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: .................................................................

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 ≥ 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

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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


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

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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.
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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 undertreatment 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 ≥ 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, ‘elevated 1-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
Normal pancreatic beta cell insulin secretion phases
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 prameal 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 reduce 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 injectable 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 injectable 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). The 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 ±0.83 mmol/L of the results of the manufacturer’s measurement procedure at glucose levels <4.2 mmol/L and within ±20% at glucose levels ≥4.2 mmol/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 ≥ 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 is 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, Zammit, & 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 ≤ 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 ≤ 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 flexibility 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-
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 ≥ 24 h and ≤ 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 sulphonylurea 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 ≥ 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 hyperglycaemia, 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 accurately 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) to 1h 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

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

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The online version of this article can be found at:

http://dvd.sagepub.com/content/13/2/103
Introduction

Diabetes is diagnosed by 2-hour BGL ≥ 11.1 mmol/L on OGTT, fasting BGL ≥ 7.0 mmol/L or HbA1C ≥ 6.5%. IFG and IGT are similarly diagnosed by elevated fasting and 2-hour BGLs. 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. Additionally Meisinger et al. identified 1-hour postload glycaemia as a long-term predictor for all-cause mortality in men without diabetes. 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. It has been suggested that recognition and management of those with NGT and 1-hour glucose ≥ 8.6 mmol/L may reduce incidence of diabetes and vascular events.

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).

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 (½–1½ units) before those meals when she elected to have more carbohydrate.

Abbreviations:

BGL blood glucose level
BMI body mass index
HbA1C glycated haemoglobin A1C
IFG impaired fasting glucose
IGT impaired glucose tolerance
NGT normal glucose tolerance
OGTT oral glucose tolerance test
SBGM self blood glucose monitoring

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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.

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

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

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.

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, 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 \textit{et al.} showed that 8.3\% of those with NGT have 1-hour BGL $\geq$ 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.

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**Declaration of conflicting interests**

The authors have no conflicts of interest to declare.

**References**


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

<table>
<thead>
<tr>
<th>Amount Carbohydrate (g)</th>
<th>Recommended By:</th>
</tr>
</thead>
</table>
| 15                      | • Diabetes Australia (Diabetes Australia, 2009)  
                           • Singapore Diabetes Association (Singapore Diabetes Society, 2010)  
                           • Diabetes New Zealand (Diabetes New Zealand, 2008) |
| 15 - 20                 | • Diabetes UK (Diabetes UK, 2011)  
                           • American Diabetes Association – Standards of Medical Care (2013) (American Diabetes Association, 2013)  
| 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

<table>
<thead>
<tr>
<th>WTR (min)</th>
<th>Recommended By:</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>• Diabetes New Zealand (Diabetes New Zealand, 2008)</td>
</tr>
<tr>
<td>10 - 15</td>
<td>• Diabetes Australia (Diabetes Australia, 2009)</td>
</tr>
</tbody>
</table>
• 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)  
• Diabetes UK (Diabetes UK, 2011)  
• 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

<table>
<thead>
<tr>
<th>Groups compared pairwise</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 g/10 min - 15 g/5 min</td>
<td>0.000</td>
</tr>
<tr>
<td>20 g/5 min - 20 g/10 min</td>
<td>0.017</td>
</tr>
<tr>
<td>15 g/10 min - 20 g/10 min</td>
<td>0.032</td>
</tr>
<tr>
<td>15 g/10 min - 15 g/5 min</td>
<td>0.395</td>
</tr>
<tr>
<td>20 g/5 min - 15 g/5 min</td>
<td>0.663</td>
</tr>
<tr>
<td>15 g/10 min - 20 g/5 min</td>
<td>0.839</td>
</tr>
</tbody>
</table>

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

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

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

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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 BGAT3 and HyPOS4 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),4,9 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 opinion7,9,11 or older studies12–14 using intravenous, regular or medium-acting insulin, but no long-acting insulin. Free-living people treated with current insulin regimens incorporating short- and
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
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/H11350 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 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/m²]  | 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‡                    |

| 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. 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. 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

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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 6th 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: \( \kappa = \frac{a - e}{1 - e} \), 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

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

† %, Percent agreement; ‡ κ, Cohen’s kappa; § CI, confidence interval
5.4 Paper 3

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

**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. Copyright © 2012 John Wiley & Sons.

**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 to two episodes per week with increased frequency of severe hypoglycaemia with longer duration of insulin treatment. The reported rate in insulin-treated type 2 diabetes is lower and 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.

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. It has been estimated that 6–10% of deaths in people with type 1 diabetes are caused by hypoglycaemia. People with diabetes are reported to fear hypoglycaemia more than the long-term complications of diabetes.

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. 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. Specific treatment foods recommended are glucose, sugar, carbonated beverages, jelly beans, jelly babies etc., honey and fruit juice. Subsequent ingestion of longer-lasting carbohydrate is then recommended to aid continued normalisation of blood glucose levels. Secondly, there are specific recommendations for quantity of primary treating carbohydrate, ranging from 15g (Australia/Singapore/Canada) to 15–30g (European Association for the Study of Diabetes (EASD)). For others see Table...
quantity of carbohydrate are based on expert consensus, or other studies based on superseded insulin regimens. 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.

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. 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 (SI) 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). 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, showed values >0.61 (substantial agreement) for 12 questions and 0.47–0.58 (acceptable agreement) for the other two. The return rate for the questionnaire was 74% (n=119), above an acceptable rate of 65% for self-completed questionnaires.

Measures
Demographics. Descriptive statistics were used for subject demographics. The chi-squared test ($\chi^2$) was used to compare categorical variables; and extended Fisher’s exact test for age, diabetes treatment and duration ($>2 \times \chi^2$ 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 $\leq 0.70$ was categorised as quick-acting, 56–69 medium-acting and $\leq 55$ slow-acting carbohydrate.) GI values were averaged from the Online Appendix To The International Tables of Glycemic Index. Statistical analysis. This was performed using PASW, version 18, SPSS Statistics, IBM Corporation, USA, and extended Fisher’s exact test by Gunma online database.

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. 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
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 and also in patient education material. GI is now the universally accepted way of assessing rate of action of carbohydrate but traditional specification of treatment foods preceded the advent of GI and some recommended foods may now be less than ideal.

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 and initial treatment may be effective for less than an hour 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 respondents 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., only 33% of these reported using quantities consistent with the lowest recommendations (15g).³,⁹,¹² compared with 46.4% reporting quantities within the minimally increased EASD recommendations (15–30g).³ 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.²⁹ 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

CHAPTER 6: FOOD AND REPEAT HYPOGLYCAEMIA IN INSULIN REQUIRING DIABETES

6.1 Paper 4

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

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...
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]. Sommerfeld 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 ($\geq 2 \times 2$ 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 $\kappa$ 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.
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>
<thead>
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<th>Question topic</th>
<th>Test–retest by interview</th>
<th>% Item responseb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of hypoglycaemia</td>
<td>94.7</td>
<td>0.91</td>
<td>0.71–1.00</td>
</tr>
<tr>
<td>Hypoglycaemic symptoms yes/no</td>
<td>78.9</td>
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<td>0.84</td>
<td>0.60–1.00</td>
</tr>
<tr>
<td>Follow-up with food yes/no</td>
<td>89.5</td>
<td>0.76</td>
<td>0.53–1.00</td>
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<tr>
<td>Food used for follow-up</td>
<td>84.6</td>
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<tr>
<td>Gender (m/f)</td>
<td>63/59</td>
<td>100</td>
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<tr>
<td>Age (years) (N, %)</td>
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<tr>
<td>18–25</td>
<td>8 (6.6)</td>
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<td>26–45</td>
<td>31 (25.4)</td>
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<td>46–65</td>
<td>56 (45.9)</td>
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<td>&gt;65</td>
<td>27 (22.1)</td>
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<tr>
<td>Treatment (SII/CSII) (N, %)</td>
<td>111/11</td>
<td>100</td>
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<td>(SII subcutaneous insulin injection, y years)</td>
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<tr>
<td>Duration (years) (N, %)</td>
<td></td>
<td>100</td>
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<tr>
<td>0–5</td>
<td>14 (11.5)</td>
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<tr>
<td>6–15</td>
<td>39 (31.9)</td>
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<td>16–30</td>
<td>46 (37.7)</td>
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<td>&gt;30</td>
<td>23 (18.9)</td>
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| Test–retest reliability and response rates of questionnaire items |

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

<table>
<thead>
<tr>
<th>Question topic</th>
<th>Test–retest by interview</th>
<th>% Item responseb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of hypoglycaemia</td>
<td>94.7</td>
<td>0.91</td>
<td>0.71–1.00</td>
</tr>
<tr>
<td>Hypoglycaemic symptoms yes/no</td>
<td>78.9</td>
<td>0.69</td>
<td>0.39–0.92</td>
</tr>
<tr>
<td>Repeat hypoglycaemia yes/no</td>
<td>84.2</td>
<td>0.57</td>
<td>0.21–0.84</td>
</tr>
<tr>
<td>Frequency of repeat hypoglycaemia</td>
<td>94.7</td>
<td>0.89</td>
<td>0.63–1.00</td>
</tr>
<tr>
<td>Initial treatment food</td>
<td>88.9</td>
<td>0.84</td>
<td>0.60–1.00</td>
</tr>
<tr>
<td>Follow-up with food yes/no</td>
<td>89.5</td>
<td>0.76</td>
<td>0.53–1.00</td>
</tr>
<tr>
<td>Food used for follow-up</td>
<td>84.6</td>
<td>0.61</td>
<td>0.32–0.84</td>
</tr>
</tbody>
</table>

a Percent agreement

b Percent of total responders answering item

\( \kappa \) Cohen’s kappa, CI confidence interval

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
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.

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

<table>
<thead>
<tr>
<th>Frequency hypoglycaemia (events/wk) ($N$, %)</th>
<th>Percent responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>97.5</td>
</tr>
<tr>
<td>1–3</td>
<td>61 (50)</td>
</tr>
<tr>
<td>3–5</td>
<td>48 (39.4)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>Unanswered</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypoglycaemic symptoms (y/n) ($N$, %)</th>
<th>94.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(82.8/11.5)</td>
<td></td>
</tr>
<tr>
<td>Unanswered</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td>Repeat hypoglycaemia (y/n) ($N$, %)</td>
<td>100</td>
</tr>
<tr>
<td>(8.2/91.8)</td>
<td></td>
</tr>
<tr>
<td>Frequency repeat hypoglycaemia ($N$, %)</td>
<td>100</td>
</tr>
<tr>
<td>Often</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td>Rarely</td>
<td>14 (11.5)</td>
</tr>
<tr>
<td>Never</td>
<td>99 (81.2)</td>
</tr>
</tbody>
</table>

| Initial treatment food (y/n) ($N$, %) | 100  |
| (100/0)                             |      |
| Follow-up food (y/n) ($N$, %)       | 98.4 |
| (58.2/40.2)                         |      |
| Unanswered                          | 2 (1.6) |

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

**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.

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REFERENCES


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

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>
<thead>
<tr>
<th>National associations</th>
<th>Potential hypoglycaemic effect</th>
<th>Duration of hypoglycaemia • y/n time</th>
<th>Food with alcohol</th>
<th>Snack later</th>
<th>Possible insulin reduction</th>
<th>Recommends further information</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association</td>
<td>y</td>
<td>• y</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>y</td>
</tr>
<tr>
<td>Canadian Diabetes Association</td>
<td>y</td>
<td>• y</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>y</td>
</tr>
<tr>
<td>Diabetes Australia</td>
<td>y</td>
<td>• up to 24 h</td>
<td>y</td>
<td>y</td>
<td>y</td>
<td>y</td>
</tr>
<tr>
<td>Diabetes New Zealand</td>
<td>y</td>
<td>• y</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>y</td>
</tr>
<tr>
<td>Diabetes New Zealand</td>
<td>y</td>
<td>• n</td>
<td>y</td>
<td>n</td>
<td>y</td>
<td>y</td>
</tr>
<tr>
<td>Diabetic Society Singapore</td>
<td>y</td>
<td>• n.s.</td>
<td>y</td>
<td>y</td>
<td>n</td>
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</tr>
<tr>
<td>Diabetes UK</td>
<td>y</td>
<td>• y</td>
<td>y</td>
<td>y</td>
<td>n</td>
<td>y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• up to 16 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

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**Conflict of interest**

None.

**REFERENCES**


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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

Hypoglycaemia in inpatients with diabetes on nasogastric feeding

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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. Copyright © 2014 John Wiley & Sons.

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Key words
hypoglycaemia; nasogastric feeding; diabetes; retrospective

Introduction
Hypoglycaemia is a common complication of treatment with insulin and sulphonylurea agents. Swift identification and management of mild hypoglycaemic episodes prevent progression to severe hypoglycaemia which has been associated with increased morbidity as has increased duration of hypoglycaemia. 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. There is extensive literature on diabetes specific formula feeds, mainly with regard to post-feed hyperglycaemia, but less quantifying hypoglycaemia.

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. Severe hypoglycaemia is formally defined as ‘an event requiring assistance of another person to actively administer carbohydrate’; 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 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 other studies.
Descriptive statistics were used for subject demographics, χ² 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 nasogastic 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).
Discussion

Hypoglycaemic episodes were not uncommon in these patients. Comparison with other nasogastric studies is difficult due to lack of quantification of hypoglycaemic events. Rates of hypoglycaemia in this study (PPD 10.9%; PTG 3.5%) were higher than the two comparable studies (PPD – not reported and 1.1–1.3%; PTG – 1.4–5.4% and 1.1–1.3%), especially as both defined hypoglycaemia as <3.9 mmol/L; the higher cut-off point would be expected to identify more hypoglycaemic episodes. Frequency of BGM also varied from 6.1±1.6/day (this study) compared to 4/day,3 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 study9 included subjects on dual oral and enteral feeding which may tend to decrease frequency of hypoglycaemia.1,6,8

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.

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


Drug notes

Find out how non-diabetes drugs impact diabetes patients. Visit the Practical Diabetes website and click on drug notes

Bromocriptine Brometanide Carbamazepine Cistazolol Dabigatran Darbepoetin alfa Diazoxide Diginox Dipryridamole Dronedaron Duoxetine Erythromycin Labetalol Lidocaine Methyldopa Metoclopramide Omacor Prasugrel Quinine sulphate Ranolazine Spironolactone Testosterone Torcetrapib

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8.4 Paper 7

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
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What is This?
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 $\geq 3$ 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
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 patients with diabetes, with a reported incidence ranging from 7.7% to 20%. It has been shown to be significantly associated with both increased length of hospital stay and mortality. 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. 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.

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). 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. 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, while Curkendall et al used different cutoff levels (70 mg/dL [3.9 mmol/L] and 50 mg/dL [2.8 mmol/L]).

In the critical care situation, intensive blood glucose monitoring is in place, allowing swift identification and treatment of hypoglycemic episodes, 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. 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 and similar longer-term assessments of insulin regimens and formula feeds, 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. 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. Databases searched were as follows:


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].
**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. 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 that referenced hypoglycemia judged suitable for inclusion (Table 1). In these studies, hypoglycemia was variously referenced as an outcome, clinical data, or an adverse event, with the primary study objective being the assessment/comparison of insulin regimens or nasogastric feed products. 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), referencing Finney et al; < 70 mg/dL (3.9 mmol/L), referencing Dinardo et al and the American Association of Clinical Endocrinologists and American Diabetes Association consensus statement; < 60 mg/dL (3.3 mmol/L), unreferenced and 1 referencing Centennial Medical Center policies; and 2 studies 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,
2-6), and the rationale for this was, in the main, not specified. Where specified, frequency was tailored to study objectives, and it is reasonable to presume that the 2 retrospective studies 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 reported 2 ways. The most common reporting method (6 studies) 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) and percentage of total blood glucose levels < 70 mg/dL (3.9 mmol/L) (2 studies). One study each reported frequency of hypoglycemia as patient-days with 1 or more hypoglycemic events and percentage of time with blood glucose level < 60 mg/dL (3.3 mmol/L).

### 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design: EV</th>
<th>Patient Type (No.)</th>
<th>Intervention: Limitations</th>
<th>Study Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pohl</td>
<td>Randomized double blind control trial: II</td>
<td>Non–critically ill patients with insulin-treated diabetes FPG ≥ 120.6 mg/dl (6.7 mmol/L) receiving ≥ 84 d enteral nutrition (105)</td>
<td>Standard feed and diabetes-specific low-carbohydrate feed: Sample reduced to 55 by study endpoint Two insulin regimens: Small sample size but no dropout.</td>
<td>Diabetes-specific feed showed significant improvement in total daily insulin dose and FPG. No significant difference between groups for glycemic control or triglycerides.</td>
</tr>
<tr>
<td>Korytkowski</td>
<td>Prospective randomized open label trial: III-2</td>
<td>Non–critically ill patients with insulin-treated diabetes with 2 or more BGL &gt; 129.6 mg/dl (7.2 mmol/L) receiving enteral nutrition (50)</td>
<td>Two enteral feeds: Small sample size with significant dropout.</td>
<td>No significant difference between feeds for BGL, lipids, or insulin dose.</td>
</tr>
<tr>
<td>Cortinovis</td>
<td>Prospective nonrandomized control study: III-1</td>
<td>Non–critically ill patients with insulin-treated diabetes receiving enteral nutrition (38)</td>
<td>Two enteral feeds: Small sample size with significant dropout.</td>
<td>No significant difference between feeds for BGL, lipids, or insulin dose.</td>
</tr>
<tr>
<td>Cook</td>
<td>Retrospective cohort study: III-2</td>
<td>Non–critically ill patients with insulin-treated diabetes receiving continuous enteral nutrition (159)</td>
<td>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).</td>
<td>Significant difference in mean BGL between insulin aspart and NPH (4 hourly or 6 hourly) (P &lt; .001), no significant difference between NPH groups.</td>
</tr>
<tr>
<td>Hsia</td>
<td>Retrospective cohort study: III-2</td>
<td>Non–critically ill patients with insulin-treated diabetes receiving ≥ 3 d continuous enteral nutrition (22)</td>
<td>Three insulin regimens: Retrospective, nonrandomized, and small sample size, Nil (observational only): Small sample size, 20 of 24 participants completing.</td>
<td>Biphasic insulin produces less hypoglycemia and is a safe regimen in these patients.</td>
</tr>
<tr>
<td>Oyibo</td>
<td>Observational case series: IV</td>
<td>Non–critically ill patients with insulin-treated diabetes receiving ≥ 14 d enteral nutrition (24)</td>
<td>Three insulin regimens: Retrospective, nonrandomized, and small sample size, Nil (observational only): Small sample size, 20 of 24 participants completing.</td>
<td>Twice daily insulin regimen safe for these patients.</td>
</tr>
<tr>
<td>Fatati</td>
<td>Observational case series: IV</td>
<td>Non–critically ill patients receiving insulin receiving ≥ 7 d enteral nutrition (8 of 25 participants with diabetes)</td>
<td>Three insulin regimens: Retrospective, nonrandomized, and small sample size, Nil (observational only): Small sample size, 20 of 24 participants completing.</td>
<td>Glargine insulin regimen safe for these patients.</td>
</tr>
<tr>
<td>Putz</td>
<td>Observational case study: —</td>
<td>Non–critically ill patient with insulin-treated diabetes receiving continuous enteral feeding (1)</td>
<td>Three insulin regimens: Retrospective, nonrandomized, and small sample size, Nil (observational only): Case study</td>
<td>Glargine insulin safe for continuous enteral feeding.</td>
</tr>
</tbody>
</table>

Abbreviations: BGL, blood glucose level; EV, evidence level; FPG, fasting plasma glucose; NPH, neutral protamine Hagedorn.


*Hypoglycemia reported as adverse event.*

*Hypoglycemia reported as outcome.*

*Hypoglycemia reported as clinical data.*
Table 2
Included Studies (n = 9): Quantitative Data on Hypoglycemia

<table>
<thead>
<tr>
<th>Study: Grouping (No.)</th>
<th>Duration of Data Collection</th>
<th>Hypoglycemia, mg/dL (mmol/L)</th>
<th>Total EVTs</th>
<th>Patients With EVT, %</th>
<th>Patient Days With 1+ EVT, %</th>
<th>Total BGL &lt; 70 mg/dL, %</th>
<th>Time With EVT, %</th>
<th>Assess BGL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pohl19</td>
<td>84 d</td>
<td>&lt; 60 (3.3)</td>
<td>1</td>
<td>2.1</td>
<td></td>
<td></td>
<td>2/d</td>
<td></td>
</tr>
<tr>
<td>Diabetes feed (34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard feed (21)</td>
<td></td>
<td></td>
<td>5</td>
<td>10.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korytkowski17</td>
<td>6 ± 2.2 d</td>
<td>&lt; 70 (3.9)</td>
<td></td>
<td></td>
<td>2.7</td>
<td>1.3</td>
<td>Max 6/day</td>
<td></td>
</tr>
<tr>
<td>Glargine insulin (25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sliding scale insulin (25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leon-Sanz29</td>
<td>Mdn, 13 d</td>
<td>&lt; 60 (3.3)</td>
<td>7</td>
<td>3.9</td>
<td></td>
<td></td>
<td>3/d</td>
<td></td>
</tr>
<tr>
<td>High MFA feed (18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High CHO feed (14)</td>
<td></td>
<td></td>
<td>5</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortinovis27</td>
<td>3 d</td>
<td>&lt; 80 (4.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4+/d</td>
<td></td>
</tr>
<tr>
<td>Standard regimen (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol regimen (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook et al26</td>
<td>Variable</td>
<td>&lt; 60 (3.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Insulin aspart (31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH every 4 h (52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>NPH every 6 h (76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>Hsia16</td>
<td>3 d</td>
<td>&lt; 70 (3.9)</td>
<td>5</td>
<td>5.4</td>
<td></td>
<td></td>
<td>4/d</td>
<td></td>
</tr>
<tr>
<td>Glargine/lispro (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic insulin 2/d (8)</td>
<td></td>
<td></td>
<td>2</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic insulin 3/d (6)</td>
<td></td>
<td></td>
<td>1</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oyibo30</td>
<td>Observational study (24)</td>
<td>Variable</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5+/d</td>
</tr>
<tr>
<td>Fatati28</td>
<td>Observational study (8)</td>
<td>7 d</td>
<td>&lt; 80 (4.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6/d (4/7)</td>
</tr>
<tr>
<td>Putz21</td>
<td>Case study (1)</td>
<td>3+ mo</td>
<td>Not defined</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4/d</td>
</tr>
</tbody>
</table>

Abbreviations: BGL, blood glucose level; CHO, carbohydrate; EVT, event; MFA, monounsaturated fatty acid; NPH, neutral protamine Hagedorn.

*3.9 mmol/L.
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).

**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) to < 63 mg/dL (3.5 mmol/L) and < 60 mg/dL (3.3 mmol/L) 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; 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, 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\(^1\) and the Society of Hospital Medicine\(^2\) 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,\(^3,5\) 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**


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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 $\geq 8.6$mmol/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.
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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

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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.


   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.

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   Dr Jill Sherriff
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   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.


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   Dr Jill Sherriff

   Dr Kim Stanton
APPENDIX 2

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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.

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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
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:

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Blood test immediately and record on <strong>Blood test form A.</strong></td>
</tr>
<tr>
<td>2.</td>
<td>Give __ mls carbotest.</td>
</tr>
<tr>
<td>3.</td>
<td>Record patients symptoms on checklist provided.</td>
</tr>
<tr>
<td>4.</td>
<td>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.</td>
</tr>
<tr>
<td>5.</td>
<td>Obtain verbal consent for further blood testing. If consent, go to step 6, if no consent offer complex carbohydrate and usual information.</td>
</tr>
<tr>
<td>6.</td>
<td>Blood test every 30 minutes while patient is in clinic and record on <strong>Blood test form B.</strong></td>
</tr>
<tr>
<td>7.</td>
<td>Give patient <strong>Home blood test form C</strong> 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.</td>
</tr>
</tbody>
</table>
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
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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)

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood sugar</th>
<th>Symptoms (please tick)</th>
</tr>
</thead>
</table>
| Blood sugar less than 3.5 |             | □ Sweating  
□ Hunger  
□ Shaking, weakness  
□ Irritability  
□ Light headedness/Headache  
□ Lack of concentration/behaviour change.  
□ Numbness around the lips and fingers  
□ Other ____________________  
□ None  
□ Comment__________________________________ |
| Treat         | (60 mls carbotest) | □ Sweating  
□ Hunger  
□ Shaking, weakness  
□ Irritability  
□ Light headedness/Headache  
□ Lack of concentration/behaviour change.  
□ Numbness around the lips and fingers  
□ Other ____________________  
□ None  
□ 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  

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood sugar</th>
<th>Symptoms (please tick)</th>
</tr>
</thead>
</table>
| Blood sugar less than 3.5 | FROM ABOVE | □ Sweating  
□ Hunger  
□ Shaking, weakness  
□ Irritability  
□ Light headedness/Headache  
□ Lack of concentration/behaviour change.  
□ Numbness around the lips and fingers  
□ Other ____________________ |
| Treat         | (60 mls carbotest) | □ Sweating  
□ Hunger  
□ Shaking, weakness  
□ Irritability  
□ Light headedness/Headache  
□ Lack of concentration/behaviour change.  
□ Numbness around the lips and fingers  
□ 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

<table>
<thead>
<tr>
<th>Time after hypo</th>
<th>Blood sugar</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mins</td>
<td></td>
<td></td>
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<tr>
<td>1 hour</td>
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<tr>
<td>1 hour 30 mins</td>
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<tr>
<td>3 hour 30 mins</td>
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<tr>
<td>4 hours</td>
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<td></td>
</tr>
<tr>
<td>Time after hypo</td>
<td>Blood sugar</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
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<tr>
<td>30 mins</td>
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<td>1 hour</td>
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<td>1 hour 30 mins</td>
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<tr>
<td>2 hours</td>
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<tr>
<td>2 hour 30 mins</td>
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</tr>
<tr>
<td>3 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hour 30 mins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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).
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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.
DATA COLLECTION AND ENTRY FORM 1  GENERAL – NASOGASTRIC

<table>
<thead>
<tr>
<th>* HbA1c</th>
<th></th>
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<tbody>
<tr>
<td>* Standard monitoring yes/no</td>
<td></td>
</tr>
<tr>
<td>* Treatment (QID, BD, Long acting, SS, other)</td>
<td></td>
</tr>
<tr>
<td>* Feed pattern (bolus/continuous)</td>
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<tr>
<td>* Feed type (high cho/low cho/oth)</td>
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</table>

Total Bgl

| No Bgl ≤ 3.5 mmol/L |  |
| * % Bgl ≤ 3.5 mmol/L |  |
| No Bgl > 10 mmol/L |  |
| * % Bgl ≥ 10 mmol/L |  |
| * ≥ 75% 3.5 – 10 yes/no |  |
| * No of hypoglycaemic episodes < 2 mmol/l |  |
| * No episodes > 3h |  |
| * Reason for hypoglycemia |  |
| 1. Insulin pattern |  |
| 2. Feed stopped/insulin unchanged |  |
| 3. Other |  |

* = Enter data on database  Red font = Data to be collected  Green font = Calculated data
<table>
<thead>
<tr>
<th>ID</th>
<th>Hypo level &gt; or ≤ 2 mmol/L</th>
<th>Time of hypo</th>
<th>Duration of hypo</th>
<th>Extra monitoring carried out? Yes/No</th>
<th>Time of last short acting insulin</th>
<th>Feed held? (from – to)</th>
<th>Other reason for hypo?</th>
<th>Glucose given</th>
<th>Insulin changed?</th>
<th>Feed changed?</th>
<th>Other?</th>
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APPENDIX 4

RECOMMENDATIONS - HYPOGLYCAEMIA AND ALCOHOL
Alcohol and insulin

It is important to understand the way alcohol and insulin interact.

There is an increased risk of hypoglycaemia following alcohol. This risk may persist for greater than 12 hours after drinking alcohol.

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

<table>
<thead>
<tr>
<th>1 small wineglass (100ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 nip/ measure spirits (30mls)</td>
</tr>
<tr>
<td>1 middy beer or 1 can light beer (375mls)</td>
</tr>
</tbody>
</table>


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


10.1016/j.ecl.2010.05.003 [doi]


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