glucose level?

   □ Yes □ No

6. If yes, when would you expect this to happen?

   _____

7. If yes, after how many standard drinks (approximately) would you expect this to happen? (for standard drinks amount see on back)

   _____ standard drinks.

   *Thank you for your participation. If you would like further information on alcohol and insulin please ask the clinic dietitians or educators.*

This project is registered as a clinical audit (number _101209-05) )/ Curtin University Ethics Approval HR 02/2011

**DATA COLLECTION AND ENTRY FORM 1 GENERAL – NASOGASTRIC**

| | | | | |
|---|---|---|---|---|
| * No | | | | |
| ID | | | | |
| *HbA1c | | | | |
| *Standard monitoring yes/no | | | | |
| *Treatment (QID, BD, Long acting, SS, other) | | | | |
| *Feed pattern (bolus/continuous) | | | | |
| * Feed type (high cho/low cho/oth | | | | |
| | | | | |
| Total Bgls | | | | |
| No Bgls < 3.5mmol/L | | | | |
| * **% Bgls < 3.5 mmol/L** | | | | |
| No Bgls > 10 mmol/L | | | | |
| * **% Bgl s > 10 mmol/L** | | | | |
| * **? > 75% 3.5 – 10 (yes/no)** | | | | |
| * No of hypoglycaemic episodes < 2 mmol/l | | | | |
| * No episodes > 3h | | | | |
| * **Reason for hypoglycemia**<br>1. Insulin pattern<br>2. Feed stopped/insulin unchanged<br>3. Other | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

* = Enter data on database  Red font = Data to be collected  Green font = Calculated data

This project is registered as a clinical audit (number 101209-05)/Curtin University Ethics Approval HR 02/2011

**DATA COLLECTION FORM 2 – NASOGASTRIC PROJECT**

| ID | Hypo level > or ≤ 2 mmol/L | Time of hypo | Duration of hypo | Extra monitoring carried out? Yes/no | Time of last short acting insulin | Feed held? (from – to) | Other reason for hypo? | Response to hypo | | | | | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Glucose given | Insulin changed? | | Feed changed? | | Other ? | |
| | | | | | | | | | temporarily | ongoing | temporarily | ongoing | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |

**APPENDIX 4**

**RECOMMENDATIONS - HYPOGLYCAEMIA AND ALCOHOL**

# Alcohol and insulin

## It is important to understand the way alcohol and insulin interact.

## <u>There is an increased risk of hypoglycaemia following alcohol. This risk may persist for greater than 12 hours after drinking alcohol.</u>

Alcohol causes the liver to "shut down" its production of glucose. This causes a drop in blood glucose 4 - 6 hours (or more) after drinking alcohol. The extent of this drop largely depends on the **amount** of alcohol. Drinking more than two standard drinks will cause a significant drop during the night and sometimes the next day.

**RECOMMENDATIONS**

1. DRINK MODERATELY - Preferably less than 2 standard drinks (see below).

2. Have alcohol with a meal or substantial starch containing snack as food slows down the absorption of alcohol.

3. Have another meal or substantial starch containing snack several hours afterwards if drinking more than 2 standard drinks.

4. Choose a low sugar drink where possible (dry wine or spirits).

5. Space your drinks using a nonalcoholic beverage such as juice, soda water or diet soft drink

6. If you drink more than 4 standard drinks in the evening, reduce your bed time insulin **by 25% and you may also need to reduce the next mornings insulin dose.**

7. Check your blood glucose response. **During the 24 hours following excessive alcohol ingestion check your blood glucose on each occasion before driving or before operating heavy/dangerous machinery**

**STANDARD DRINKS**
1 small wineglass (100ml)
1 nip/ measure spirits (30mls)
1 middy beer or 1 can light beer (375mls)

Diabetic Unit
Royal Perth Hospital
March 2010

**BIBLIOGRAPHY**

Aaboe, K., Knop, F. K., Vilsboll, T., Deacon, C. F., Holst, J. J., Madsbad, S., & Krarup, T. (2010). Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. *Diabetes, Obesity & Metabolism, 12*(4), 323-333. doi: DOM1167 [pii] 10.1111/j.1463-1326.2009.01167.x [doi]

Abdul-Ghani, M. A., Abdul-Ghani, T., Ali, N., & DeFronzo, R. A. (2008). One-Hour Plasma Glucose Concentration and the Metabolic Syndrome Identify Subjects at High Risk for Future Type 2 Diabetes. *Diabetes Care, 31*(8), 1650-1655. doi: 10.2337/dc08-0225

Abdul-Ghani, M. A., & DeFronzo, R. A. (2009). Pathophysiology of prediabetes. *Current Diabetes Reports, 9*(3), 193-199.

Ahmed, A. T., Karter, A. J., Warton, E. M., Doan, J. U., & Weisner, C. M. (2008). The relationship between alcohol consumption and glycemic control among patients with diabetes: the Kaiser Permanente Northern California Diabetes Registry. *Journal of General Internal Medicine, 23*(3), 275-282. doi: 10.1007/s11606-007-0502-z

Alish, C. J., Garvey, W. T., Hegazi, R. A., Hustead, D. S., Maki, K. C., Mustad, V. A., & Sacks, G. S. (2010). A diabetes-specific enteral formula improves glycemic variability in patients with type 2 diabetes. *Diabetes Technology & Therapeutics, 12*(6), 419+.

Alvarez-Guisasola, F., Yin, D. D., Nocea, G., Qiu, Y., & Mavros, P. (2010). Association of hypoglycemic symptoms with patients' rating of their health-related quality of life state: a cross sectional study. *Health And Quality Of Life Outcomes, 8*, 86. doi: 10.1186/1477-7525-8-86

American Diabetes Association. (2005). Defining and Reporting Hypoglycemia in Diabetes. *Diabetes Care, 28*(5), 1245-1249. doi: 10.2337/diacare.28.5.1245

American Diabetes Association. (2008a). Introduction. *Diabetes Care, 31*(Supplement 1), S1-S2. doi: 10.2337/dc08-S001

American Diabetes Association. (2008b). Nutrition Recommendations and Interventions for Diabetes. *Diabetes Care, 31*(Supplement 1), S61-S78. doi: 10.2337/dc08-S061

American Diabetes Association. (2011). Standards of Medical Care in Diabetes—2011. *Diabetes Care, 34*(Supplement 1), S11-S61. doi: 10.2337/dc11-S011

American Diabetes Association. (2012). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care, 35*(Supplement 1), S64-S71. doi: 10.2337/dc12-s064

American Diabetes Association. (2013a). Diabetes and Driving. *Diabetes Care, 36*(Supplement 1), S80-S85. doi: 10.2337/dc13-S080

American Diabetes Association. (2013b). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care, 36*(Supplement 1), S67-S74. doi: 10.2337/dc13-S067

American Diabetes Association. (2013c). Standards of Medical Care in Diabetes—2013. *Diabetes Care, 36*(Supplement 1), S11-S66. doi: 10.2337/dc13-S011

American Diabetes Association. (2014a). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 37 Suppl 1*, S81-90. doi: 10.2337/dc14-S081

American Diabetes Association. (2014b). Standards of Medical Care in Diabetes—2014. *Diabetes Care, 37*(Supplement 1), S14-S80. doi: 10.2337/dc14-S014

American Diabetes Association, E. A. f. t. S. o. D., International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. (2007). Consensus statement on the worldwide standardisation of the HbA1c measurement. *Diabetologia, 50*(10), 2042-2043. doi: 10.1007/s00125-007-0789-7

Amiel, S. A., Dixon, T., Mann, R., & Jameson, K. (2008). Hypoglycaemia in Type 2 diabetes. *Diabetic Medicine, 25*(3), 245-254. doi: DME2341 [pii] 10.1111/j.1464-5491.2007.02341.x [doi]

Amiel, S. A. M. D. F. (2009). Hypoglycemia: From the Laboratory to the Clinic. *Diabetes Care, 32*(8), 1364-1371.

Anderbro, T., Amsberg, S., Adamson, U., Bolinder, J., Lins, P. E., Wredling, R., . . . Johansson, U. B. (2010). Fear of hypoglycaemia in adults with Type 1 diabetes. *Diabetic Medicine, 27*(10), 1151-1158. doi: 10.1111/j.1464-5491.2010.03078.x [doi]

Angelopoulos, T. P., & Doupis, J. (2014). Sodium-Glucose linked transporter 2 (SGLT2) inhibitors--fighting diabetes from a new perspective. *Advances in Therapy, 31*(6), 579-591. doi: 10.1007/s12325-014-0127-7

Anthony, M. (2007). Treatment of hypoglycemia in hospitalized adults: a descriptive study.*The Diabetes Educator, 33*(4), 709-715. doi: 33/4/709 [pii] 10.1177/0145721707303806 [doi]

Asian-Pacific Type 2 Diabetes Policy Group. (2002). Type 2 Diabetes Practical Targets and Treatments Retrieved from International Diabetes Federation. www.idf.org/idfwpr-type-2-diabetes-pratical-targets-and-treatments website:

Atkinson, F. S., Foster-Powell, K., & Brand-Miller, J. C. (2008). International Tables of Glycemic Index and Glycemic Load Values: 2008. *Diabetes Care, 31*(12), 2281-2283. doi: 10.2337/dc08-1239

Aung, P. P., Strachan, M. W., Frier, B. M., Butcher, I., Deary, I. J., & Price, J. F. (2012). Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetic Medicine, 29*(3), 328-336. doi: 10.1111/j.1464-5491.2011.03505.x

Australian Institute of Health and Welfare. (2013). Prevalence of diabetes (AIHW) https://www.aihw.gov.au/diabetes-indicators/prevalence/

Australian Bureau of Statistics. (2011a). Adult Literacy in Western Australia. (November 2013). Retrieved from http://www.abs.gov.au/ ausstats/

Australian Bureau of Statistics. (2011b). The Australian Health Survey. Retrieved from http://www.abs.gov.au/ausstats/

Australian Bureau of Statistics. (2012). *Alcohol consumption* 4364.0.55.001 - Australian Health Survey: First Results, 2011-12

Australian Institute of Health and Welfare. (2012). AIHW analysis of National Mortality Database (NMD). https://www.aihw.gov.au/diabetes-indicators/deaths/

Australian Institute of Health and Welfare. (2013). Diabetes Complications. Retrieved from https://www.aihw.gov.au/diabetes/complications/

Avery, L., Flynn, D., van Wersch, A., Sniehotta, F. F., & Trenell, M. I. (2012). Changing Physical Activity Behavior in Type 2 Diabetes: A systematic review and meta-analysis of behavioral interventions. *Diabetes Care, 35*(12), 2681-2689. doi: 10.2337/dc11-2452

Bahar, A., Makhlough, A., Yousefi, A., Kashi, Z., & Abediankenari, S. (2013). Correlation between prediabetes conditions and microalbuminuria. *Nephro-urology Monthly, 5*(2), 741-744. doi: 10.5812/numonthly.7646

Bantle, J. P., Wylie-Rosett, J., Albright, A. L., Apovian, C. M., Clark, N. G., Franz, M. J., Wheeler, M. L. (2008). Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care, 31 Suppl 1*, S61-78. doi: 31/Supplement_1/S61 [pii] 10.2337/dc08-S061 [doi]

Barnard, K., Sinclair, J. M. A., Lawton, J., Young, A. J., & Holt, R. I. G. (2012). Alcohol-associated risks for young adults with Type 1 diabetes: a narrative review. *Diabetic Medicine, 29*(4), 434-440. doi: 10.1111/j.1464-5491.2012.03579.x

Barnett, A. H., Cradock, S., Fisher, M., Hall, G., Hughes, E., & Middleton, A. (2010). Key considerations around the risks and consequences of hypoglycaemia in people with type 2 diabetes. *International Journal of Clinical Practice, 64*(8), 1121-1129. doi: 10.1111/j.1742-1241.2009.02332.x

Barrou, Z., Lemaire, A., Boddaert, J., & Verny, M. (2008). [Diabetes mellitus and cognition: is there a link?]. *Psychologie & Neuropsychiatrie du Vieillissement, 6*(3), 189-198. doi: 10.1684/pnv.2008.0136

Baruch, Y., & Holtom, B. C. (2008). Survey response rate levels and trends in organizational research. *Human Relations, 61*(8), 1139-1160.

Beck, F., & Peretti-Watel, P. (2002). The Impact of Data Collection Methodology on the Reporting of Illicit Drug Use by Adolescents. *Population-E, 57*(3), 571 - 592.

Bergenstal, R. M., Klonoff, D. C., Garg, S. K., Bode, B. W., Meredith, M., Slover, R. H., . . . Kaufman, F. R. (2013). Threshold-based insulin-pump interruption for reduction of hypoglycemia. *New England Journal of Medicine, 369*(3), 224-232. doi: 10.1056/NEJMoa1303576

Bergman, M. (2013). Pathophysiology of prediabetes and treatment implications for the prevention of type 2 diabetes mellitus. *Endocrine, 43*(3), 504-513. doi: 10.1007/s12020-012-9830-9

Berkow, S. E. P. C. N. S., Barnard, N., Eckart, J., & Katcher, H. (2010). Four Therapeutic Diets: Adherence and Acceptability. *Canadian Journal of Dietetic Practice and Research, 71*(4), 199-204.

Bianchi, C., Miccoli, R., Trombetta, M., Giorgino, F., Frontoni, S., Faloia, E., . . . Del Prato, S. (2013). Elevated 1-hour postload plasma glucose levels identify subjects with normal glucose tolerance but impaired beta-cell function,

insulin resistance, and worse cardiovascular risk profile: the GENFIEV study. *Journal of Clinical Endocrinology and Metabolism, 98*(5), 2100-2105. doi: 10.1210/jc.2012-3971

Bloomfield, H. E., Greer, N., Newman, D., MacDonald, R., Carlyle, M., Fitzgerald, P., . . . Wilt, T. J. (2012). *Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes - A Systematic Review of the Evidence*. Washington DC.

Bohme, P., Bertin, E., Cosson, E., & Chevalier, N. (2013). Fear of hypoglycaemia in patients with type 1 diabetes: do patients and diabetologists feel the same way? *Diabetes and Metabolism, 39*(1), 63-70. doi: 10.1016/j.diabet.2012.10.006

Bolli, G. B., & Fanelli, C. G. (1999). Physiology of glucose counterregulation to hypoglycemia. *Endocrinology and Metabolism Clinics of North America, 28*(3), 467-493, v.

Bolli, G. B. (2001). Physiological insulin replacement in type 1 diabetes mellitus. *Experimental and Clinical Endocrinology and Diabetes, 109 Suppl 2*, S317-332. doi: 10.1055/s-2001-18591

Bonds, D. E., Miller, M. E., Bergenstal, R. M., Buse, J. B., Byington, R. P., Cutler, J. A., . . . Sweeney, M. E. (2010). The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *British Medical Journal, 340*, b4909.

Boren, S. A., & Clarke, W. L. (2010). Analytical and clinical performance of blood glucose monitors. *Journal of Diabetes Science & Technology, 4*(1), 84-97.

Boucai, L., Southern, W. N., & Zonszein, J. (2011). Hypoglycemia-associated Mortality Is Not Drug-associated but Linked to Comorbidities. *The American Journal of Medicine, 124*(11), 1028-1035. doi: 10.1016/j.amjmed.2011.07.011

Bowling, A. (2005). Mode of questionnaire administration can have serious effects on data quality. *Journal of Public Health (Oxf), 27*(3), 281-291. doi: 10.1093/pubmed/fdi031

Boyle, P. J., & Zrebiec, J. (2007). Management of diabetes-related hypoglycemia. *Southern Medical Journal, 100*(2), 183-194.

Braithwaite, S. S., Buie, M. M., Thompson, C. L., Baldwin, D. F., Oertel, M. D., Robertson, B. A., & Mehrotra, H. P. (2004). Hospital hypoglycemia: not only treatment but also prevention. *Endocrine Practice, 10 Suppl 2*, 89-99. doi: yhaganyxu61fp4g1 [pii]

Brand-Miller, J. C., Stockmann, K., Atkinson, F., Petocz, P., & Denyer, G. (2009). Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: analysis of a database of more than 1000 foods. *The American Journal of Clinical Nutrition, 89*(1), 97-105. doi: 10.3945/ajcn.2008.26354

Brand-Miller, J., & Buyken, A. E. (2012). The glycemic index issue. *Current Opinion in Lipidology, 23*(1), 62-67. doi: 10.1097/MOL.0b013e32834ec705 [doi]

Brand-Miller, J., McMillan-Price, J., Steinbeck, K., & Caterson, I. (2008). Carbohydrates--the good, the bad and the whole grain. *Asia Pacific Journal of Clinical Nutrition, 17 Suppl 1*, 16-19.

Breuer, H. W., & Ptak, P. (2012). [Hypoglycemia - frequency, causes, induced costs]. *Deutsche Medizinische Wochenschrift, 137*(19), 988-992. doi: 10.1055/s-0031-1299014 [doi]

Briscoe, V. J., & Davis, S. N. (2006). Hypoglycemia in Type 1 and Type 2 Diabetes: Physiology, Pathophysiology, and Management. *Clinical Diabetes, 24*(3), 115-121. doi: 10.2337/diaclin.24.3.115

Briscoe, V. J., Tate, D. B., & Davis, S. N. (2007). Type 1 diabetes: exercise and hypoglycemia. *Appl Physiol Nutr Metab, 32*(3), 576-582. doi: 10.1139/h07-025

Brodovicz, K. G., Mehta, V., Zhang, Q., Zhao, C., Davies, M. J., Chen, J., . . . Engel, S. S. (2013). Association between hypoglycemia and inpatient mortality and length of hospital stay in hospitalized, insulin-treated patients. *Current Medical Research and Opinion, 29*(2), 101-107. doi: 10.1185/03007995.2012.754744

Brodows, R. G., Williams, C., & Amatruda, J. M. (1984). Treatment of insulin reactions in diabetics. *Journal of the American Medical Association, 252*(24), 3378-3381.

Bruce, D. G., Chisholm, D. J., Storlien, L. H., & Kraegen, E. W. (1988). Physiological importance of deficiency in early prandial insulin secretion in

non-insulin-dependent diabetes. *Diabetes, 37*(6), 736-744. doi: 10.2337/diabetes.37.6.736

Cain, E., Ackroyd-Stolarz, S., Alexiadis, P., & Murray, D. (2003). Prehospital hypoglycemia: the safety of not transporting treated patients. *Prehospital Emergency Care, 7*(4), 458-465. doi: S1090312703002193 [pii]

Campbell, M. D., Walker, M., Trenell, M. I., Jakovljevic, D. G., Stevenson, E. J., Bracken, R. M., . . . West, D. J. (2013). Large pre- and postexercise rapid-acting insulin reductions preserve glycemia and prevent early- but not late-onset hypoglycemia in patients with type 1 diabetes. *Diabetes Care, 36*(8), 2217-2224. doi: 10.2337/dc12-2467

Canadian Diabetes Association. (2012). Hypoglycemia. *2012*. Retrieved from http://www.diabetes.ca/ website:

Carroll, M. F., Burge, M. R., & Schade, D. S. (2003). Severe hypoglycemia in adults. *Reviews in Endocrine and Metabolic Disorders, 4*(2), 149-157.

Caumo, A., & Luzi, L. (2004). First-phase insulin secretion: does it exist in real life? Considerations on shape and function. *American Journal Physiology and Endocrine Metabolism, 287*(3), E371-385. doi: 10.1152/ajpendo.00139.2003

Cengiz, E., & Tamborlane, W. V. (2009). A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technology Therapeutics, 11 Suppl 1*, S11-16. doi: 10.1089/dia.2009.0002

Ceriello, A., & Colagiuri, S. (2008). International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. *Diabetic Medicine, 25*(10), 1151-1156. doi: 10.1111/j.1464-5491.2008.02565.x

Ceriello, A., Lansink, M., Rouws, C. H., van Laere, K. M., & Frost, G. S. (2009). Administration of a new diabetes-specific enteral formula results in an improved 24h glucose profile in type 2 diabetic patients. *Diabetes Research and Clinical Practice, 84*(3), 259-266. doi: S0168-8227(09)00073-4 [pii] 10.1016/j.diabres.2009.02.013 [doi]

Chen, T., Xu, F., Su, J. B., Wang, X. Q., Chen, J. F., Wu, G., . . . Wang, X. H. (2013). Glycemic variability in relation to oral disposition index in the subjects with different stages of glucose tolerance. *Diabetology Metabolic Syndrome, 5*(1), 38. doi: 10.1186/1758-5996-5-38

Cheyne, E. H., Sherwin, R. S., Lunt, M. J., Cavan, D. A., Thomas, P. W., & Kerr, D. (2004). Influence of alcohol on cognitive performance during mild

hypoglycaemia; implications for Type 1 diabetes. *Diabetic Medicine, 21*(3), 230-237.

Chimen, M., Kennedy, A., Nirantharakumar, K., Pang, T. T., Andrews, R., & Narendran, P. (2012). What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia, 55*(3), 542-551. doi: 10.1007/s00125-011-2403-2

Chlup, R., Peterson, K., Zapletalova, J., Kudlova, P., & Seckar, P. (2010). Extended prandial glycemic profiles of foods as assessed using continuous glucose monitoring enhance the power of the 120-minute glycemic index. *Journal of Diabetes Science Technology, 4*(3), 615-624.

Choi, B. C., & Pak, A. W. (2005). Peer reviewed: A Catalog of Biases in Questionnaires. *Preventing Chronic Disease [electronic resource]*. *2*(1).

Choudhary, P., & Amiel, S. A. (2011). Hypoglycaemia: current management and controversies. *Postgraduate Medical Journal, 87*(1026), 298-306. doi: pgmj.2008.068197 [pii] 10.1136/pgmj.2008.068197 [doi]

Christiansen, M., Bailey, T., Watkins, E., Liljenquist, D., Price, D., Nakamura, K., . . . Peyser, T. (2013). A new-generation continuous glucose monitoring system: improved accuracy and reliability compared with a previous-generation system. *Diabetes Technology Therapy, 15*(10), 881-888. doi: 10.1089/dia.2013.0077

Clarke, S. F., & Foster, J. R. (2012). A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *British Journal of Biomedical Science, 69*(2), 83-93.

Clauson, K. A., Zeng-Treitler, Q., & Kandula, S. (2010). Readability of patient and health care professional targeted dietary supplement leaflets used for diabetes and chronic fatigue syndrome. *Journal of Alternative and Complementary Medicine, 16*(1), 119-124. doi: 10.1089/acm.2008.0611 [doi]

Colagiuri, S., Sandbaek, A., Carstensen, B., Christensen, J., Glumer, C., Lauritzen, T., & Borch-Johnsen, K. (2003). Comparability of venous and capillary glucose measurements in blood. *Diabetic Medicine, 20*(11), 953-956. doi: 1048 [pii]

Colak, A., Akinci, B., Diniz, G., Turkon, H., Ergonen, F., Yalcin, H., & Coker, I. (2013). Postload hyperglycemia is associated with increased subclinical inflammation in patients with prediabetes. *Scandinavian Journal of Clinical*

*and Laboratory Investigation, 73*(5), 422-427. doi: 10.3109/00365513.2013.798870

Connor, H., Annan, F., Bunn, E., Frost, G., McGough, N., Sarwar, T., & Thomas, B. (2003). The implementation of nutritional advice for people with diabetes. *Diabetic Medicine, 20*(10), 786-807. doi: 1104 [pii]

Consoli, A., & Di Fulvio, P. (2013). Anti-diabetes agents and hypoglycemia. *Italian Journal Cardiology (Rome), 14*(12), 9-14. doi: 10.1714/1375.15276

Cook, C. B., Wellik, K. E., Kongable, G. L., & Shu, J. (2012). Assessing inpatient glycemic control: what are the next steps? *Journal Diabetes Science Technology, 6*(2), 421-427.

Corathers, S. D., Peavie, S., & Salehi, M. (2013). Complications of diabetes therapy. *Endocrinology and Metabolism Clinics of North America, 42*(4), 947-970. doi: 10.1016/j.ecl.2013.06.005

Cortinovis, F., Colombo, O., & Sileo, F. (2011). Efficacy of a protocol for blood glucose control in enteral nutrition. *Mediterranean Journal of Nutrition and Metabolism, 4*(1), 47-52.

Cowie, C. C., Rust, K. F., Ford, E. S., Eberhardt, M. S., Byrd-Holt, D. D., Li, C., . . . Geiss, L. S. (2009). Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care, 32*(2), 287-294. doi: 10.2337/dc08-1296

Cox, D. J., Gonder-Frederick, L., Polonsky, W., Schlundt, D., Kovatchev, B., & Clarke, W. (2001). Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care, 24*(4), 637-642.

Cox, D. J., Gonder-Frederick, L. A., Kovatchev, B. P., & Clarke, W. L. (2001). Self-treatment of hypoglycemia while driving. *Diabetes Research and Clinical Practice, 54*(1), 17-26. doi: S0168-8227(01)00274-1 [pii]

Cox, D. J., Irvine, A., Gonder-Frederick, L., Nowacek, G., & Butterfield, J. (1987). Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care, 10*(5), 617-621.

Cox, D. J., Penberthy, J. K., Zrebiec, J., Weinger, K., Aikens, J. E., Frier, B., . . . Clarke, W. (2003). Diabetes and Driving Mishaps: Frequency and correlations from a multinational survey. *Diabetes Care, 26*(8), 2329-2334. doi: 10.2337/diacare.26.8.2329

Craig, M., Twigg, S., Donaghue, K., Cheung, N., Cameron, F., Conn, J., . . . Silink, M. (2011). National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults. *Canberra: Australian Government Department of Health and Ageing*.

Cryer, P. E. (1999). Symptoms of hypoglycemia, thresholds for their occurrence, and hypoglycemia unawareness. *Endocrinology and Metabolism Clinics of North America, 28*(3), 495-500, v-vi.

Cryer, P. E. (2009). Preventing hypoglycaemia: what is the appropriate glucose alert value? *Diabetologia, 52*(1), 35-37. doi: 10.1007/s00125-008-1205-7 [doi]

Cryer, P. E. (2010). Hypoglycemia in type 1 diabetes mellitus. *Endocrinology and Metabolism Clinics of North America, 39*(3), 641-654. doi: S0889-8529(10)00034-4 [pii]
10.1016/j.ecl.2010.05.003 [doi]

Cryer, P. E. (2011). Elimination of Hypoglycemia From the Lives of People Affected by Diabetes. *Diabetes, 60*(1), 24-27. doi: 10.2337/db10-1359

Cryer, P. E. (2012). Severe Hypoglycemia Predicts Mortality in Diabetes. *Diabetes Care, 35*(9), 1814-1816. doi: 10.2337/dc12-0749

Cryer, P. E. (2013). Hypoglycemia-associated autonomic failure in diabetes. *Handbook of Clinical Neurology, 117*, 295-307. doi: 10.1016/b978-0-444-53491-0.00023-7

Cryer, P. E., Axelrod, L., Grossman, A. B., Heller, S. R., Montori, V. M., Seaquist, E. R., & Service, F. J. (2009). Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism, 94*(3), 709-728. doi: 10.1210/jc.2008-1410

Cryer, P. E., Davis, S. N., & Shamoon, H. (2003). Hypoglycemia in diabetes. *Diabetes Care, 26*(6), 1902-1912.

Cryer, P. E., Fisher, J. N., & Shamoon, H. (1994). Hypoglycemia. *Diabetes Care, 17*(7), 734-755. doi: 10.2337/diacare.17.7.734

Cubeddu, L. X., & Hoffmann, I. S. (2010). One-hour postload plasma glucose levels, a predictor of additional risk for diabetes: prevalence, mechanisms, and associated cardiovascular and metabolic risk factors in Hispanics. *Metabolic Syndrome and Related Disorders, 8*(5), 395-402. doi: 10.1089/met.2010.0010 [doi]

Cummings, S. M., Savitz, L. A., & Konrad, T. R. (2001). Reported response rates to mailed physician questionnaires. *Health Services Research, 35*(6), 1347-1355.

Cummins, E., Royle, P., Snaith, A., Greene, A., Robertson, L., McIntyre, L., & Waugh, N. (2010). Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technology Assessment, 14*(11), iii-iv, xi-xvi, 1-181. doi: 10.3310/hta14110

Curkendall, S. M., Natoli, J. L., Alexander, C. M., Nathanson, B. H., Haidar, T., & Dubois, R. W. (2009). Economic and clinical impact of inpatient diabetic hypoglycemia. *Endocrine Practice, 15*(4), 302-312. doi: 10.4158/ep08343.or

Dafne Study Group. (2002). Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ, 325*(7367), 746.

d'Emden, M. C., Shaw, J. E., Colman, P. G., Colagiuri, S., Twigg, S. M., Jones, G. R., . . . Cheung, N. W. (2012). The role of HbA1c in the diagnosis of diabetes mellitus in Australia. *Medical Journal of Australia, 197*(4), 220-221.

Davis, R. E., Couper, M. P., Janz, N. K., Caldwell, C. H., & Resnicow, K. (2010). Interviewer effects in public health surveys. *Health Education Research, 25*(1), 14-26. doi: 10.1093/her/cyp046

Davis, T. C., Michielutte, R., Askov, E. N., Williams, M. V., & Weiss, B. D. (1998). Practical Assessment of Adult Literacy in Health Care. *Health Education and Behavior, 25*(5), 613-624. doi: 10.1177/109019819802500508

Davis, W. A., Bruce, D. G., & Davis, T. M. E. (2006). Is Self-Monitoring of Blood Glucose Appropriate for All Type 2 Diabetic Patients?: The Fremantle Diabetes Study. *Diabetes Care, 29*(8), 1764-1770. doi: 10.2337/dc06-0268

DCCT Research Group. (1990). Diabetes Control and Complications Trial (DCCT): Update. *Diabetes Care, 13*(4), 427-433. doi: 10.2337/diacare.13.4.427

de-Leeuw, E. (2005). To mix or not to mix data collection modes in surveys. *Journal of Official Statistics, 21*(2), 233-255.

de Galan, B. E., Schouwenberg, B. J., Tack, C. J., & Smits, P. (2006). Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *Netherlands Journal of Medicine, 64*(8), 269-279.

Deedwania, P., Patel, K., Fonarow, G. C., Desai, R. V., Zhang, Y., Feller, M. A., . . . Ahmed, A. (2013). Prediabetes is not an independent risk factor for incident heart failure, other cardiovascular events or mortality in older adults: Findings from a population-based cohort study. *International Journal of Cardiology*. doi: 10.1016/j.ijcard.2013.05.038

Deepak, P. J., Sunitha, K., Nagaraj, J., Sanjukta, A., & Bhattacharyya, A. (2003). Inpatient management of diabetes: survey in a tertiary care centre. *Postgraduate Medical Journal, 79*(936), 585-587. doi: 10.1136/pmj.79.936.585

del Carmen Crespillo, M., Olveira, G., de Adana, M. S., Rojo-Martinez, G., Garcia-Aleman, J., Olvera, P., . . . Munoz, A. (2003). Metabolic effects of an enteral nutrition formula for diabetes: comparison with standard formulas in patients with type 1 diabetes. *Clinical Nutrition, 22*(5), 483-487.

Del Prato, S., & Tiengo, A. (2001). The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus. *Diabetes/Metabolism Research and Reviews, 17*(3), 164-174. doi: 10.1002/dmrr.198 [pii]

Deusenberry, C. M., Coley, K. C., Korytkowski, M. T., & Donihi, A. C. (2012). Hypoglycemia in Hospitalized Patients Treated with Sulfonylureas. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, n/a-n/a. doi: 10.1002/j.1875-9114.2011.01088.x

Devaraj, S., Hirany, S. V., Burk, R. F., & Jialal, I. (2001). Divergence between LDL oxidative susceptibility and urinary F(2)-isoprostanes as measures of oxidative stress in type 2 diabetes. *Clinical Chemistry, 47*(11), 1974-1979.

Diabetes Australia. (2009). *Treating Hypoglycemia.* www.diabetesaustralia.au

Diabetes Co UK, F. (2013). Is my blood sugar too low? Retrieved from http://www.diabetes.co.uk/forum/threads/type-2-blood-glucose-readings.38474/

Diabetes Education Study Group of the European Association for the Study of Diabetes. (1998). Teaching Letter 2, Hypoglycemia. www.desg.org/

Diabetes New Zealand. (2008). http://www.diabetes.org.nz/living_with_diabetes/

DiNardo, M., Noschese, M., Korytkowski, M., & Freeman, S. (2006). The medical emergency team and rapid response system: finding, treating, and preventing hypoglycemia. *Joint Commission Journal on Quality & Patient Safety, 32*(10), 591-595.

Dobson, K., & Scott, A. (2007). Review of ICU nutrition support practices: implementing the nurse-led enteral feeding algorithm. *Nursing in Critical Care, 12*(3), 114-123. doi: 10.1111/j.1478-5153.2007.00222.x

Donnelly, L. A., Morris, A. D., Frier, B. M., Ellis, J. D., Donnan, P. T., Durrant, R., . . . Leese, G. P. (2005). Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabetic Medicine, 22*(6), 749-755. doi: DME1501 [pii] 10.1111/j.1464-5491.2005.01501.x [doi]

Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P. D., . . . Huang, G. D. (2009). Glucose control and vascular complications in veterans with type 2 diabetes. *New England Journal of Medicine, 360*(2), 129-139. doi: 10.1056/NEJMoa0808431

Edwards, P., Roberts, I., Clarke, M., DiGuiseppi, C., Pratap, S., Wentz, R., & Kwan, I. (2002). Increasing response rates to postal questionnaires: systematic review. *British Medical Journal, 324*(7347), 1183.

Eiland, L., Goldner, W., Drincic, A., & Desouza, C. (2014). Inpatient hypoglycemia: a challenge that must be addressed. *Current Diabetes Reports, 14*(1), 445. doi: 10.1007/s11892-013-0445-1

Elia, M., Ceriello, A., Laube, H., Sinclair, A. J., Engfer, M., & Stratton, R. J. (2005). Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. *Diabetes Care, 28*(9), 2267-2279. doi: 28/9/2267 [pii]

Elliott, J. A., Abdulhadi, N. N., Al-Maniri, A. A., Al-Shafaee, M. A., & Wahlstrom, R. (2013). Diabetes self-management and education of people living with diabetes: a survey in primary health care in Muscat Oman. *PLoS One, 8*(2), e57400. doi: 10.1371/journal.pone.0057400

Elliott, M. B., Schafers, S. J., McGill, J. B., & Tobin, G. S. (2012). Prediction and prevention of treatment-related inpatient hypoglycemia. *Journal of Diabetes Science & Technology, 6*(2), 302-309.

Elliott, J., Jacques, R. M., Kruger, J., Campbell, M. J., Amiel, S. A., Mansell, P., . . . Heller, S. R. (2014). Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with Type 1 diabetes. *Diabetic Medicine, 31*(7), 847-853. doi: 10.1111/dme.12441

Endocrinology Expert Group. (2009). *Endocrinology, Therapeutic Guidelines Ltd*. Melbourne, Victoria, Australia.

Engler, P., Ramsey, S., & Smith, R. (2013). Alcohol use of diabetes patients: the need for assessment and intervention. *Acta Diabetologica, 50*(2), 93-99. doi: 10.1007/s00592-010-0200-x

Evans, C., & Crawford, B. (1999). Patient self-reports in pharmacoeconomic studies. Their use and impact on study validity. *Pharmacoeconomics, 15*(3), 241-256.

Evans, K. M., Kerr, D., & Flanagan, D. E. (2006). Diabetes and alcohol: time for realistic advice based on the evidence. *Practical Diabetes International, 23*(6), 267-272. doi: 10.1002/pdi.974

Fan, H., Pan, Q., Zhang, P., Liu, J., Xu, Y., & Yang, X. (2013). Influence of islet function on typing and prognosis of new-onset diabetes after intensive insulin therapy. *Medical Science Monitor, 19*, 787-793. doi: 10.12659/msm.889099

Fanelli, C. G., Pampanelli, S., Porcellati, F., Bartocci, L., Scionti, L., Rossetti, P., & Bolli, G. B. (2003). Rate of fall of blood glucose and physiological responses of counterregulatory hormones, clinical symptoms and cognitive function to hypoglycaemia in Type I diabetes mellitus in the postprandial state. *Diabetologia, 46*(1), 53-64. doi: 10.1007/s00125-002-0948-9

Fatati, G., Mirri, E., Del Tosto, S., Palazzi, M., Vendetti, A. L., Mattei, R., & Puxeddu, A. (2005). Use of insulin glargine in patients with hyperglycaemia receiving artificial nutrition. *Acta Diabetologica, 42*(4), 182-186. doi: 10.1007/s00592-005-0200-4

Fatourechi, M. M., Kudva, Y. C., Murad, M. H., Elamin, M. B., Tabini, C. C., & Montori, V. M. (2009). Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *Journal of Clinical Endocrinology & Metabolism, 94*(3), 729-740. doi: jc.2008-1415 [pii] 10.1210/jc.2008-1415 [doi]

Feinkohl, I., Aung, P. P., Keller, M., Robertson, C. M., Morling, J. R., McLachlan, S., . . . Price, J. F. (2014). Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the edinburgh type 2 diabetes study. *Diabetes Care, 37*(2), 507-515. doi: 10.2337/dc13-1384

Ferrannini, E., Nannipieri, M., Williams, K., Gonzales, C., Haffner, S. M., & Stern, M. P. (2004). Mode of Onset of Type 2 Diabetes from Normal or Impaired Glucose Tolerance. *Diabetes, 53*(1), 160-165. doi: 10.2337/diabetes.53.1.160

Finfer, S., Liu, B., Chittock, D. R., Norton, R., Myburgh, J. A., McArthur, C, Robinson, B. G. (2012). Hypoglycemia and risk of death in critically ill patients. *New England Journal of Medicine, 367*(12), 1108-1118. doi: 10.1056/NEJMoa1204942

Finney, S. J., Zekveld, C., Elia, A., & Evans, T. W. (2003). Glucose control and mortality in critically ill patients. *Journal of the American Medical Association, 290*(15), 2041-2047. doi: 10.1001/jama.290.15.2041

Fleming, M., Brown, R., & Brown, D. (2004). The efficacy of a brief alcohol intervention combined with %CDT feedback in patients being treated for type 2 diabetes and/or hypertension. *Journal of Studies on Alcohol, 65*(5), 631-637.

Ford, E. S., Zhao, G., & Li, C. (2010). Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *Journal of the American College of Cardiology, 55*(13), 1310-1317. doi: 10.1016/j.jacc.2009.10.060

Franz, M. J., Bantle, J. P., Beebe, C. A., Brunzell, J. D., Chiasson, J. L., Garg, A., . . . Wheeler, M. (2003). Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care, 26 Suppl 1*, S51-61.

Friedman, D. B., & Hoffman-Goetz, L. (2006). A systematic review of readability and comprehension instruments used for print and web-based cancer information. *Health Education and Behavior, 33*(3), 352-373. doi: 33/3/352 [pii] 10.1177/1090198105277329 [doi]

Frier, B. M. (2009). Defining hypoglycaemia: what level has clinical relevance? *Diabetologia, 52*(1), 31-34. doi: 10.1007/s00125-008-1209-3 [doi]

Galassetti, P., Tate, D., Neill, R. A., Richardson, A., Leu, S. Y., & Davis, S. N. (2006). Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. *Am J Physiol Endocrinol Metab, 290*(6), E1109-1117. doi: 10.1152/ajpendo.00244.2005

Garber, A. J., Ligthelm, R., Christiansen, J. S., & Liebl, A. (2007). Premixed insulin treatment for type 2 diabetes: analogue or human? *Diabetes Obesity & Metabolism, 9*(5), 630-639. doi: 10.1111/j.1463-1326.2006.00654.x

Garg, S. K., Brazg, R. L., Bailey, T. S., Buckingham, B. A., Slover, R. H., Klonoff, D. C., . . . Kaufman, F. R. (2014). Hypoglycemia Begets Hypoglycemia: The Order Effect in the ASPIRE In-Clinic Study. *Diabetes Technology & Therapeutics*. doi: 10.1089/dia.2013.0219

Gaston, S. F. (1992). Outcomes of hypoglycemia treated by standardized protocol in a community hospital. *Diabetes Educator, 18*(6), 491-494.

Geddes, J., Schopman, J. E., Zammitt, N. N., & Frier, B. M. (2008). Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. *Diabetic Medicine, 25*(4), 501-504. doi: DME2413 [pii] 10.1111/j.1464-5491.2008.02413.x [doi]

Genuth, S. (2008). The UKPDS and its global impact. *Diabetic Medicine, 25 Suppl 2*, 57-62. doi: 10.1111/j.1464-5491.2008.02504.x

Gerstein, H. C., Santaguida, P., Raina, P., Morrison, K. M., Balion, C., Hunt, D., . . . Booker, L. (2007). Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: A systematic overview and meta-analysis of prospective studies. *Diabetes Research and Clinical Practice, 78*(3), 305-312. doi: http://dx.doi.org/10.1016/j.diabres.2007.05.004

Gill, G. V., Woodward, A., Casson, I. F., & Weston, P. J. (2009). Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes--the 'dead in bed' syndrome revisited. *Diabetologia, 52*(1), 42-45. doi: 10.1007/s00125-008-1177-7

Glasgow, A. M., Tynan, D., Schwartz, R., Hicks, J. M., Turek, J., Driscol, C., . . . Getson, P. R. (1991). Alcohol and drug use in teenagers with diabetes mellitus. *Journal of Adolescent Health, 12*(1), 11-14.

Goldstein, D. E., Little, R. R., Lorenz, R. A., Malone, J. I., Nathan, D. M., & Peterson, C. M. (2004). Tests of glycemia in diabetes. *Diabetes Care, 27 Suppl 1*, S91-93.

Gonder-Frederick, L. A., Vajda, K. A., Schmidt, K. M., Cox, D. J., Devries, J. H., Erol, O., . . . Snoek, F. J. (2013). Examining the Behaviour subscale of the Hypoglycaemia Fear Survey: an international study. *Diabetic Medicine, 30*(5), 603-609. doi: 10.1111/dme.12129

Goodall, I. (2005). HbA1c standardisation destination--global IFCC Standardisation. How, why, where and when--a tortuous pathway from kit manufacturers, via inter-laboratory lyophilized and whole blood comparisons to designated national comparison schemes. *Clinical Biochemical Reviews, 26*(1), 5-19.

Guelfi, K. J., Jones, T. W., & Fournier, P. A. (2007). New insights into managing the risk of hypoglycaemia associated with intermittent high-intensity exercise in individuals with type 1 diabetes mellitus: implications for existing guidelines. *Sports Medicine, 37*(11), 937-946.

Guelfi, K. J., Ratnam, N., Smythe, G. A., Jones, T. W., & Fournier, P. A. (2007). Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. *Am J Physiol Endocrinol Metab, 292*(3), E865-870. doi: 10.1152/ajpendo.00533.2006

Guettier, J. M., & Gorden, P. (2006). Hypoglycemia. *Endocrinology and Metabolism Clinics of North America, 35*(4), 753-766, viii-ix. doi: 10.1016/j.ecl.2006.09.005

Gumna University. (2002). http://aoki2.si.gunma-u.ac.jp/exact/exact.html (Statistics database). Retrieved June 2011

Gunning, R. R., & Garber, A. J. (1978). Bioactivity of instant glucose. Failure of absorption through oral mucosa. *Journalof the American Medical Association, 240*(15), 1611-1612.

Haffner, S. M., Mykkanen, L., Festa, A., Burke, J. P., & Stern, M. P. (2000). Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation, 101*(9), 975-980.

Hagelberg, A., Ivert, T., Efendic, S., Ohrvik, J., & Anderson, R. E. (2008). Insulin glargine improves glycaemic control after coronary surgery in patients with diabetes or pre-diabetes. *Scandinavian Cardiovascular Journal, 42*(1), 71-76. doi: 10.1080/14017430701721756

Halimi, S. (2010). Acute consequences of hypoglycaemia in diabetic patients. *Diabetes and Metabolism, 36 Suppl 3*, S75-83. doi: 10.1016/s1262-3636(10)70471-7

Hanas, R., & John, G. (2010). 2010 consensus statement on the worldwide standardization of the hemoglobin A(1c) measurement. *Diabetes Research and Clinical Practice, 90*(2), 228-230. doi: 10.1016/j.diabres.2010.05.011

Hanefeld, M., & Bramlage, P. (2013). Insulin use early in the course of type 2 diabetes mellitus: the ORIGIN trial. *Current Diabetes Reports*, *13*(3), 342-349. doi: 10.1007/s11892-013-0366-z

Hanley, A. J., Wagenknecht, L. E., Norris, J. M., Bryer-Ash, M., Chen, Y. I., Anderson, A. M., . . . Haffner, S. M. (2009). Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family study. *Diabetologia, 52*(10), 2079-2086. doi: 10.1007/s00125-009-1464-y

Harada, N., Fukushima, M., Toyoda, K., Mitsui, R., Izuka, T., Taniguchi, A., . . . Inagaki, N. (2008). Factors responsible for elevation of 1-h postchallenge plasma glucose levels in Japanese men. *Diabetes Research and Clinical Practice, 81*(3), 284-289. doi: 10.1016/j.diabres.2008.04.011

Harbour, R., & Miller, J. (2001). A new system for grading recommendations in evidence based guidelines. *British Medical Journal, 323*(7308), 334-336.

Harjutsalo V, Forsblom C, & P, G. (2011). Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *British Medical Journal, 343*. doi: 10.1136/bmj.d5364

Harper, J. (2007). Glucose control in the intensive care unit: how it is done. *Proceedings of the Nutrition Society, 66*(3), 362-366. doi: 10.1017/s0029665107005629

Haus, J. M., Solomon, T. P. J., Marchetti, C. M., Edmison, J. M., González, F., & Kirwan, J. P. (2010). Free Fatty Acid-Induced Hepatic Insulin Resistance is Attenuated Following Lifestyle Intervention in Obese Individuals with Impaired Glucose Tolerance. *Journal of Clinical Endocrinology & Metabolism, 95*(1), 323-327. doi: 10.1210/jc.2009-1101

Hawkshead, J., & Krousel-Wood, M. A. (2007). Techniques for measuring medication adherence in hypertensive patients in outpatient settings. *Disease Management & Health Outcomes, 15*(2), 109-118.

Hejlesen, O. K., Andreassen, S., Cavan, D. A., & Hovorka, R. (1996). Analysing the hypoglycaemic counter-regulation: a clinically relevant phenomenon? *Computer Methods and Programs in Biomedicine, 50*(3), 231-240.

Heller, S. (2002). Reducing hypoglycaemia with insulin analogues. *International Journal of Obesity and Related Metabolic Disorders, 26 Suppl 3*, S31-36. doi: 10.1038/sj.ijo.0802175

Heller, S. R. (1999). Diabetic hypoglycaemia. *Baillieres Best Practice Research Clinical Endocrinology Metabolism, 13*(2), 279-294.

Heller, S. R., Amiel, S. A., & Mansell, P. (1999). Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. U.K. Lispro Study Group. *Diabetes Care, 22*(10), 1607-1611.

Hermanns, N., Kulzer, B., Kubiak, T., Krichbaum, M., & Haak, T. (2007). The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients with type 1 diabetes. *Diabetes/Metabolism Research and Reviews, 23*(7), 528-538. doi: 10.1002/dmrr.710 [doi]

Hermanns, N., Kulzer, B., Krichbaum, M., Kubiak, T., & Haak, T. (2010). Long-term effect of an education program (HyPOS) on the incidence of severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care, 33*(3), e36. doi: 10.2337/dc09-1656

Hermanns, N., Plate, M., Kulzer, B., Fischer, B., Linn, T., Bretzel, R., & Haak, T. (2008). Effect of experimentally induced hypoglycemia and different insulin levels on feelings of hunger in type 1 diabetic patients. *Experimental and Clinical Endocrinology and Diabetes, 116*(5), 255-261. doi: 10.1055/s-2007-993143

Hermansen, K., Fontaine, P., Kukolja, K. K., Peterkova, V., Leth, G., & Gall, M. A. (2004). Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia, 47*(4), 622-629. doi: 10.1007/s00125-004-1365-z

Hirsch, I. B. (2005). Insulin analogues. *New England Journal of Medicine, 352*(2), 174-183. doi: 10.1056/NEJMra040832

Hofman, Z., Lansink, M., Rouws, C., van Drunen, J. D. E., & Kuipers, H. (2007). Diabetes specific tube feed results in improved glycaemic and triglyceridaemic control during 6 h continuous feeding in diabetes patients. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, 2*(2), 44-50. doi: http://dx.doi.org/10.1016/j.eclnm.2007.02.001

Hong, J., Zhang, Y. F., Gu, W. Q., Zhang, Y. W., Su, Y. X., Chi, Z. N., . . . Ning, G. (2008). Insulin sensitivity and first-phase insulin secretion in obese Chinese with hyperglycemia in 30 and/or 60 min during glucose tolerance tests. *Endocrine, 34*(1-3), 75-80. doi: 10.1007/s12020-008-9106-6 [doi]

Hopper, I., Billah, B., Skiba, M., & Krum, H. (2011). Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with

prediabetes: meta-analysis of randomised controlled clinical trials. *Eur J Cardiovascular Prevention and Rehabilitation, 18*(6), 813-823. doi: 10.1177/1741826711421687

Hsia, E., Seggelke, S. A., Gibbs, J., Rasouli, N., & Draznin, B. (2011). Comparison of 70/30 Biphasic Insulin With Glargine/Lispro Regimen in Non–Critically Ill Diabetic Patients on Continuous Enteral Nutrition Therapy. *Nutrition in Clinical Practice, 26*(6), 714-717. doi: 10.1177/0884533611420727

Hsieh, A., & Twigg, S. M. (2014). The enigma of the dead-in-bed syndrome: Challenges in predicting and preventing this devastating complication of type 1 diabetes. *Journal of Diabetes and Its Complications*. doi: 10.1016/j.jdiacomp.2014.04.005

Husband, A. C., Crawford, S., McCoy, L. A., & Pacaud, D. (2010). The effectiveness of glucose, sucrose, and fructose in treating hypoglycemia in children with type 1 diabetes. *Pediatric Diabetes, 11*(3), 154-158. doi: PDI558 [pii] 10.1111/j.1399-5448.2009.00558.x [doi]

Iacovidou, A., & Hakim, N. (2013). Recent advances in pancreatic transplantation. *Experimental and Clinical Transplantation, 11*(6), 471-474.

Idris, I., Pillai, A., Fernando, D. J., Thomson, G., & Tate, H. (2013). Responders to insulin therapy at 18 months in adults with newly diagnosed diabetes: which insulin regimen? *Diabetic Medicine, 30*(3), e95-100. doi: 10.1111/dme.12096

International Diabetes Federation. (2011). Clinical Guidelines. 2012 http://www.idf.org/guidelines

International Diabetes Federation. (2013). IDF Diabetes Atlas 6th edition. Retrieved from http://www.idf.org/sites/default/files/5E_IDFAtlasPoster_2012_EN.pdf

Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., . . . Matthews, D. R. (2012). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care, 35*(6), 1364-1379. doi: 10.2337/dc12-0413

Iscoe, K. E., & Riddell, M. C. (2011). Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. *Diabetic Medicine, 28*(7), 824-832. doi: 10.1111/j.1464-5491.2011.03274.x

Jaser, S. S., Yates, H., Dumser, S., & Whittemore, R. (2011). Risky business: risk behaviors in adolescents with type 1 diabetes. *The Diabetes Educator, 37*(6), 756-764. doi: 10.1177/0145721711422610

Jayawardena, R., Ranasinghe, P., Byrne, N. M., Soares, M. J., Katulanda, P., & Hills, A. P. (2012). Prevalence and trends of the diabetes epidemic in South Asia: a systematic review and meta-analysis. *BMC Public Health, 12*, 380. doi: 10.1186/1471-2458-12-380

Jensen, V. F., Bogh, I. B., & Lykkesfeldt, J. (2014). Effect of insulin-induced hypoglycaemia on the CNS: Evidence from experimental studies. *Journal of Neuroendocrinology*. doi: 10.1111/jne.12133

Jones, E., Sinclair, J. M., Holt, R. I., & Barnard, K. D. (2013). Social networking and understanding alcohol-associated risk for people with type 1 diabetes: friend or foe? *Diabetes Technology & Therapeutics, 15*(4), 308-314. doi: 10.1089/dia.2012.0327

Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature, 444*(7121), 840-846.

Kang, Y., Lu, J. M., Sun, J. F., Li, C. L., Wang, X. L., Zhang, X. Q., . . . Mu, Y. M. (2009). [Characteristics of glycemic excursion in different subtypes of impaired glucose intolerance]. *Zhonghua Yi Xue Za Zhi, 89*(10), 669-672.

Karter, A. J., Parker, M. M., Moffet, H. H., Spence, M. M., Chan, J., Ettner, S. L., & Selby, J. V. (2006). Longitudinal Study of New and Prevalent Use of Self-Monitoring of Blood Glucose. *Diabetes Care, 29*(8), 1757-1763. doi: 10.2337/dc06-2073

Kedia, N. (2011). Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach. *Diabetes, Metabolic Syndrome And Obesity: Targets And Therapy, 4*, 337.

Kelley, K., Clark, B., Brown, V., & Sitzia, J. (2003). Good practice in the conduct and reporting of survey research. *International Journal for Quality in Health Care, 15*(3), 261-266. doi: 10.1093/intqhc/mzg031

Kerry, C., Mitchell, S., Sharma, S., Scott, A., & Rayman, G. (2013). Diurnal temporal patterns of hypoglycaemia in hospitalized people with diabetes may reveal potentially correctable factors. *Diabetic Medicine, 30*(12), 1403-1406. doi: 10.1111/dme.12256

Kilpatrick, E. S., Rigby, A. S., Goode, K., & Atkin, S. L. (2007). Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. *Diabetologia, 50*(12), 2553-2561. doi: 10.1007/s00125-007-0820-z

Kim, J. Y., Goran, M. I., Toledo-Corral, C. M., Weigensberg, M. J., Choi, M., & Shaibi, G. Q. (2013). One-hour glucose during an oral glucose challenge prospectively predicts beta-cell deterioration and prediabetes in obese Hispanic youth. *Diabetes Care, 36*(6), 1681-1686. doi: 10.2337/dc12-1861

Kim, Y., Rajan, K. B., Sims, S. A., Wroblewski, K. E., & Reutrakul, S. (2014). Impact of glycemic variability and hypoglycemia on adverse hospital outcomes in non-critically ill patients. *Diabetes Research and Clinical Practice*. doi: 10.1016/j.diabres.2013.11.026

Kinsley, B. T., Weinger, K., Bajaj, M., Levy, C. J., Simonson, D. C., Quigley, M., . . . Jacobson, A. M. (1999). Blood glucose awareness training and epinephrine responses to hypoglycemia during intensive treatment in type 1 diabetes. *Diabetes Care, 22*(7), 1022-1028. doi: 10.2337/diacare.22.7.1022

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., & Nathan, D. M. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine, 346*(6), 393-403. doi: 10.1056/NEJMoa012512

Korytkowski, M. T., Salata, R. J., Koerbel, G. L., Selzer, F., Karslioglu, E., Idriss, A. M., . . . Toledo, F. G. (2009). Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. *Diabetes Care, 32*(4), 594-596. doi: 32/4/594 [pii] 10.2337/dc08-1436 [doi]

Krinsley, J. S., & Grover, A. (2007). Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Critical Care Medicine, 35*(10), 2262-2267. doi: 10.1097/01.ccm.0000282073.98414.4b

Krnacova, V., Kubena, A., Macek, K., Bezdek, M., Smahelova, A., & Vlcek, J. (2012). Severe hypoglycaemia requiring the assistance of emergency medical services--frequency, causes and symptoms. *Biomedical papers of the Medical Faculty of the University Palacky, 156*(3), 271-277. doi: 10.5507/bp.2012.037

Kucera, M. L., & Graham, J. P. (1998). Insulin lispro, a new insulin analog. *Pharmacotherapy*, *18*(3), 526-538.

Kuzuya, T., Nakagawa, S., Satoh, J., Kanazawa, Y., Iwamoto, Y., Kobayashi, M., . . . Kadowaki, T. (2002). Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetes Research and Clinical Practice*, *55*(1), 65-85.

Langendam, M., Luijf, Y. M., Hooft, L., Devries, J. H., Mudde, A. H., & Scholten, R. J. (2012). Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews*, *1*, CD008101. doi: 10.1002/14651858.CD008101.pub2

Lawton, J., Rankin, D., Cooke, D. D., Elliott, J., Amiel, S., & Heller, S. (2013). Self-treating hypoglycaemia: a longitudinal qualitative investigation of the experiences and views of people with Type 1 diabetes. *Diabetic Medicine*, *30*(2), 209-215. doi: 10.1111/dme.12007

Leckie, A. M., Graham, M. K., Grant, J. B., Ritchie, P. J., & Frier, B. M. (2005). Frequency, Severity, and Morbidity of Hypoglycemia Occurring in the Workplace in People With Insulin-Treated Diabetes. *Diabetes Care*, *28*(6), 1333-1338. doi: 10.2337/diacare.28.6.1333

Leiter L, Y. J., Chiasson J, Harris S, Kleinstiver P, Sauriol L (2005). Assessment of the Impact of Fear of Hypoglycemic Episodes on Glycemic and Hypoglycemia Management *Canadian Journal Of Diabetes*, *29*(3), 186 - 192.

León-Sanz, M., García-Luna, P. P., Planas, M., Sanz-París, A., Gómez-Candela, C., Casimiro, C., & Group, t. A. S.-S. C. (2005). Glycemic and Lipid Control in Hospitalized Type 2 Diabetic Patients: Evaluation of 2 Enteral Nutrition Formulas (Low Carbohydrate-High Monounsaturated Fat vs High Carbohydrate). *Journal of Parenteral and Enteral Nutrition*, *29*(1), 21-29. doi: 10.1177/014860710502900121

Levitzky, Y. S., Pencina, M. J., D'Agostino, R. B., Meigs, J. B., Murabito, J. M., Vasan, R. S., & Fox, C. S. (2008). Impact of Impaired Fasting Glucose on Cardiovascular Disease: The Framingham Heart Study. *Journal of the American College of Cardiology*, *51*(3), 264-270. doi: http://dx.doi.org/10.1016/j.jacc.2007.09.038

Ley, P., & Florio, T. (1996). The use of readability formulas in health care. *Psychology, Health & Medicine*, *1*(1), 7-28.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology, 62*(10), e1-34. doi: 10.1016/j.jclinepi.2009.06.006

Lleva, R. R., & Inzucchi, S. E. (2011). Hospital management of hyperglycemia. *Current Opinion in Endocrinology, Diabetes, and Obesity, 18*(2), 110-118. doi: 10.1097/MED.0b013e3283447a6d

Lloyd, D. A., & Powell-Tuck, J. (2004). Artificial nutrition: principles and practice of enteral feeding. *Clinics in Colon and Rectal Surgery, 17*(2), 107-118. doi: 10.1055/s-2004-828657

Lu, J., Zang, J., & Li, H. (2013). Impact of Three Oral Antidiabetic Drugs on Markers of beta-Cell Function in Patients with Type 2 Diabetes: A Meta-Analysis. *PLoS One, 8*(10), e76713. doi: 10.1371/journal.pone.0076713

Luo, P., Cheng, Q., Chen, B., Li, Y., Wu, J., Zhang, X., . . . Lv, X. (2013). Hypoglycemia and Blood Glucose Fluctuations in the Application of a Sensor-Augmented Insulin Pump. *Diabetes Technology & Therapeutics,* doi: 10.1089/dia.2013.0078

Ly, T. T., Nicholas, J. A., Retterath, A., Lim, E. M., Davis, E. A., & Jones, T. W. (2013). Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *Journal of the American Medical Association, 310*(12), 1240-1247. doi: 10.1001/jama.2013.277818

MacLeod, S. F., Terada, T., Chahal, B. S., & Boule, N. G. (2013). Exercise lowers postprandial glucose but not fasting glucose in type 2 diabetes: a meta-analysis of studies using continuous glucose monitoring. *Diabetes/Metabolism Research and Reviews, 29*(8), 593-603. doi: 10.1002/dmrr.2461

Madhu, S. V., Muduli, S. K., & Avasthi, R. (2013). Abnormal glycemic profiles by CGMS in obese first-degree relatives of type 2 diabetes mellitus patients. *Diabetes Technology & Therapeutics, 15*(6), 461-465. doi: 10.1089/dia.2012.0333

Magee, M. C. (2012). Improving IV insulin administration in a community hospital. *Journal of Visualized Experiments,* (64), e3705. doi: 10.3791/3705

Magrys, S. A., & Olmstead, M. C. (2014). Alcohol intoxication alters cognitive skills mediated by frontal and temporal brain regions. *Brain and Cognition, 85C*, 271-276. doi: 10.1016/j.bandc.2013.12.010

Mandel, A. L., & Breslin, P. A. (2012). High endogenous salivary amylase activity is associated with improved glycemic homeostasis following starch ingestion in adults. *Journal of Nutrition, 142*(5), 853-858. doi: 10.3945/jn.111.156984

Mann, J. I., De Leeuw, I., Hermansen, K., Karamanos, B., Karlstrom, B., Katsilambros, N., . . . Vessby, B. (2004). Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. *Nutrition, Metabolism, And Cardiovascular Diseases, 14*(6), 373-394.

Manterola, C., Munoz, S., Grande, L., & Bustos, L. (2002). Initial validation of a questionnaire for detecting gastroesophageal reflux disease in epidemiological settings. *Journal of Clinical Epidemiology, 55*(10), 1041-1045. doi: S0895435602004547 [pii]

Marbury, T. C., Schwartz, S., Rosenberg, M. A., Jariwala, N., Becker, R. H., & Johnston, P. S. (2008). A pilot study to examine the feasibility of insulin glargine in subjects with impaired fasting glucose, impaired glucose tolerance or new-onset type 2 diabetes. *Experimental and Clinical Endocrinology and Diabetes, 116*(5), 282-288. doi: 10.1055/s-2007-1022521

Marchesini, G., Veronese, G., Forlani, G., Forlani, G., Ricciardi, L. M., & Fabbri, A. (2014). The management of severe hypoglycemia by the emergency system: The HYPOTHESIS study. *Nutr Metab Cardiovasc Dis*. doi: 10.1016/j.numecd.2014.05.012

Martínez-Aguayo, A., Araneda, J. C., Fernandez, D., Gleisner, A., Perez, V., & Codner, E. (2007). Tobacco, alcohol, and illicit drug use in adolescents with diabetes mellitus*. *Pediatric Diabetes, 8*(5), 265-271. doi: 10.1111/j.1399-5448.2007.00307.x

Mason, C. C., Hanson, R. L., & Knowler, W. C. (2007). Progression to type 2 diabetes characterized by moderate then rapid glucose increases. *Diabetes, 56*(8), 2054-2061. doi: 10.2337/db07-0053

Maynard, G. A., Huynh, M. P., & Renvall, M. (2008). Iatrogenic Inpatient Hypoglycemia: Risk Factors, Treatment, and Prevention. *Diabetes Spectrum, 21*(4), 241-247. doi: 10.2337/diaspect.21.4.241

Mazer, M., & Chen, E. (2009). Is subcutaneous administration of rapid-acting insulin as effective as intravenous insulin for treating diabetic ketoacidosis? *Annals of Emergency Medicine, 53*(2), 259-263.

McAndrew, L., Schneider, S. H., Burns, E., & Leventhal, H. (2007). Does patient blood glucose monitoring improve diabetes control? A systematic review of the literature. *The Diabetes Educator, 33*(6), 991-1010.

McCall, A. L., & Farhy, L. S. (2013). Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. *Minerva Endocrinologica, 38*(2), 145-163.

McCormack, P. L. (2014). Exenatide Twice Daily: A Review of Its Use in the Management of Patients with Type 2 Diabetes Mellitus. *Drugs*. doi: 10.1007/s40265-013-0172-6

McCoy, R. G., Van Houten, H. K., Ziegenfuss, J. Y., Shah, N. D., Wermers, R. A., & Smith, S. A. (2013). Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. *Endocrine Practice, 19*(5), 792-799. doi: 10.4158/ep12382.or

McCrimmon, R. (2009). Glucose sensing during hypoglycemia: lessons from the lab. *Diabetes Care, 32*(8), 1357-1363. doi: 10.2337/dc09-0123

McCrimmon, R. J., Shaw, M., Fan, X., Cheng, H., Ding, Y., Vella, M. C., . . . Sherwin, R. S. (2008). Key role for AMP-activated protein kinase in the ventromedial hypothalamus in regulating counterregulatory hormone responses to acute hypoglycemia. *Diabetes, 57*(2), 444-450. doi: 10.2337/db07-0837

McIntyre, H. D., Knight, B. A., Harvey, D. M., Noud, M. N., Hagger, V. L., & Gilshenan, K. S. (2010). Dose adjustment for normal eating (DAFNE) - an audit of outcomes in Australia. *Medical Journal of Australia, 192*(11), 637-640.

McKeage, K., & Goa, K. L. (2001). Insulin glargine: a review of its therapeutic use as a long-acting agent for the management of type 1 and 2 diabetes mellitus. *Drugs, 61*(11), 1599-1624.

Medical Update Co. UK. (2013). Hypoglycemia. Retrieved from http://medicalupdate.co.uk/files/2013_Feb_DiabetesClapham-Web_download.pdf website:

Meisinger, C., Wölke, G., Brasche, S., Strube, G., & Heinrich, J. (2006). Postload Plasma Glucose and 30-Year Mortality Among Nondiabetic Middle-Aged Men From the General Population: The ERFORT Study. *Annals of Epidemiology, 16*(7), 534-539. doi: 10.1016/j.annepidem.2005.10.008

Melanson, K. J., Westerterp-Plantenga, M. S., Saris, W. H., Smith, F. J., & Campfield, L. A. (1999). Blood glucose patterns and appetite in time-blinded humans: carbohydrate versus fat. *American Journal of Physiology, 277*(2 Pt 2), R337-345.

Mellbin, L. G., Ryden, L., Riddle, M. C., Probstfield, J., Rosenstock, J., Diaz, R., . . . Gerstein, H. C. (2013). Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *European Heart Journal, 34*(40), 3137-3144. doi: 10.1093/eurheartj/eht332

Mendez, C. E., Mok, K. T., Ata, A., Tanenberg, R. J., Calles-Escandon, J., & Umpierrez, G. E. (2013). Increased glycemic variability is independently associated with length of stay and mortality in noncritically ill hospitalized patients. *Diabetes Care, 36*(12), 4091-4097. doi: 10.2337/dc12-2430

Miller-Hagan, R. S., & Janas, B. G. (2002). Drinking Perceptions and Management Strategies of College Students With Diabetes. *The Diabetes Educator, 28*(2), 233-244. doi: 10.1177/014572170202800209

Miller, C. D., Phillips, L. S., Ziemer, D. C., Gallina, D. L., Cook, C. B., & El-Kebbi, I. M. (2001). Hypoglycemia in patients with type 2 diabetes mellitus. *Archives of Internal Medicine, 161*(13), 1653-1659.

Milman, S., & Crandall, J. P. (2011). Mechanisms of vascular complications in prediabetes. *Medical Clinics of North America, 95*(2), 309-325, vii. doi: 10.1016/j.mcna.2010.11.004

Minges, K. E., Zimmet, P., Magliano, D. J., Dunstan, D. W., Brown, A., & Shaw, J. E. (2011). Diabetes prevalence and determinants in Indigenous Australian populations: A systematic review. *Diabetes Research and Clinical Practice, 93*(2), 139-149. doi: 10.1016/j.diabres.2011.06.012

Moghissi, E. (2004). Hospital management of diabetes: beyond the sliding scale. *Cleveland Clinic Journal of Medicine, 71*(10), 801-808.

Moghissi, E. S., Korytkowski, M. T., DiNardo, M., Einhorn, D., Hellman, R., Hirsch, I. B., . . . Umpierrez, G. E. (2009). American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. *Diabetes Care, 32*(6), 1119-1131. doi: 10.2337/dc09-9029

Moher, D., Cook, D. J., Eastwood, S., Olkin, I., Rennie, D., & Stroup, D. F. (1999). Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet, 354*(9193), 1896-1900.

Moher, D., & Tricco, A. C. (2008). Issues related to the conduct of systematic reviews: a focus on the nutrition field. *American Journal of Clinical Nutrition, 88*(5), 1191-1199.

Mori, Y., Ohta, T., Tanaka, T., Morohoshi, Y., Matsuura, K., Yokoyama, J., & Utsunomiya, K. (2011). Effects of a low-carbohydrate diabetes-specific formula in type 2 diabetic patients during tube feeding evaluated by continuous glucose monitoring. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, 6*(2), e68-e73. doi: http://dx.doi.org/10.1016/j.eclnm.2011.01.010

Myers, V., Boyer, B., Herbert, J., Barakat, L., & Scheiner, G. (2007). Fear of Hypoglycemia and Self Reported Posttraumatic Stress in Adults with Type I Diabetes Treated by Intensive Regimens. *Journal of Clinical Psychology in Medical Settings, 14*(1), 11-21. doi: 10.1007/s10880-007-9051-1

Nair, K. M., Levine, M., Lohfeld, L. H., & Gerstein, H. C. (2007). I take what I think works for me": a qualitative study to explore patient perception of diabetes treatment benefits and risks. *The Canadian Journal of Clinical Pharmacology, 14*(2), e251-e259.

Nathan, D. M. (2014). The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care, 37*(1), 9-16. doi: 10.2337/dc13-2112

Nathan, D. M., Davidson, M. B., DeFronzo, R. A., Heine, R. J., Henry, R. R., Pratley, R., & Zinman, B. (2007). Impaired Fasting Glucose and Impaired Glucose Tolerance. *Diabetes Care, 30*(3), 753-759. doi: 10.2337/dc07-9920

National Health and Medical Research Council. (2008). *Alcohol and Health in Australia*. http://www.nhmrc.gov.au/your-health/alcohol-guidelines/alcohol-and-health-australia.

Ng, J. M., Cox, H., Longbotham, D., Kilpatrick, E. S., Atkin, S. L., & Allan, B. J. (2009). Hypoglycemia and Clinical Outcomes in Patients With Diabetes Hospitalized in the General Ward. *Diabetes Care, 32*(12), e151. doi: 10.2337/dc09-1341

Nirantharakumar, K., Marshall, T., Kennedy, A., Narendran, P., Hemming, K., & Coleman, J. J. (2012). Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. *Diabetic Medicine, 29*(12), e445-448. doi: 10.1111/dme.12002

O'Toole, B. I., Catts, S. V., Outram, S., Pierse, K. R., & Cockburn, J. (2009). The Physical and Mental Health of Australian Vietnam Veterans 3 Decades After the War and Its Relation to Military Service, Combat, and Post-Traumatic Stress Disorder. *American Journal of Epidemiology, 170*(3), 318-330. doi: 10.1093/aje/kwp146

Official Statistics of Finland (OSF). (2012). *Causes of death [e-publication]*. http://www.stat.fi/til/ksyyt/2011/ksyyt_2011_2012-12-21_tie_001_en.html.

Okamoto, K., Ohsuka, K., Shiraishi, T., Hukazawa, E., Wakasugi, S., & Furuta, K. (2002). Comparability of epidemiological information between self- and interviewer-administered questionnaires. *Journal of Clinical Epidemiology, 55*(5), 505-511.

Oyibo, S. O., Sagi, S. V., & Home, C. (2012). Glycaemic control during enteral tube feeding in patients with diabetes who have had a stroke: a twice-daily insulin regimen. *Practical Diabetes, 29*(4), 135-139. doi: 10.1002/pdi.1678

Papargyri, P., Ojeda Rodriguez, S., Corrales Hernandez, J. J., Mories Alvarez, M. T., Recio Cordova, J. M., Delgado Gomez, M., . . . Miralles Garcia, J. M. (2013). An observational 7-year study of continuous subcutaneous insulin infusion for the treatment of type 1 diabetes mellitus. *Endocrinología y Nutrición,* doi: 10.1016/j.endonu.2013.09.003

Paranjape, S. A., Chan, O., Zhu, W., Horblitt, A. M., McNay, E. C., Cresswell, J. A., . . . Sherwin, R. S. (2010). Influence of insulin in the ventromedial hypothalamus on pancreatic glucagon secretion in vivo. *Diabetes, 59*(6), 1521-1527. doi: 10.2337/db10-0014

Parfitt, V. J., & Bhake, R. (2012). An analysis of all cases of severe hypoglycaemia presenting to a major teaching hospital over one year. *Diabetic Medicine, 29*, 131.

Park, Y. W., Chang, Y., Sung, K. C., Ryu, S., Sung, E., & Kim, W. S. (2006). The sequential changes in the fasting plasma glucose levels within normoglycemic range predict type 2 diabetes in healthy, young men. *Diabetes Research and Clinical Practice, 73*(3), 329-335. doi: 10.1016/j.diabres.2006.02.006

Patterson, C. C., Dahlquist, G., Harjutsalo, V., Joner, G., Feltbower, R. G., Svensson, J., . . . Soltesz, G. (2007). Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. *Diabetologia, 50*(12), 2439-2442. doi: 10.1007/s00125-007-0824-8

Pedersen-Bjergaard, U., Reubsaet, J. L., Nielsen, S. L., Pedersen-Bjergaard, S., Perrild, H., Pramming, S., & Thorsteinsson, B. (2005). Psychoactive drugs, alcohol, and severe hypoglycemia in insulin-treated diabetes: analysis of 141 cases. *American Journal of Medicine, 118*(3), 307-310. doi: 10.1016/j.amjmed.2004.07.054

Peng, C. Y., So, T. S., Stage, F. K., & St. John, E. P. (2002). The use and interpretation of logistic regression in higher education journals: 1988 - 1999. *Research in Higher Education, 43*, 259 - 293.

Perry, L., & McConney, A. (2010). Does the SES of the school matter? An examination of socioeconomic status and student achievement using PISA 2003. *The Teachers College Record, 112*(4), 7-8.

Persenius, M. W., Hall-Lord, M. L., Baath, C., & Larsson, B. W. (2008). Assessment and documentation of patients' nutritional status: perceptions of registered nurses and their chief nurses. *Journal of Clinical Nursing, 17*(16), 2125-2136. doi: 10.1111/j.1365-2702.2007.02202.x

Pickup, J. C., & Sutton, A. J. (2008). Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabetic Medicine, 25*(7), 765-774. doi: 10.1111/j.1464-5491.2008.02486.x

Pietraszek, A., Gregersen, S., & Hermansen, K. (2010). Alcohol and type 2 diabetes. A review. *Nutrition, Metabolism, and Cardiovascular Diseases, 20*(5), 366-375.

Plosker, G. L. (2014). Sitagliptin: A Review of Its Use in Patients with Type 2 Diabetes Mellitus. *Drugs*. doi: 10.1007/s40265-013-0169-1

Plougmann, S., Hejlesen, O., Turner, B., Kerr, D., & Cavan, D. (2003). The effect of alcohol on blood glucose in Type 1 diabetes--metabolic modelling and integration in a decision support system. *International Journal of Medical Informatics, 70*(2-3), 337-344.

Pohl, M., Mayr, P., Mertl-Roetzer, M., Lauster, F., Haslbeck, M., Hipper, B., . . . Rahlfs, V. W. (2009). Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: stage II of a randomized, controlled multicenter trial. *Journal of Parenteral and Enteral Nutrition, 33*(1), 37-49. doi: 0148607108324582 [pii] 10.1177/0148607108324582 [doi]

Pohl, M., Mayr, P., Mertl-Roetzer, M., Lauster, F., Lerch, M., Eriksen, J., . . . Rahlfs, V. W. (2005). Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. *European Journal of Clinical Nutrition, 59*(11), 1221-1232. doi: 10.1038/sj.ejcn.1602232

Putz, D., & Kabadi, U. M. (2002). Insulin glargine in continuous enteric tube feeding. *Diabetes Care, 25*(10), 1889-1890.

Ramchandani, N., Cantey-Kiser, J. M., Alter, C. A., Brink, S. J., Yeager, S. D., Tamborlane, W. V., & Chipkin, S. R. (2000). Self-Reported Factors That Affect Glycemic Control in College Students With Type 1 Diabetes. *The Diabetes Educator, 26*(4), 656-666. doi: 10.1177/014572170002600413

Rana, O. A., Byrne, C. D., & Greaves, K. (2014). Intensive glucose control and hypoglycaemia: a new cardiovascular risk factor? *Heart, 100*(1), 21-27. doi: 10.1136/heartjnl-2013-303871

Rasmussen, B. M., Orskov, L., Schmitz, O., & Hermansen, K. (2001). Alcohol and glucose counterregulation during acute insulin-induced hypoglycemia in type 2 diabetic subjects. *Metabolism: Clinical and Experimental, 50*(4), 451-457. doi: 10.1053/meta.2001.21697

Rattray, J., & Jones, M. C. (2007). Essential elements of questionnaire design and development. *Journal of Clinical Nursing, 16*(2), 234-243.

Richardson, T., Weiss, M., Thomas, P., & Kerr, D. (2005). Day After the Night Before: Influence of evening alcohol on risk of hypoglycemia in patients with type 1 diabetes. *Diabetes Care, 28*(7), 1801-1802.

Riddle, M. C., Rosenstock, J., Vlajnic, A., & Gao, L. (2013). Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes, Obesity & Metabolism,* doi: 10.1111/dom.12225

Roberts, C. (2008). Modelling patterns of agreement for nominal scales. *Statistics in Medicine, 27*(6), 810-830. doi: 10.1002/sim.2945

Roberts, K., & Smith, A. (2003). Outcome of diabetic patients treated in the prehospital arena after a hypoglycaemic episode, and an exploration of treat and release protocols: a review of the literature. *Emergency Medicine Journal, 20*(3), 274-276.

Rodin, J., Wack, J., Ferrannini, E., & DeFronzo, R. A. (1985). Effect of insulin and glucose on feeding behavior. *Metabolism: Clinical and Experimental, 34*(9), 826-831.

Rotella, C., Pala, L., & Mannucci, E. (2013). Role of Insulin in the Type 2 Diabetes Therapy: Past, Present and Future. *International Journal of Endocrinology* and *Metabolism, 11*(3), 137-144. doi: 10.5812/ijem.7551

Rubin, R. R., & Peyrot, M. (2001). Psychological issues and treatments for people with diabetes. *Journal of Clinical Psychology, 57*(4), 457-478.

Rusavy, Z., Lacigova, S., & Kvapil, M. (2013). [What has the largest study in the history of diabetology brought us?]. *Vnitrni Lekarstvi, 59*(3), 160-164.

Saloranta, C., Guitard, C., Pecher, E., de Pablos-Velasco, P., Lahti, K., Brunel, P., & Groop, L. (2002). Nateglinide Improves Early Insulin Secretion and Controls Postprandial Glucose Excursions in a Prediabetic Population. *Diabetes Care, 25*(12), 2141-2146. doi: 10.2337/diacare.25.12.2141

Saw, S. M., & Ng, T. P. (2001). The design and assessment of questionnaires in clinical research. *Singapore Medical Journal, 42*(3), 131-135.

Scaramuzza, A., De Palma, A., Mameli, C., Spiri, D., Santoro, L., & Zuccotti, G. V. (2010). Adolescents with type 1 diabetes and risky behaviour. *Acta Paediatrica, 99*(8), 1237-1241. doi: 10.1111/j.1651-2227.2010.01813.x

Schalm, R. L., & Kelloway, E. K. (2001). The relationship between response rate and effect size in occupational health psychology research. *Journal of Occupational Health Psychology, 6*(2), 160-163.

Scheen, A. J., & Lefebvre, P. J. (2004). [Reactive hypoglycaemia, a mysterious, insidious but non dangerous critical phenomenon]. *Revue Medicale de Liege, 59*(4), 237-242.

Schmid, S. M., Jauch-Chara, K., Hallschmid, M., Oltmanns, K. M., Born, J., & Schultes, B. (2008). Short-term nocturnal hypoglycaemia increases morning food intake in healthy humans. *Diabetic Medicine, 25*(2), 232-235. doi: 10.1111/j.1464-5491.2007.02347.x

Schnipper, J. L., Magee, M., Larsen, K., Inzucchi, S. E., & Maynard, G. (2008). Society of hospital medicine glycemic control task force summary: Practical recommendations for assessing the impact of glycemic control efforts. *Journal of Hospital Medicine, 3*(S5), 66-75. doi: 10.1002/jhm.356

Scholtes, V. A., Terwee, C. B., & Poolman, R. W. (2011). What makes a measurement instrument valid and reliable? *Injury, 42*(3), 236-240. doi: 10.1016/j.injury.2010.11.042

Schopman, J. E., Simon, A. C., Hoefnagel, S. J., Hoekstra, J. B., Scholten, R. J., & Holleman, F. (2014). The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews, 30*(1), 11-22. doi: 10.1002/dmrr.2470

Seaquist, E. R., Anderson, J., Childs, B., Cryer, P., Dagogo-Jack, S., Fish, L., . . . Vigersky, R. (2013). Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care, 36*(5), 1384-1395. doi: 10.2337/dc12-2480

Sechterberger, M. K., Bosman, R. J., Oudemans-van Straaten, H. M., Siegelaar, S. E., Hermanides, J., Hoekstra, J. B., & De Vries, J. H. (2013). The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study. *Critical Care, 17*(2), R52. doi: 10.1186/cc12572

Sheetz, M. J., & King, G. L. (2002). Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *Journal of the Americal Medical Association, 288*(20), 2579-2588.

Shiu, A. T., & Wong, R. Y. (2002). Fears and worries associated with hypoglycaemia and diabetes complications: perceptions and experience of Hong Kong Chinese clients. *Journal of Advanced Nursing, 39*(2), 155-163.

Shiu, A. T. Y., & Wong, R. Y. M. (2000). Fear of hypoglycaemia among insulin-treated Hong Kong Chinese patients: implications for diabetes patient education. *Patient Education and Counseling, 41*(3), 251-261.

Sigal, R. J., Kenny, G. P., Wasserman, D. H., Castaneda-Sceppa, C., & White, R. D. (2006). Physical activity/exercise and Type 2 diabetes A consensus statement from the American Diabetes Association. *Diabetes Care, 29*(6), 1433-1438.

Siler, S. Q., Neese, R. A., Christiansen, M. P., & Hellerstein, M. K. (1998). The inhibition of gluconeogenesis following alcohol in humans. *American Journal of Physiology-Endocrinology And Metabolism, 275*(5), E897-E907.

Singapore Diabetes Society. (2010). Diabetes and Hypoglycemia. *www.diabetes.org.sg.*

Sitzia, J., & Wood, N. (1998). Response rate in patient satisfaction research: an analysis of 210 published studies. *International Journal for Quality in Health Care, 10*(4), 311-317.

Skrivarhaug, T., Bangstad, H. J., Stene, L. C., Sandvik, L., Hanssen, K. F., & Joner, G. (2006). Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia, 49*(2), 298-305. doi: 10.1007/s00125-005-0082-6

Skyler, J. S., Bergenstal, R., Bonow, R. O., Buse, J., Deedwania, P., Gale, E. A., . . . Sherwin, R. S. (2009). Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *Journal of the American College of Cardiology, 53*(3), 298-304. doi: 10.1016/j.jacc.2008.10.008

Slama, G., Traynard, P.-Y., Desplanque, N., Pudar, H., Dhunputh, I., Letanoux, M., . . . Tchobroutsky, G. (1990). The Search for an Optimized Treatment of Hypoglycemia: Carbohydrates in Tablets, Solution, or Gel for the Correction of Insulin Reactions. *Archives of Internal Medicine, 150*(3), 589-593. doi: 10.1001/archinte.1990.00390150083016

Socransky, S. J., Pirrallo, R. G., & Rubin, J. M. (1998). Out-of-hospital treatment of hypoglycemia: refusal of transport and patient outcome. *Academic Emergency Medicine, 5*(11), 1080-1085.

Somerset, A., Coffey, R., Jones, L., & Murphy, C. V. (2014). The impact of prediabetes on glycemic control and clinical outcomes postburn injury. *J Journal of burn care & research, 35*(1), 5-10. doi: 10.1097/BCR.0b013e3182a2adea

Sommerfield, A. J., Ewing, F. M. E., Strachan, M. W. J., Deary, I. J., Aitken, G., & Frier, B. M. (2003). Self-treatment of mild symptomatic hypoglycaemia by people with insulin-treated diabetes. *Diabetic Medicine, 20*(8), 686-687. doi: 10.1046/j.1464-5491.2003.09281.x

Sorensen, M., & Johansen, O. E. (2010). Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. *Scandinavian Journal of Clinical and Laboratory Investigation, 70*(6), 385-391. doi: 10.3109/00365513.2010.491869

Stagnaro-Green, A., Barton, M. K., Linekin, P. L., Corkery, E., deBeer, K., & Roman, S. H. (1995). Mortality in hospitalized patients with hypoglycemia and severe hyperglycemia. *Mount Sinai Journal of Medicine, 62*(6), 422-426.

Stahn, A., Pistrosch, F., Ganz, X., Teige, M., Koehler, C., Bornstein, S., & Hanefeld, M. (2014). Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: silent hypoglycemias and silent arrhythmias. *Diabetes Care, 37*(2), 516-520. doi: 10.2337/dc13-0600

Stefanova, S. D., Cox, C., & Hill, M. (2013). Hypoglycaemia: causes, risk factors and pathophysiology. *Nursing Standard, 27*(42), 42-48.

Stein, C., Devore, R., & Wojcik, B. (2005). *Calculation of the Kappa Statistic for Inter-Rater Reliability: The Case Where Raters Can Select Multiple Responses from a Large Number of Categories*. Paper presented at the SUGI 30 Proceedings, Philadelphia, Pennsylvania

Stockwell, T., Donath, S., Cooper-Stanbury, M., Chikritzhs, T., Catalano, P., & Mateo, C. (2004). Under-reporting of alcohol consumption in household surveys: a comparison of quantity–frequency, graduated–frequency and recent recall. *Addiction, 99*(8), 1024-1033. doi: 10.1111/j.1360-0443.2004.00815.x

Strote, J., Simons, R., & Eisenberg, M. (2008). Emergency medical technician treatment of hypoglycemia without transport. *The American Journal of*

*Emergency Medicine*, *26*(3), 291-295. doi: http://dx.doi.org/10.1016/j.ajem.2007.05.030

Su, G., Mi, S., Tao, H., Li, Z., Yang, H., Zheng, H., . . . Ma, C. (2011). Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. *Cardiovascular Diabetology, 10,* 19. doi: 10.1186/1475-2840-10-19

Su, J. B., Chen, T., Xu, F., Wang, X. Q., Chen, J. F., Wu, G., . . . Wang, X. H. (2013). Glycemic variability in normal glucose regulation subjects with elevated 1-h postload plasma glucose levels. *Endocrine*. doi: 10.1007/s12020-013-0047-3

Subar, A. F., Ziegler, R. G., Thompson, F. E., Johnson, C. C., Weissfeld, J. L., Reding, D., . . . Hayes, R. B. (2001). Is shorter always better? Relative importance of questionnaire length and cognitive ease on response rates and data quality for two dietary questionnaires. *American Journal of Epidemiology, 153*(4), 404-409.

Succurro, E., Marini, M. A., Arturi, F., Grembiale, A., Lugarà, M., Andreozzi, F., . . . Sesti, G. (2009). Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. *Atherosclerosis, 207*(1), 245-249. doi: 10.1016/j.atherosclerosis.2009.04.006

Sumner, J., Baber, C., & Williams, V. (2000). What do patients with type 1 diabetes know about hypoglycaemia? *Practical Diabetes International, 17*(6), 187-190. doi: 10.1002/1528-252x(200009)17:6<187::aid-pdi74>3.0.co;2-i

Swinnen, S. G., Hoekstra, J. B., & DeVries, J. H. (2009). Insulin Therapy for Type 2 Diabetes. *Diabetes Care*, *32*(suppl 2), S253-S259. doi: 10.2337/dc09-S318

Swinnen, S. G., Mullins, P., Miller, M., Hoekstra, J. B., & Holleman, F. (2009). Changing the glucose cut-off values that define hypoglycaemia has a major effect on reported frequencies of hypoglycaemia. *Diabetologia, 52*(1), 38-41. doi: 10.1007/s00125-008-1147-0 [doi]

Tabak, A. G., Herder, C., Rathmann, W., Brunner, E. J., & Kivimaki, M. (2012). Prediabetes: a high-risk state for diabetes development. *Lancet, 379*(9833), 2279-2290. doi: 10.1016/s0140-6736(12)60283-9

Taheri, N., Iraj, B., Amini, M., Amini, P., & Aminorroaya, A. (2010). Cardiovascular risk factors in relatives of type 2 diabetics with normal glucose tolerance test

and elevated one-hour plasma glucose. *Endokrynologia Polska, 61*(4), 359-363.

Tan, P., Chen, H. C., Taylor, B., & Hegney, D. (2012). Experience of hypoglycaemia and strategies used for its management by community-dwelling adults with diabetes mellitus: a systematic review. The *International Journal of Evidence-Based Healthcare, 10*(3), 169-180. doi: 10.1111/j.1744-1609.2012.00276.x

Temelkova-Kurktschiev, T. S., Koehler, C., Henkel, E., Leonhardt, W., Fuecker, K., & Hanefeld, M. (2000). Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care, 23*(12), 1830-1834.

Testa, M. A., Gill, J., Su, M., Turner, R. R., Blonde, L., & Simonson, D. C. (2012). Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. *Journal of Clinical Endocrinology and Metabolism, 97*(10), 3504-3514. doi: 10.1210/jc.2012-1763

Thomas, R. M., Francis Gerstel, P. A., Williams, E. C., Sun, H., Bryson, C. L., Au, D. H., & Bradley, K. A. (2012). Association between alcohol screening scores and diabetic self-care behaviors. *Family Medicine, 44*(8), 555-563.

Thunander, M., Petersson, C., Jonzon, K., Fornander, J., Ossiansson, B., Torn, C., . . . Landin-Olsson, M. (2008). Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. *Diabetes Research and Clinical Practice, 82*(2), 247-255. doi: 10.1016/j.diabres.2008.07.022

Tirimacco, R., Koumantakis, G., Erasmus, R., Mosca, A., Sandberg, S., Watson, I. D., . . . Gillery, P. (2013). Glucose meters - fit for clinical purpose. *Clinical Chemistry and Laboratory Medicine, 51*(5), 943-952. doi: 10.1515/cclm-2013-0011

Tirosh, A., Shai, I., Tekes-Manova, D., Israeli, E., Pereg, D., Shochat, T., . . . Rudich, A. (2005). Normal fasting plasma glucose levels and type 2 diabetes in young men. *New England Journal of Medicine, 353*(14), 1454-1462. doi: 10.1056/NEJMoa050080

Tong, Q., Ye, C., McCrimmon, R. J., Dhillon, H., Choi, B., Kramer, M. D., . . . Lowell, B. B. (2007). Synaptic glutamate release by ventromedial

hypothalamic neurons is part of the neurocircuitry that prevents hypoglycemia. *Cell Metab, 5*(5), 383-393. doi: 10.1016/j.cmet.2007.04.001

Tonyushkina, K., & Nichols, J. H. (2009). Glucose meters: a review of technical challenges to obtaining accurate results. *Journal of Diabetes Science and Technology, 3*(4), 971-980.

Torimoto, K., Okada, Y., Mori, H., & Tanaka, Y. (2013). Relationship between fluctuations in glucose levels measured by continuous glucose monitoring and vascular endothelial dysfunction in type 2 diabetes mellitus. *Cardiovascular Diabetology, 12*, 1. doi: 10.1186/1475-2840-12-1

Tourangeau, R., & Yan, T. (2007). Sensitive questions in surveys. *Psychological Bulletin, 133*(5), 859-883. doi: 2007-12463-007 [pii] 10.1037/0033-2909.133.5.859 [doi]

Turchin, A., Matheny, M. E., Shubina, M., Scanlon, J. V., Greenwood, B., & Pendergrass, M. L. (2009). Hypoglycemia and Clinical Outcomes in Patients With Diabetes Hospitalized in the General Ward. *Diabetes Care, 32*(7), 1153-1157. doi: 10.2337/dc08-2127

Turner, B. C., Jenkins, E., Kerr, D., Sherwin, R. S., & Cavan, D. A. (2001). The Effect of Evening Alcohol Consumption on Next-Morning Glucose Control in Type 1 Diabetes. *Diabetes Care, 24*(11), 1888-1893. doi: 10.2337/diacare.24.11.1888

Twigg, S. M., Kamp, M. C., Davis, T. M., Neylon, E. K., & Flack, J. R. (2007). Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association. *Medical Journal of Australia, 186*(9), 461-465. doi: twi11006_fm [pii]

UK Hypoglycaemia Study Group. (2007). Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia, 50*(6), 1140-1147. doi: 10.1007/s00125-007-0599-y [doi]

UKPDS Group. (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet, 352*(9131), 837-853.

Umpierrez, G. E., Hellman, R., Korytkowski, M. T., Kosiborod, M., Maynard, G. A., Montori, V. M., . . . Van den Berghe, G. (2012). Management of

hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism, 97*(1), 16-38. doi: 10.1210/jc.2011-2098 10.1210/jcem.97.1.zeg16a

Umpierrez, G. E., Hor, T., Smiley, D., Temponi, A., Umpierrez, D., Ceron, M., . . . Baldwin, D. (2009). Comparison of inpatient insulin regimens with detemir plus aspart versus neutral protamine hagedorn plus regular in medical patients with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism, 94*(2), 564-569. doi: 10.1210/jc.2008-1441

Umpierrez, G. E., Smiley, D., Jacobs, S., Peng, L., Temponi, A., Mulligan, P., . . . Rizzo, M. (2011). Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care, 34*(2), 256-261. doi: 10.2337/dc10-1407

Unwin, N., Shaw, J., Zimmet, P., & Alberti, K. G. (2002a). Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetic Medicine, 19*(9), 708-723.

Unwin, N., Shaw, J., Zimmet, P., & Alberti, K. G. (2002b). Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabetic Medicine, 19*(9), 708-723. doi: 835 [pii]

Vaisman, N., Lansink, M., Rouws, C. H., van Laere, K. M., Segal, R., Niv, E., . . . Morley, J. E. (2009). Tube feeding with a diabetes-specific feed for 12 weeks improves glycaemic control in type 2 diabetes patients. *Clinical Nutrition, 28*(5), 549-555. doi: http://dx.doi.org/10.1016/j.clnu.2009.05.004

van de Wiel, A. (2004). Diabetes mellitus and alcohol. *Diabetes/Metabolism Research and Reviews, 20*(4), 263-267. doi: 10.1002/dmrr.492

Vagn Korsgaard, T., & Colding-Jorgensen, M. (2006). Time-dependent mechanisms in beta-cell glucose sensing. *J Biol Phys, 32*(3-4), 289-306. doi: 10.1007/s10867-006-9017-9

Vanschoonbeek, K., Lansink, M., van Laere, K. M., Senden, J. M., Verdijk, L. B., & van Loon, L. J. (2009). Slowly digestible carbohydrate sources can be used to attenuate the postprandial glycemic response to the ingestion of diabetes-specific enteral formulas. *The Diabetes Educator, 35*(4), 631-640. doi: 0145721709335466 [pii] 10.1177/0145721709335466 [doi]

Varghese, P., Gleason, V., Sorokin, R., Senholzi, C., Jabbour, S., & Gottlieb, J. E. (2007). Hypoglycemia in hospitalized patients treated with antihyperglycemic agents. *J Hosp Med, 2*(4), 234-240. doi: 10.1002/jhm.212 [doi]

Verlohren, H. J. (1981). [Diabetes and alcohol]. *Zeitschrift fur Die Gesamte Innere Medizin und Ihre Grenzgebiete, 36*(16), 547-551.

Vetter, M. L., Amaro, A., & Volger, S. (2014). Nutritional management of type 2 diabetes mellitus and obesity and pharmacologic therapies to facilitate weight loss. *Postgraduate Medicine, 126*(1), 139-152. doi: 10.3810/pgm.2014.01.2734

Viera, A. J., & Garrett, J. M. (2005). Understanding interobserver agreement: the kappa statistic. *Family Medicine, 37*(5), 360-363.

Vignesh, J. P., & Mohan, V. (2004). Hypoglycaemia unawareness. *Journal of the Association of Physicians of India, 52*, 727-732.

Vindedzis, S. A., Marsh, B., Sherriff, J. L., Dhaliwal, S. S., & Stanton, K. G. (2012). Food selection for treatment of hypoglycaemia in insulin-treated diabetes: what happens in real life? *Practical Diabetes, 29*(7), 271-274. doi: 10.1002/pdi.1705

Voss, A. C., Maki, K. C., Garvey, W. T., Hustead, D. S., Alish, C., Fix, B., & Mustad, V. A. (2008). Effect of two carbohydrate-modified tube-feeding formulas on metabolic responses in patients with type 2 diabetes. *Nutrition, 24*(10), 990-997. doi: S0899-9007(08)00281-5 [pii] 10.1016/j.nut.2008.06.009 [doi]

Wang, C., Lv, L., Yang, Y., Chen, D., Liu, G., Chen, L., . . . Ran, X. (2012). Glucose fluctuations in subjects with normal glucose tolerance, impaired glucose regulation and newly diagnosed type 2 diabetes mellitus. *Clinical Endocrinology, 76*(6), 810-815. doi: 10.1111/j.1365-2265.2011.04205.x

Wang, Y., Rimm, E. B., Stampfer, M. J., Willett, W. C., & Hu, F. B. (2005). Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *The American Journal of Clinical Nutrition, 81*(3), 555-563.

Weinberg, M. E., Bacchetti, P., & Rushakoff, R. J. (2010). Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *Journal of Diabetes Science and Technology, 4*(3), 577-582.

Wentholt, I. M., Maran, A., Masurel, N., Heine, R. J., Hoekstra, J. B., & DeVries, J. H. (2007). Nocturnal hypoglycaemia in Type 1 diabetic patients, assessed with continuous glucose monitoring: frequency, duration and associations. *Diabetic Medicine, 24*(5), 527-532. doi: 10.1111/j.1464-5491.2007.02107.x

Wexler, D. J., Meigs, J. B., Cagliero, E., Nathan, D. M., & Grant, R. W. (2007). Prevalence of Hyper- and Hypoglycemia Among Inpatients With Diabetes. *Diabetes Care, 30*(2), 367-369. doi: 10.2337/dc06-1715

Weykamp, C., John, W. G., & Mosca, A. (2009). A review of the challenge in measuring hemoglobin A1c. *Journal of Diabetes Science* and *Technology, 3*(3), 439-445.

WHO/IDF. (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF Consultation.*

Wiethop, B. V., & Cryer, P. E. (1993). Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care, 16*(8), 1131-1136. doi: 10.2337/diacare.16.8.1131

Wiggers, J. H., Sanson-Fisher, R. W., & Halpin, S. J. (1995). Prevalence and frequency of health service use: associations with occupational prestige and educational attainment. *Australian Journal of Public Health, 19*(5), 512-519.

Wild, D., von Maltzahn, R., Brohan, E., Christensen, T., Clauson, P., & Gonder-Frederick, L. (2007). A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Education and Counseling, 68*(1), 10-15. doi: S0738-3991(07)00176-0 [pii]
10.1016/j.pec.2007.05.003 [doi]

Wilmot, E. G., Edwardson, C. L., Biddle, S. J., Gorely, T., Henson, J., Khunti, K., . . . Davies, M. J. (2013). Prevalence of diabetes and impaired glucose metabolism in younger 'at risk' UK adults: insights from the STAND programme of research. *Diabetic Medicine, 30*(6), 671-675. doi: 10.1111/dme.12173

Wolever, T. M., Gibbs, A. L., Mehling, C., Chiasson, J. L., Connelly, P. W., Josse, R. G., . . . Ryan, E. A. (2008). The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but

reduction in C-reactive protein. *American Journal of Clinical Nutrition, 87*(1), 114-125.

World Health Organisation/International Diabetes Federation. (2006.). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Retrieved from http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf

Yardley, J. E., Iscoe, K. E., Sigal, R. J., Kenny, G. P., Perkins, B. A., & Riddell, M. C. (2013). Insulin pump therapy is associated with less post-exercise hyperglycemia than multiple daily injections: an observational study of physically active type 1 diabetes patients. *Diabetes Technol Ther, 15*(1), 84-88. doi: 10.1089/dia.2012.0168

Yeh, H. C., Brown, T. T., Maruthur, N., Ranasinghe, P., Berger, Z., Suh, Y. D., . . . Golden, S. H. (2012). Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Annals of Internal Medicine, 157*(5), 336-347. doi: 10.7326/0003-4819-157-5-201209040-00508

Yen, T., Williams, P., & Twigg, M. (2008). *Isolated 1 hour glucose spikers' on the 75gram oral glucose tolerance test (OGTT) show features of relative insulin deficiency and are more likely to develop IGT*. Paper presented at the Australian Diabetes Society and Australian Diabetes Educators Association Annual Scientific Meeting, Melbourne, Australia.

Zaki, R., Bulgiba, A., Nordin, N., & Azina Ismail, N. (2013). A systematic review of statistical methods used to test for reliability of medical instruments measuring continuous variables. *Iranian Journal of Basic* Medical Sciences, *16*(6), 803-807.

Zhang, Y. H., Ma, W. J., Thomas, G. N., Xu, Y. J., Lao, X. Q., Xu, X. J., . . . Yu, I. T. (2012). Diabetes and pre-diabetes as determined by glycated haemoglobin A1c and glucose levels in a developing southern Chinese population. *PLoS One, 7*(5), e37260. doi: 10.1371/journal.pone.0037260

Zhao, Y., Campbell, C. R., Fonseca, V., & Shi, L. (2012). Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care, 35*(5), 1126-1132. doi: 10.2337/dc11-2048

Zheng, F., Lu, W., Jia, C., Li, H., Wang, Z., & Jia, W. (2010). Relationships between glucose excursion and the activation of oxidative stress in patients with newly diagnosed type 2 diabetes or impaired glucose regulation. *Endocrine*, *37*(1), 201-208. doi: 10.1007/s12020-009-9296-6

Zhou, J., Li, H., Ran, X., Yang, W., Li, Q., Peng, Y., . . . Jia, W. (2011). Establishment of normal reference ranges for glycemic variability in Chinese subjects using continuous glucose monitoring. *Medical Science Monitor, 17*(1), CR9-13.

Zhou, J., Lv, X., Mu, Y., Wang, X., Li, J., Zhang, X., . . . Jia, W. (2012). The accuracy and efficacy of real-time continuous glucose monitoring sensor in Chinese diabetes patients: a multicenter study. *Diabetes Technology & Therapeutics*, *14*(8), 710-718. doi: 10.1089/dia.2012.0014

Zhou, L., Podolsky, N., Sang, Z., Ding, Y., Fan, X., Tong, Q., . . . McCrimmon, R. J. (2010). The medial amygdalar nucleus: a novel glucose-sensing region that modulates the counterregulatory response to hypoglycemia. *Diabetes*, *59*(10), 2646-2652. doi: 10.2337/db09-0995

Zhu, W., Czyzyk, D., Paranjape, S. A., Zhou, L., Horblitt, A., Szabo, G., . . . Chan, O. (2010). Glucose prevents the fall in ventromedial hypothalamic GABA that is required for full activation of glucose counterregulatory responses during hypoglycemia. *American Journal of Physiology. Endocrinology and Metabolism, 298*(5), E971-977. doi: 10.1152/ajpendo.00749.2009

Zoungas, S., Patel, A., Chalmers, J., de Galan, B. E., Li, Q., Billot, L., . . . Heller, S. (2010). Severe hypoglycemia and risks of vascular events and death. *New England Journal of Medicine*, *363*(15), 1410-1418. doi: 10.1056/NEJMoa1003795