School of Pharmacy

Pharmaceutical Care in Diabetes Mellitus

Rhonda Marise Clifford

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DECLARATION

The work described in this thesis was conducted at the Fremantle Hospital and Health Service, Diabetes Outpatient Clinic and in the Fremantle Hospital and Health Service, University Department of Medicine, Diabetes Research Unit from February 1999 to November 2002. This research was the work of the candidate, with appropriate supervision.

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

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

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ABSTRACT

People with diabetes mellitus are more likely to die from cardiovascular causes than those without diabetes, and modifiable risk factors, such as hyperglycaemia, dyslipidaemia and hypertension can be targeted in intervention programs to decrease this risk. In addition to tertiary care for patients with diabetes, there is a need for simple programs to be implemented in the community that allow the benefits of improved metabolic and blood pressure control to be realised more widely.

Pharmaceutical care comprises the detection, prevention and solution of drug-related problems in a quantifiable form, so that outcomes of care can be easily reviewed and monitored. Previous studies of pharmaceutical care programs in patients with diabetes do not provide conclusive evidence of the benefit of pharmaceutical care. The aim of this research was to evaluate the impact of the provision of pharmaceutical care to patients with diabetes mellitus in an Australian context.

In order to develop a pharmaceutical care program, the characteristics of an Australian cohort of patients with diabetes were reviewed. The Fremantle Diabetes Study (FDS), was a community-based prospective observational study of diabetes care, control and complications in a postcode-defined region of 120 097 people surrounding the port city of Fremantle in Western Australia. It was intended that the FDS annual reviews would provide important local information in order to design and implement a prospective pharmaceutical care program. A pilot pharmaceutical care program was subsequently developed for use in a diabetes outpatient clinic. This program was then modified for use in a community-based sample of type 2 diabetes mellitus patients, drawn from the FDS cohort.

Demographic parameters, including ethnicity and treatment details, were reviewed at study entry for the full FDS cohort and then over time for a subset of patients that returned for four subsequent annual assessments. Insulin use was more common in patients of Southern European origin compared with the Anglo-Celt group irrespective of the level of glycaemia, at baseline. This difference persisted during subsequent follow-up but was not associated with improved glycaemic control. These findings demonstrated that there are important ethnic differences in the management of patients with type 2 diabetes mellitus.

The pilot pharmaceutical care program was carried out in high-risk diabetes mellitus patients attending a hospital outpatient clinic. The patients had poor glycaemic control, dyslipidaemia, hypertension and/or were on three or more prescription medications. In the pharmaceutical care arm, a clinical pharmacist reviewed and monitored all aspects of the patients' drug therapy in collaboration with other health care professionals at six weekly intervals for six months. The control patients received usual outpatient care. Seventy-three patients were recruited into the study, of whom 48 (66%) were randomised to receive pharmaceutical care. One in six patients was taking complementary medicines. The pharmaceutical care program provided patients with important medication information that resulted in changes to drug therapy. However, the six-month program did not lead to an improvement in glycaemic control.

The next phase of the study adapted the pilot hospital-based pharmaceutical care program to a community-based setting. Two hundred and two type 2 diabetes mellitus FDS patients were recruited, of whom 101 (50%) were randomised to the pharmaceutical care program, and all were followed for 12-months. There were significant reductions in risk factors associated with coronary heart disease in the case but not the control group over time, specifically glycaemic control, lipid levels, and blood pressure. Glycosylated haemoglobin fell from 7.5% to 7.0% ($P<0.0001$), total cholesterol fell from 5 mmol/L to 4.6 mmol/L ($P<0.0001$), systolic blood pressure fell from 158 mmHg to 143 mmHg ($P<0.0001$) and diastolic blood pressure fell from 77mmHg to 71mmHg ($P<0.0001$). Multiple linear regression analysis confirmed that pharmaceutical care program involvement was an independent predictor of benefit after adjustment for key variables. The 10-year coronary heart disease risk for patients without a previous coronary event was reduced by 4.6% over the 12-month study period in the pharmaceutical care group ($P<0.0001$), while there was no change in the controls ($P=0.23$). This phase of the study showed that medium-term individualised pharmaceutical care reduced vascular risk factors in a community–based cohort of patients with diabetes and that provision of a multifactorial intervention can improve health outcomes in type 2 diabetes mellitus.

As part of the pharmaceutical care program, a high level of complementary medicine use was found. As a result, a study of complementary medicine use was undertaken in 351 patients

from the FDS. A convenience sample of FDS patients was interviewed regarding their use of complementary medicines. A literature search was conducted to assess the potential impact of these medicines on diabetes, concomitant medications or diabetes-related co-morbidities. Eighty-three of 351 (23.6%) patients with diabetes had consumed at least one complementary medicine in the previous year and 42% (77/183) of the products potentially necessitated additional patient monitoring or could be considered potentially inappropriate for a diabetic patient. The data indicated the need for patient disclosure of complementary medicine use and adequate monitoring for complementary medicine-related adverse events, as part of the pharmaceutical care process.

The pharmaceutical care model was established to provide a framework by which drug use could be improved to enhance patients' clinical and health-related quality of life outcomes. For the present study, a straightforward pharmaceutical care program was adapted from a hospital setting to a community setting, where the principal requirement was a clinical pharmacist who had completed a self-directed diabetes-training program. In this context, clinically relevant parameters improved over the course of the study period. Pharmaceutical care programs such as this can begin the process of translating the findings of large and expensive clinical trials into standard clinical practice.

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"There is knowledge but it will pass.....meanwhile these three remain: faith, hope and love; the greatest of these is love". (1 Corinthians 13:8,13)

PUBLICATIONS RELATED TO THE THESIS

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2. Clifford RM, Batty KT, Davis TME, Davis WA. Use of non-prescription therapies, including complementary medicines, in diabetes: the Fremantle Diabetes Study (abstract). Int J Pharm Pract 2002; 10: R19
3. Clifford RM, Batty KT, Davis WA and Davis TME. Prevalence and predictors of complementary medicine usage in diabetes: The Fremantle Diabetes Study. J Pharm Pract Res 2003; 33: 260-4

OTHER PUBLICATIONS RELATED TO DIABETES MELLITUS

1. Davis TME, Clifford RM and Davis WA. Effect of insulin therapy on quality of life in type 2 diabetes mellitus: The Fremantle Diabetes Study. Diab Res Clin Pract 2001; 52: 63-71
2. Clifford R. Review of newer oral hypoglycaemics. Fremantle Hospital and Health Service, Therapeutics in Perspective 2001; 3
3. Cull C, Davis W, Clifford R, Davis T. Aspirin use in type 2 diabetes: the Fremantle Diabetes Study (abstract). Diab Med 2002;19:S7.
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3. Clifford RM, Batty KT, Cull CA, Davis TME, Davis WA. Relationship between glycaemic control and insulin therapy in patients with type 2 diabetes form Anglo-Celt and Southern European ethnic backgrounds: The Fremantle Diabetes Study. Conference proceedings SHPA Clinical Conference, Hobart November 2001
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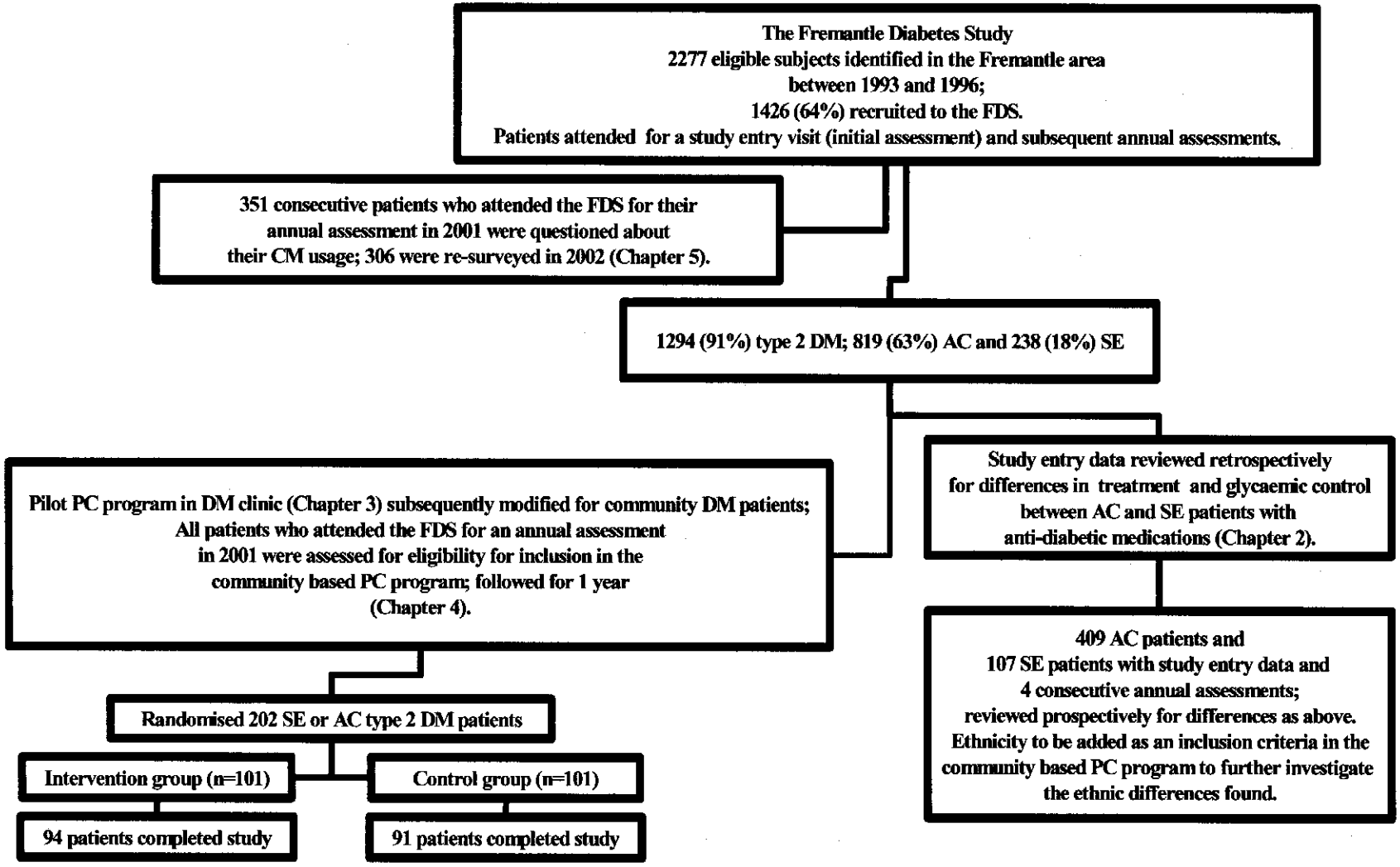
ABBREVIATIONS

AC	Anglo-Celt
ACE	angiotensin converting enzyme
ARII	angiotensin II receptor
ADA	American Diabetes Association
ALLHAT	Anti-hypertensive and lipid-lowering treatment to prevent heart attack trial
APSA	Australasian Pharmaceutical Science Association
BMI	body mass index
BP	blood pressure
CAM	complementary and alternative medicine
CHD	coronary heart disease
CI	confidence interval
CM	complementary medicine
CMEC	Complementary Medicines Evaluation Committee
CVD	cerebrovascular disease
DBP	diastolic blood pressure
DCCT	Diabetes control and complications trial
DM	diabetes mellitus
DMMR	domiciliary medication management reviews
DSM	disease state management
DQOL	diabetes quality of life
FPG	fasting plasma glucose
FDS	Fremantle Diabetes Study
FHHS	Fremantle Hospital and Health Service
HbA_{1c}	glycosylated haemoglobin
HCP	health care professional
HMR	home medication review
HOPE	Heart outcomes prevention evaluation
IDDM	insulin dependent diabetes mellitus
HRQOL	health-related quality of life
INR	international normalised ratio
IQR	interquartile range
LDL	low density lipoprotein
MI	myocardial infarction
NIDDM	non-insulin dependent diabetes mellitus
NSAID	non-steroidal anti-inflammatory drug
OCM	Office of Complementary Medicines
OR	odds ratio
OHA	oral hypoglycaemic agent

PBS	Pharmaceutical Benefits Scheme
PC	pharmaceutical care
PEER	Pharmaceutical care of the elderly in Europe research
SBP	systolic blood pressure
SE	Southern European
SF-36	short-form 36
SHPA	Society of Hospital Pharmacists of Australia
SMBG	self-monitoring of blood glucose
sd	standard deviation
TCM	traditional chinese medicine
TGA	Therapeutic Goods Administration
UK	United Kingdom
UKPDS	United Kingdom prospective diabetes study
USA	United States of America
WA	Western Australia
WHO	World Health Organisation

SUMMARY


The Fremantle Diabetes Study
2277 eligible subjects identified in the Fremantle area
between 1993 and 1996;
1426 (64%) recruited to the FDS.
Patients attended for a study entry visit (initial assessment) and subsequent annual assessments.
351 consecutive patients who attended the FDS for their annual assessment in 2001 were questioned about their CM usage; 306 were re-surveyed in 2002 (Chapter 5).
1294 (91%) type 2 DM; 819 (63%) AC and 238 (18%) SE
Pilot PC program in DM clinic (Chapter 3) subsequently modified for community DM patients;
All patients who attended the FDS for an annual assessment in 2001 were assessed for eligibility for inclusion in the community based PC program; followed for 1 year (Chapter 4).
Study entry data reviewed retrospectively for differences in treatment and glycaemic control between AC and SE patients with anti-diabetic medications (Chapter 2).
409 AC patients and
107 SE patients with study entry data and
4 consecutive annual assessments;
reviewed prospectively for differences as above.
Ethnicity to be added as an inclusion criteria in the community based PC program to further investigate the ethnic differences found.
Randomised 202 SE or AC type 2 DM patients
Intervention group (n=101)
Control group (n=101)
94 patients completed study
91 patients completed study

CHAPTER 1

LITERATURE REVIEW

INTRODUCTION

The prevalence of diabetes is on the increase and an estimated 239 million people worldwide are expected to have the condition by the year 2020.[1] Diabetes mellitus (DM) represents a serious health care challenge. It is a heterogeneous disorder characterised by varying degrees of insulin resistance and insulin deficiency, which leads to disturbances in glucose homeostasis. It is commonly associated with prolonged ill health and premature death.[2] The mortality rate in patients with DM may be up to eleven times higher than in persons without the disease.[3, 4] DM is the leading cause of blindness, renal failure and foot and leg amputations in adults in developed countries.[1]

The World Health Organisation (WHO) classification system of DM recognises two major forms of diabetes[5];

1. Type 1 diabetes mellitus, formerly known as insulin dependent diabetes mellitus (IDDM; patient is dependent on exogenous insulin for survival) and
2. Type 2 diabetes mellitus, formerly known as non-insulin dependent diabetes mellitus (NIDDM; patient is not necessarily dependent on exogenous insulin for survival).

Teamwork and collaboration are essential components of successful DM management, both to prevent complications and maintain the patients' health-related quality of life (HRQOL) over a lifetime of coping with the disease.[1]

Type 1 DM is characterised by insulin deficiency resulting from immune-mediated pancreatic beta-cell destruction. The most serious acute consequence of this is ketoacidosis. Pancreatic beta-cell destruction eventually results in absolute insulin deficiency.[1] Type 1 DM accounts for approximately ten percent of all DM cases. Type 2 DM is generally characterised by peripheral insulin resistance and relative insulin deficiency which may range from predominant insulin resistance with relative insulin deficiency to predominant insulin secretory defect with insulin resistance.[1] Type 2 DM accounts for approximately ninety percent of all DM cases.

The major risk factors in the development of type 2 DM are[3];

1. Family history of DM
2. Obesity
3. Race/ethnicity
4. Increasing age (especially greater than forty five years)
5. Previously identified impaired fasting glucose or impaired glucose tolerance
6. Hypertension
7. Hyperlipidaemia and
8. History of gestational DM.

There is evidence that good glycaemic control can slow or prevent the development of diabetes complications.[6-10] The Diabetes Control and Complications Trial (DCCT)[11, 12] demonstrated the association between the degree of glycaemic control and the development of microvascular complications in type 1 DM patients. The DCCT determined that there was an approximately 50% reduction in microvascular complications in the intensive treatment group and a non-significant tendency to fewer major cardiovascular events. Intensive control was accompanied by a significantly higher incidence of hypoglycaemia and weight gain. Mortality did not differ significantly between the groups. The DCCT investigators did advise caution in extending the findings to patients with type 2 DM without careful regard for age and coexisting diseases.

The DCCT was an important study, due to the relatively large numbers of patients included and the long follow-up period. The entire cohort of 1441 patients was followed for a mean of six and a half years, a total of more than 9300 patient years. Primary and secondary prevention cohorts were included. The care in the intensive group was carried out by an expert team of diabetologists, nurses, dietitians and behavioural specialists, and the time, effort and cost involved was considerable. It is important to note that the resources used in the intensive group are not widely available and the DCCT investigators suggested that new strategies were needed to adapt methods of intensive treatment for use in the general community in an efficient and cost effective way.

The United Kingdom Prospective Diabetes Study (UKPDS) was the largest scale long-term intervention study in newly diagnosed type 2 DM patients and involved over 5000 patients.

The UKPDS used an intensive blood glucose control policy, which achieved a median HbA_{1c} of 7% compared with 7.9% in those randomised to conventional treatment over a median 10 years follow-up.[9] The UKPDS confirmed the benefit of intense glycaemic control on microvascular disease in type 2 DM patients.[4, 8-10, 13-20] The complications of type 2 DM and the treatment and prevention of these complications, especially with respect to pharmacotherapy, will be addressed in Chapter 1, Section 1.1.

1.1 COMPLICATIONS AND TREATMENT OF TYPE 2 DIABETES MELLITUS

1.1.1 Microvascular complications

Complications such as retinopathy, nephropathy and peripheral neuropathy can lead to blindness, renal failure and limb amputations respectively.[1] The DCCT[11, 12] and the UKPDS [4, 8, 16] have demonstrated an association between microvascular complications and glycaemic control in both type 1 and type 2 DM patients.

1.1.1.1 Nephropathy

Nephropathy develops in approximately twenty percent of persons with type 2 DM. Its earliest manifiestation is microalbuminuria (urine albumin:creatinine ratio (ACR) ≥ 3 mg/mmol). Within 10 years of diagnosis of type 2 DM, one third of patients will have macroproteinuria and 0.6% will have features of renal failure.[7, 21] In patients with type 2 DM, microalbuminuria is also associated with an increase in cardiovascular mortality.[22-24]

Gaede[25] found that intensive intervention in type 2 DM patients can reduce the progression of nephropathy. The study was a randomised, open, parallel trial (n=149) conducted to determine whether intensive multifactorial intervention that included changes in behaviour and pharmacological management, slowed the initiation and progression of microvascular complications in patients who had microalbuminuria and type 2 DM.[25] The HbA_{1c} level at baseline for the standard treatment group was 8.8±1.7% and for the intensive group 8.4±1.6%; after the four year period the results were 8.6±1.9% and 7.6±1.6% respectively ($P<0.05$, across time and between groups). A doctor, nurse and dietitian provided the intensive intervention for the cases. Some of the treatment goals can be seen in Table 1.1.

Table 1.1: Multifactorial intervention in patients with type 2 DM; treatment goals in standard and intensive group[25]

Intervention	Standard Group n=76	Intensive Group n=73
Systolic blood pressure (SBP) (mmHg)	<160	<140
Diastolic blood pressure (DBP) (mmHg)	<95	<85
Glycosylated haemoglobin (HbA_{1c}) (%)	<7.5	<6.5
Angiotensin Converting Enzyme (ACE) inhibitor irrespective of blood pressure (BP)	No	Yes
Aspirin to patients with ischaemic heart disease (IHD)	Yes	Yes
Aspirin in patients with peripheral vascular disease	No	Yes
Triglycerides (mmoL/L)	<2.2	<1.7
Total cholesterol (mmoL/L)	<6.5	<5.0
High density lipoprotein (HDL) -cholesterol (mmoL/L)	>0.9	>1.1

This small study demonstrated that intensive multifactorial intervention in patients with type 2 DM and microalbuminuria slowed the progression of nephropathy, as well as progression of retinopathy and autonomic neuropathy. This study was not designed to assess which aspect of the multifactorial intervention resulted in the results seen, but highlighted the need for intensive intervention in type 2 DM patients to see clinically relevant improvements in diabetes control.

Various treatments have been investigated to determine whether pharmacological intervention can slow the progression of nephropathy, in particular ACE inhibitors.[16, 26-31] Some of these studies concluded that the reduction in microalbuminuria seen with ACE inhibitors could not be simply attributable to good BP control[26-33], while others, including the findings of the UKPDS[16] concluded that "the suggestion that ACE inhibitors have a specific renal protective effect in the treatment of type 2 DM is not supported".

There was some controversy over the role of ACE inhibitors in slowing the progression of nephropathy until 2000, when the Heart Outcomes Prevention Evaluation (HOPE) study found that the ACE inhibitor ramipril provided nephroprotection.[34-36] This benefit was

independent of ramipril's effect on BP and was determined in over 3000 people. The HOPE study was a landmark study and solved the controversy surrounding ACE inhibition and DM. The use of ACE inhibitors in DM patients is now considered standard therapy.[37, 38] The HOPE study concluded that, "the treatment represents a vasculoprotective and renoprotective effect for people with diabetes".[34] Angiotensin receptor II (ARII) blockers have also been shown to slow the progression of nephropathy in patients with type 2 DM.[39, 40] Like ACE inhibitors, the renoprotective effect appears independent of the drugs ability to lower BP.

Management of patients with microalbuminuria and/or nephropathy must also focus on good glycaemic control, good BP control, lowering of cholesterol levels where necessary and cessation of smoking.[1, 23]

1.1.1.2 Neuropathy

The manifestations of neuropathy in DM are extensive. Abnormalities can be detected in most patients who have had DM for five to ten years. Peripheral neuropathy can cause sensory loss in the feet and legs resulting in the loss of protective sensation in the feet.[1]

Other symptoms include impotence, gastrointestinal dysfunction, lack of sweating in the feet, resting tachycardia and a fall in SBP on standing. Good glycaemic control to slow the progression of neuropathy is paramount.[8]

1.1.1.3 Retinopathy

Retinopathy is seen in about 15% of patients who have had DM for more than 15 years. In the Australia and the United States of America (USA), DM is the leading cause of blindness.[1] Microangiopathy affecting the retina develops over a number of years. Vision is not affected by all retinopathies, but regular review is important for controlling the condition and maintaining vision. All patients with diabetes should receive ophthalmologic examinations at least annually.[1] Again good glycaemic control is the key to slowing the progression of retinopathy.[9]

1.1.2 Macrovascular complications

Type 2 DM usually presents as part of a syndrome of metabolic abnormalities, which include hyperglycaemia, central obesity, dyslipidaemia, hypercoagulation, hypertension and insulin resistance.[1] Type 2 DM is associated with a two to three fold increased risk of cardiovascular

morbidity and mortality and an increased risk of developing congestive heart failure.[7, 41] The relative risk of stroke in patients with diabetes is also increased 2 to 3 fold. Aggressive antihypertensive therapy and routine anticoagulation therapy for atrial fibrillation may reduce the risk of stroke.[42] In addition to stroke, treating hypertension in persons with DM reduces other cardiovascular endpoints.[20]

Several potentially modifiable risk factors for coronary heart disease (CHD) in type 2 DM patients have been identified.[8] The risk factors include hyperglycaemia, hypertension, dyslipidaemia and smoking. Drug treatment options for hyperglycaemia, hypertension and dyslipidaemia will be discussed in turn.

1.1.2.1 Hyperglycaemia

Dietary and lifestyle modification are the first line interventions in all type 2 DM patients unless the patient is acutely unwell. It is usual to institute dietary management for the first three months following diagnosis and then reassess blood glucose levels.[1] The nutritional goals for people with DM are similar to those for a healthy diet in the non-diabetic population with the aim of attaining and maintaining good control of blood glucose, lipids and BP. The dietary modification in type 2 DM patients must involve weight reduction in those patients who are overweight or obese. Type 2 DM patients should be encouraged to reduce the intake of refined carbohydrate (sugars) and fats in favour of unrefined carbohydrates (for example starch), so that the latter makes up at least half of the patient's total energy intake.[1] A wide variety of foods should be included in the diet, with particular emphasis on foods containing a high proportion of dietary fibre. As well as being generally beneficial, dietary fibre may retard the absorption rate of sugars in the diet, and aid in glycaemic control.[43] When dietary management succeeds, the benefits are undisputed. Blood glucose, lipids and BP fall, and life expectancy may be prolonged by three to four months for each kilogram lost during the first year of treatment.[44] However, dietary compliance over long periods tends to be poor.[45, 46]

Lifestyle changes must include appropriate levels of exercise (minimum of 30 minutes three times a week; ideally 30 minutes daily), minimisation of alcohol intake and cessation of smoking.[47] Most patients with type 2 DM have a reduced functional capacity for exercise and a thorough physical assessment (with special reference to CHD) is recommended before

the patient begins any exercise program. The exercise program should normally begin slowly and the need for persistence should be emphasised.[47] However, permanent lifestyle changes are difficult to achieve.[45, 46]

The American Diabetes Association (ADA) recommends that action should be taken in the type 2 DM patient whose fasting plasma glucose (FPG) concentration exceeds 7.8 mmoL/L and the HbA_{1c} value is more than 8%.[48] The target should be FPG < 6.7 mmol/L and HbA_{1c} < 7%.[49] These targets may be achievable in the early stages of the disease but become more difficult to achieve as the disease progresses. Drugs available to maintain glycaemic control include metformin, sulphonylureas, acarbose, insulin, meglitinides and the thiazolidinediones.

No study to date has determined the drug regimen of choice for type 2 DM.[8, 9, 13, 19] The main translatable finding of the UKPDS is that intensive therapy of type 2 DM is beneficial.[15] It is also estimated that a two percent reduction of HbA_{1c} over a four-year period would be associated with significant decreases in proliferative retinopathy and sensory neuropathy in patients with type 2 DM.[7]

1.1.2.1.1 Metformin

1.1.2.1.1.1 Mechanism

Metformin is a biguanide that may reduce glucose absorption from the intestine, increase uptake of glucose into the tissues from the blood, reduce liver production of glucose and reduce insulin requirements for disposal of glucose. It has no effect on insulin secretion.[50, 51] Metformin can be used either as initial therapy, as add-on therapy when sulphonylurea alone has failed and diet and exercise are no longer maintaining appropriate blood glucose levels, or in combination with insulin therapy.[49] Metformin and sulphonylureas cause similar reductions in FPG concentrations in patients with type 2 DM.[49]

1.1.2.1.1.2 Features of metformin and place in therapy

Metformin decreases appetite, can promote weight loss and has a beneficial effect on serum lipids. Reductions in triglycerides in hypertriglyceridaemic individuals with type 2 DM can be up to fifty percent. Total cholesterol levels often show a small decrease (up to ten percent).[51] Metformin does not usually induce hypoglycaemia because metformin has an antihyperglycaemic action rather than the hypoglycaemic actions typical of sulphonylureas

and insulin. Metformin is often be preferred as initial therapy in the obese patient because it promotes weight loss.[13] The features of metformin and its place in therapy can be seen in Table 1.2.

Table 1.2: Metformin: features and place in therapy [13, 19, 49, 52, 53]

Variable	Comment
Type of therapy	Monotherapy; combination therapy with a sulphonylurea or a meglitinide; combination with insulin; combination with a thiazolidinedione
Indications	After failure of diet and exercise in type 2 DM, especially in overweight patients; after failure with sulphonylureas; combination therapy with insulin; combination with a thiazolidinedione
Tablet sizes	500mg, 850mg and 1g
Dose range	250mg – 3g in daily divided doses (maximal effect is seen at doses of 2g daily)
Treatment schedule	Taken with meals; increase dose slowly; maximum dose 3g daily
Contraindications	Moderate to severe renal or hepatic disease; cardiac or respiratory insufficiency; any hypoxic condition; severe infection; alcohol abuse; history of lactic acidosis; pregnancy
Side effects	Gastrointestinal symptoms and metallic taste; may impair absorption of vitamin B12 and folic acid (rarely causes deficiency); hypothetical risk of lactic acidosis with listed contraindications
Bioavailability	50-60%
Blood concentration	Maximal 1-2 hours after an oral dose; negligible binding to blood proteins
Blood half life	1.5 – 4.9 hours
Metabolism	Not measurably metabolised
Elimination	Ninety percent eliminated in the urine in twelve hours
Availability	Available on the Australian Pharmaceutical Benefits Scheme (PBS)[54]

Metformin has been shown to lower both FPG levels and HbA_{1c} in moderately obese patients with type 2 DM who were inadequately controlled by diet.[55] The primary failure rate for metformin is reported to be 5-20% but this includes patients who discontinue the drug

because of initial gastrointestinal side effects. Secondary failures are reported to be five to ten percent per year, which is similar to sulphonylureas.[49] The data from UKPDS indicate that metformin is as effective as insulin or sulphonylurea therapy in decreasing both FPG levels and HbA_{1c}, without causing weight gain, hypoglycaemia or hyperinsulinaemia.[56] The UKPDS 34[13] showed that among overweight patients allocated intensive blood glucose control, metformin showed a greater effect than sulphonylureas or insulin for any DM related endpoint, all-cause mortality and stroke. Early addition of metformin in sulphonylurea treated patients was associated with an increased risk for diabetes-related deaths and all-cause mortality in over-weight and non-over-weight patients (both subsets of patients were reviewed separately and together). The reason for this increased risk is currently unknown and requires further study to clarify the place of metformin and sulphonylureas in the treatment of type 2 DM. Overall, metformin does seem to be advantageous as a first-line pharmacological therapy in diet-treated over-weight patients with type 2 DM. It can also be used first-line in normal weight type 2 DM patients.[13, 15]

1.1.2.1.1.3 Side effects

Metformin is now the only biguanide available for use in Australia and it has a ten fold lower risk of lactic acidosis than its predecessor phenformin.[57] Metformin should be used with caution in patients with any risk factors that may precipitate lactic acidosis, such as moderate to severe renal failure[13], although evidence for this is mainly from case reports.

Diarrheoa is a common side effect of metformin and may limit its use.[49] This side effect can be minimised by starting at a low dose (250mg to 500mg daily) and slowly titrating upwards according to FPG results. Long-term therapy with metformin is associated with decreased intestinal absorption of cyanocobalamin and folate, but anaemia has developed in few patients.[49]

1.1.2.1.1.4 Potentially significant drug interactions

Renal clearance of metformin may be reduced by concurrent administration of cimetidine.[58] The proposed mechanism is competition between cimetidine and metformin for proximal tubular secretion. If cimetidine is introduced to a patient on a stable dose of metformin, the patient should monitor the blood glucose closely.

1.1.2.1.2 Sulphonylureas

1.1.2.1.2.1 Mechanism

The mechanism of action of sulphonylureas is currently thought to be beta cell receptor specific stimulation of insulin release from the pancreas, thereby increasing circulating levels of insulin.[55, 59] There is evidence that insulin levels fall over the ensuing months or years after commencing therapy, although the drugs often retain their effectiveness as hypoglycaemics. Sulphonylureas may also have effects on reducing glucose production in the liver and increasing glucose uptake by skeletal muscle cells,[43] although these effects are relatively minor.

1.1.2.1.2.2 Place in therapy

The UKPDS 33[8] showed that intensive blood-glucose control by either sulphonylureas or insulin substantially decreased the risk of microvascular complications, but not macrovascular disease. An intensive blood-glucose control policy was associated with an average HbA_{1c} of 7.0% over the duration of the study compared with 7.9% in conventionally managed patients.

Sulphonylureas are generally used in type 2 DM patients who do not respond to diet alone, do not require insulin and are not obese.[3] Sulphonylureas are contraindicated in severe insulin deficiency, pregnancy, in intercurrent illness, and in perioperative patients (because of their prolonged hypoglycaemia). How long sulphonylureas remain effective cannot be predicted, and patients must be reviewed regularly.[44] Approximately two thirds of patients who begin therapy with a sulphonylurea respond, although depending on glycaemic targets, twenty percent or more eventually require additional therapy.[47] There are several identified causes of secondary failure in patients receiving sulphonylureas. These include addition of drugs causing hyperglycaemia, non-adherence to dietary requirements or drug therapy, stressors (CHD, infection, surgery, thyrotoxicosis, trauma) and/or weight gain.[47]

Currently there are four sulphonylureas listed on the PBS in Australia; glibenclamide, gliclazide, glipizide and glimepiride (Table 1.3).[54]

Table 1.3: Characteristics of sulphonylureas currently listed on the Australian PBS[50, 54, 60]

Agent	Daily dose	Tablet strength	Duration of effect	Half life
Glibenclamide	5mg (elderly 2.5mg); max 15mg	2.5 and 5mg	20-29 hours	10 hours (longer in impaired renal function)
Gliclazide	40-80mg; max 320mg (divided doses)	80mg	10-15 hours	6-15 hours
	30-90mg daily (single dose)	30mg MR*	24 hours	
Glipizide	2.5-5mg; max 40mg (divided doses)	5mg	14-16 hours	1-5 hours
Glimepiride	1-8mg daily (single dose)	1,2,3 and 4mg	24 hours	5 hours

*MR = modified release

1.1.2.1.2.3 Pharmacokinetics

Sulphonylureas are almost completely absorbed following oral administration. The rates of absorption, biotransformation and duration of action differ for each compound. They are metabolised by the liver and excreted predominately in the urine. Glibenclamide is a typical long acting agent, which is excreted as metabolites in the bile and urine.[61] Due to an enhanced risk of accumulation, this drug should be avoided in patients with moderate to severe renal disease in favour of an agent that is solely hepatically metabolised, such as gliclazide.

1.1.2.1.2.4 Potentially significant drug and food interactions

Many drugs interact with sulphonylureas and may interfere with diabetes control.[44] Important interactions include aspirin and sulphonamides. A study in which high dose aspirin was introduced to glibenclamide therapy resulted in an increase in the free fraction of glibenclamide and potential hypoglycaemia.[62] Patients on low dose aspirin did not experience this effect. Patients on stable sulphonylurea therapy should be counselled to take paracetamol for pain, rather than aspirin as high dose aspirin may cause hypoglycemia. The literature has varying reports concerning non-steroidal anti-inflammatory drugs (NSAID) and sulphonylureas; the interaction is probably not of clinical significance at standard doses.[59] Introduction of sulphonamides to stable sulphonylurea therapy can cause severe

hypoglycaemia. This interaction is more significant with the longer acting sulphonylureas.[63,64]

Alcohol blocks gluconeogenesis and the surge in hepatic glucose output, that is crucial for recovery from hypoglycaemia and may subsequently cause hypoglycaemia, in patients on sulphonylureas. Average amounts of alcohol (<2 standard drinks per day for a male) should not cause a problem, but consumption of large amounts of alcohol or binge drinking may precipitate hypoglycaemia.[61]

There are case reports of patients developing hypoglycaemia with concurrent administration of glibenclamide and ACE inhibitors.[65] The proposed mechanism of action is increased insulin mediated removal of glucose in skeletal muscle and tissues via a vasodilatory action of ACE inhibitors. When patients on stable sulphonylurea therapy are commenced on an ACE inhibitor they should be informed that sudden hypoglycaemia has been reported and that they should monitor their blood glucose levels.

Concurrent administration of some antacids containing magnesium hydroxide may increase the rate of absorption of some sulphonylureas.[66, 67] Patients should be counselled to separate administration of antacids and sulphonylureas by two hours to avoid potential hypoglycaemia.

Rifampicin induces hepatic metabolizing enzymes and larger doses of some sulphonylureas may be required to control blood glucose levels during concomitant therapy.[68] When the rifampicin is ceased the doses must be reduced to prevent hypoglycaemia.

There any many other reported interactions in the literature between sulphonylureas and other drugs but most have unproved clinical relevance. Introduction of a new drug to a patient on stabilised sulphonylurea therapy warrants an increase in frequency of blood glucose monitoring and appropriate counselling of the patient.

1.1.2.1.2.5 Side effects

The main side effects of sulphonylureas are nausea, epigastric fullness, heartburn, hypoglycaemia, hyperinsulinaemia, weight gain and liver enzyme elevations. Sulphonylureas

act via endogenous insulin and their main side effects of hypoglycaemia and weight gain are generally predictable and dose related. Hypoglycaemia, although relatively uncommon, may be severe and difficult to reverse.[47] Certain risk factors may predispose a patient to hypoglycaemic episodes and these include increased age, renal dysfunction and decreased energy intake.[69] Enhanced therapeutic monitoring may be warranted in patients with the above risk factors.

Skin rashes can occur with sulphonylureas. Sulphonylureas are chemically related to sulphonamides but do not share the same pharmacological adverse effect profile. Severe hypersensitivity reactions (e.g. blood dyscrasias and Stevens Johnson syndrome) are rare.[43]

1.1.2.1.3 Acarbose

Acarbose is an alpha-glucosidase enzyme inhibitor and can diminish postprandial blood glucose by delaying carbohydrate absorption from the small intestine.[70] It is a useful addition to other oral treatments for lowering blood glucose, especially if insulin may not be desired or is inappropriate. Careful titration of the dose of acarbose is necessary to minimise side effects. The starting dose should be 25mg taken at the beginning of each meal. The dose can be increased every four to eight weeks, depending on response. Doses greater than 300mg should not be required.[1]

There are significant compliance problems with acarbose due to the high incidence of flatulence and diarrhoea and the necessity to take acarbose three times a day for maximum benefit. A randomised double blind trial showed that acarbose significantly improved glycaemic control over three years in patients with type 2 DM, irrespective of concomitant therapy.[70] In patients who continued to take acarbose for the full three years a reduction in HbA_{1c} of 0.5% was seen. This may be a clinically relevant reduction in HbA_{1c}, as acarbose is used in combination with other agents and may be added to avoid progression to insulin therapy.

Acarbose alone does not cause hypoglycaemia but, when used in combination with a sulphonylurea, hypoglycaemia may result. The hypoglycaemia caused by this combination cannot be treated with oral carbohydrates because acarbose delays its absorption. Patients on

acarbose should use glucose tablets, glucose liquid or glucagon injections for the treatment of hypoglycaemia. [71]

Acarbose is listed on the Australian PBS for type 2 DM patients whose blood glucose concentrations are inadequately controlled despite diet, exercise and maximal tolerated doses of other oral anti-diabetic agents, and where insulin therapy is inappropriate.[54]

1.1.2.1.4 Thiazolidinediones

These drugs have been described as insulin sensitisers because they have been shown to enhance glycaemic control, lower insulin levels and promote glucose utilisation in the tissues. They do not cause hypoglycaemia, weight gain or lactic acidosis.[72] The currently available thiazolidinediones, or glitazones are pioglitazone and rosiglitazone, and these drugs have been recently listed on the Australian PBS.[54]

About 40 cases of serious hepatic dysfunction were reported with the use of troglitazone, including rarely, severe hepatocellular damage, hepatic necrosis and hepatic failure.[73] Among troglitazone patients who started treatment in 1998, the estimated risk of liver-related death was approximately 1 in 100,000.[73] Troglitazone has subsequently been withdrawn from the market. The level of liver dysfunction seen with troglitazone has not been demonstrated with the newer glitazones, but vigilance is required. Liver function tests should be performed regularly and the thiazolidinedione should be discontinued in the presence of unexplained deterioration of liver function.[73]

1.1.2.1.5 Meglitinides

Meglitinides, such as repaglinide act as prandial glucose regulators.[74] Repaglinide is short acting with a rapid onset of effect and should be taken shortly before a meal. It should not be taken if the meal is missed. Long-term glycaemic control is similar to that seen with sulphonylureas and the tolerability profile is also similar.[75] Repaglinide is not listed on the Australian PBS and is rarely used in clinical practice in Australia.[54]

1.1.2.1.6 Insulin

Over the long natural history of type 2 DM, up to 30% of patients eventually fail to respond to oral agents and require insulin.[19, 60] The decision to start insulin is dependent on many factors including age, complications, symptoms, concomitant diseases and overall life expectancy. Increased hepatic output of glucose, especially at night, is the main determinant of fasting hyperglycaemia in patients with type 2 DM.[50] The bedtime administration of an intermediate acting insulin can be very beneficial as this may improve glycaemic control through only one injection a day. In some cases, patients who are failing oral therapy are switched to a multiple-insulin injection regimen similar to that given to type 1 DM patients.[76] Commonly, type 2 DM patients may be given twice daily subcutaneous injections of premixed short and intermediate insulins.[60]

There is no standard dose of insulin and requirements depend on many factors such as diet, weight, exercise levels, stress and illness.[77] Each patient's needs must be determined individually and may change on a day-to-day basis and over the course of the disease. A typical daily dose might be in the order of 0.5-0.7units/kg/day split into 1-4 injections and possibly 2 or 3 different types of insulin. Treatment schedules need to be reviewed regularly and adjusted as necessary.[77]

The results of UKPDS 33[8] showed that intensive blood glucose control whether by insulin or oral therapy substantially decreased the risk of microvascular complications. Exogenous insulin has been suggested as a potentially harmful treatment because *in-vitro* studies with raised insulin concentrations induced atheroma.[8] The UKPDS[8] did not find any evidence of this. Intensive blood glucose control does have some disadvantages in that the risk of hypoglycaemia and weight gain is higher.

1.1.2.1.7 Summary

A simple treatment algorithm for the management of type 2 DM can be seen in Figure 1.1.

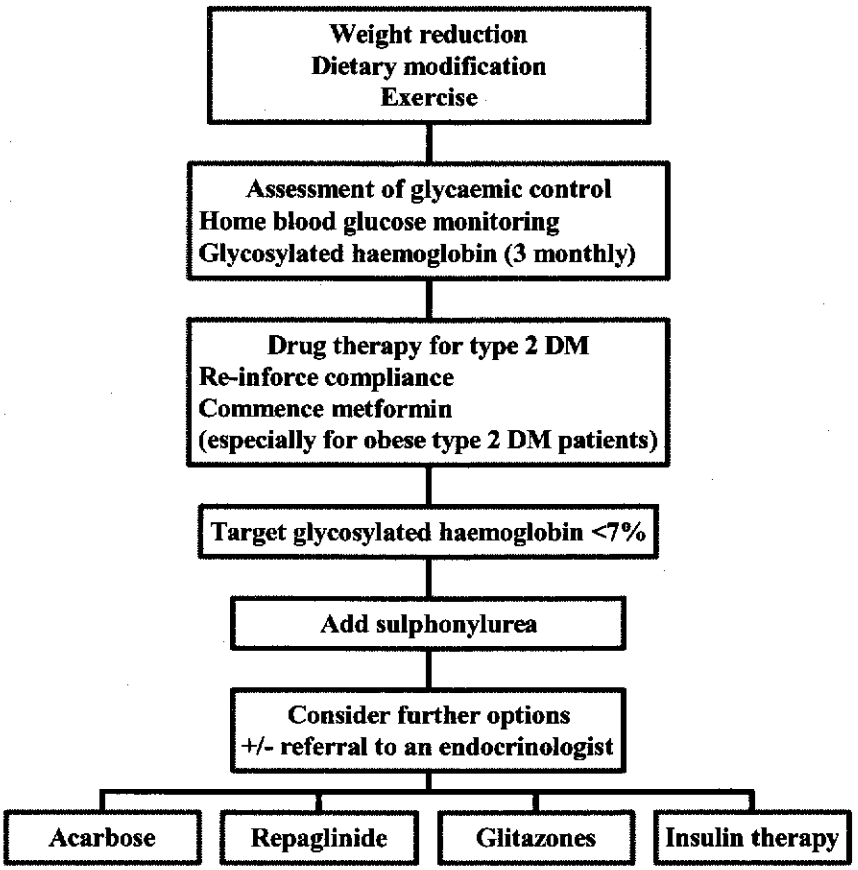


Figure 1.1: Management of type 2 DM[60]

1.1.2.2 Dyslipidaemia

Aggressive treatment of dyslipidaemia in DM is essential.[78, 79] Plasma cholesterol is an independent risk factor for CHD and the risk is higher in people with DM than in the non-diabetic population.[1] Determination of the lipid profile (total cholesterol, triglycerides, low density lipoprotein (LDL) and HDL-cholesterol) should form a part of the annual assessment of the diabetic patient. Targets for patients with diabetes should include reaching a total cholesterol of <4.0mmol/L, an LDL-cholesterol of <2.5mmol/L, an HDL-cholesterol of >1.0mmol/L and triglycerides of <2.0mmol/L.[80] Emphasis needs to be placed on weight reduction, exercise and restriction of saturated fat, cholesterol, sugar, sodium chloride and alcohol.

The efficacy and tolerability of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins, puts them as first-line therapy for hypercholesterolaemia.[80] Simvastatin, pravastatin, fluvastatin and atorvastatin are currently available in Australia.[54] For patients who cannot tolerate statins or need combination therapy fibrates are a useful alternative.[80] Of the fibrates, gemfibrozil and fenofibrate are currently available in Australia. Fenofibrate is only available via clinical trial.

A recent quantitative systemic review has also confirmed that fish oil supplementation (containing omega-3 fatty acids) in type 2 DM lowers triglycerides.[81] The review did emphasise that further research was needed into the use of fish oils in type 2 DM, however they may provide a useful alternative or addition to DM patients with raised triglycerides.

1.1.2.3 Hypertension

The development of stroke and microvascular disease in patients with DM is related to hypertension. Tight control of BP in hypertensive patients with type 2 DM substantially reduced the cost of complications, increased the interval without complications, increased survival, and had a cost effectiveness ratio that compared favourably with accepted healthcare programs.[21, 82, 83] Hypertension in DM also responds well to weight loss and exercise.[84]

In UKPDS 38, tight control of BP reduced death caused by DM by 32%.[4] The Hypertension in Diabetes Study was a multicentre, randomised, controlled trial embedded within the UKPDS that was designed to determine whether tight BP control (less than 150/85 mmHg), reduced morbidity and mortality in hypertensive patients with type 2 DM, compared to less tight control. Of the 4297 patients recruited to UKPDS, 1544 (38%) had hypertension (defined as a BP of > 160/90 mmHg or antihypertensive therapy) and, of these, 1148 were eligible for the Hypertension in Diabetes Study. Recruitment ran over a four-year period. Patients visited study clinics every three to four months and BP was measured and adjustments to medications were made where necessary and appropriate. The median follow up to the end of the trial was 8.4 years. Patients allocated to tight BP control compared with less tight control had a 24% reduction in risk of developing any end point related to diabetes (P=0.005). Tight BP control also resulted in a reduction of 44% for stroke, 56% for heart failure and 37% for microvascular disease. UKPDS suggested the goal with BP reduction could be as low as SBP <135 mmHg and DBP <85 mmHg. The UKPDS achieved a mean

BP of 144/82 mmHg in the tight control group. The UKPDS concluded that "tight control of BP achieves a clinically important reduction in the risks of deaths related to DM, complications related to DM, progression of diabetic retinopathy, and deterioration in visual acuity".[4]

While it is clear that lowering BP is important in patients with diabetes, optimal treatment of hypertension in DM continues to be controversial. The currently recommended goal in clinical management is a BP of 135/85mmHg or lower.[4, 82, 85] Recently, the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [86] concluded that thiazide diuretics were the preferred first-line treatment, in non-diabetic patients. Subgroup analyses of comparative trials, including the ALLHAT trial, have demonstrated no advantage of ACE inhibitors over thiazides in people with DM and no renal disease.[87] The results of the Second National Blood Pressure Study[88] contradicted the results of ALLHAT and concluded that treatment with ACE inhibitors leads to better outcomes than treatment with diuretics.

The controversies will continue to persist but it would appear that the data is leaning towards the use of ACE inhibitors in DM patients, as first line anti-hypertensive therapy, especially in light of their other proven benefits in DM patients.[34-36, 87, 89]

1.1.2.4 Summary

Addressing the complications of DM with appropriate lifestyle modification and pharmacotherapy are essential components in reducing the morbidity and mortality associated with type 2 DM. Optimal pharmacotherapy will continue to be reviewed and modified according to the ongoing results of large-scale trials. It is also clear that multifactorial interventions targeting lifestyle modification and appropriate pharmacotherapy are necessary in DM. Different ethnic groups have differences in rates of complications and response to pharmacotherapy.[14, 90] Ethnic issues in the treatment of DM have not been widely addressed in the Australian population.

1.2. ETHNIC DIFFERENCES IN DIABETES MELLITUS

1.2.1 Background

There have been many studies which have demonstrated that different ethnic groups have differences in the prevalence of DM, glycaemic control, and development of DM complications.[5,45,90-111] While the prevalence of DM in the Australian Aboriginal population has been widely studied,[106, 109, 112-114] and is known to be much higher than the DM prevalence in Australians of European decent, there have been few studies, reviewing the prevalence of DM, levels of DM complications or treatment differences in individual non-Aboriginal Australian ethnic groups.

The 1989-90 National Health Survey reviewed the prevalence of self-reported DM in an Australian context.[115] The study documented the age-standardised prevalence of self reported DM by country of birth and language spoken at home (Table 1.4). In comparison with people born in Australia, Southern Europeans (SEs) had a higher incidence of DM. When English was not the language spoken at home, DM prevalence was higher by 60%. The age and gender trends seen in this survey were consistent with other Australian surveys[106, 116], which show a predominance of males and an increasing prevalence with age, until the late 70s.

Table 1.4: Age-standardised prevalence (%) of self-reported DM/high blood sugar levels in Australia[115]

	Males	**Females**
Country of birth:		
Australia	1.6	1.7
UK/Ireland	1.4	1.8
Western Europe	1.0	0.7
Southern Europe	3.3	3.5
South-East Asia	2.0	2.8
Language spoken at home:		
English	1.7	1.9
Other	2.9	3.0

The Visual Impairment Project (VIP) followed over 4000 patients in Melbourne and rural Victoria, in the mid 1990s and 83% participated in Melbourne and 91% in rural Victoria.[102,

[117] The mean age in this cross-sectional study was 58 years, with a self-reported prevalence of DM in Melbourne of 5.2% and 4.9% in rural Victoria. This self-reported prevalence figure is comparable to that seen in the Blue Mountains Eye Study.[96] Participants in the VIP study were classified into various ethnic groups on the basis of their report of their parents' country of birth (Table 1.5).

DM prevalence, adjusted for age, sex and BMI was significantly higher among subjects with Italian and Greek ethnicity compared with subjects of Anglo-Celt (AC) ethnicity. The conclusion from the Visual Impairment Project was that people with self-reported DM in Victoria in the mid 1990s, were more likely to be male, older, overweight and of Mediterranean ethnicity. The ethnicity data were consistent with the 1989/90 National Health Survey which found a higher prevalence of self-reported DM across all ages among SEs (3.4%) compared with people born in Australia (1.65%).[115]

Table 1.5: Ethnicity data for the Visual Impairment Project (self-report) [102]

Ethnicity	**Diabetes % in subgroup n=239**	**No diabetes % in subgroup n=4,478**	**Odds ratio (OR)***
AC	60	73.9	1
Italian	14.9	7.7	1.83
Greek	10.2	5.6	2.08
Other European	11.9	9.8	1.37
Other	3.0	3.0	1.77

*adjusted for age, sex, BMI and ethnicity

The 1989/90 National Health Survey[115] and the Visual Impairment Project[102] are the only two Australian studies that have reviewed prevalence of DM in ethnic groups in Australia and both agree that SE ethnicity may be a risk factor for the development of DM. Further investigation into whether this has an impact on development of DM complications or alters treatment requires investigation.

There have been a number of studies that have reviewed ethnic differences in the prevalence, development of DM complications and differences in treatment in various ethnic groups in

the UK.[93, 118-120] Understandably none have reviewed SEs in comparison to ACs. The main UK studies have compared white Caucasians (predominantly ACs) with people of Asian descent living in the UK. White Caucasians in the UK in the 1990s were reported to have a prevalence of DM of around 4%, which is similar to the non-aboriginal population in Australia. People of Asian descent living in the UK appear to have one of the highest DM prevalence rates in the world.[94, 119, 120] Unfortunately, the UK data do not add to the small amount of Australian evidence that suggests SE ethnicity may be a risk factor for the development of DM.

The UKPDS gave the first detailed prospective evaluation of the relationship between self-reported ethnicity and parameters such as BP, lipids, FPG and HbA_{1c}.[91] Other studies have assessed cross-sectional data of newly diagnosed patients or patients with a longer duration of DM and found ethnic differences in vascular risk factors.[121-125] The UKPDS was the first prospective review of these data.[14, 91]

The UKPDS reviewed three ethnic groups, white Caucasians (predominantly ACs), Indian Asians and Afro-Caribbean living in the UK and concluded that;

1. There are important differences in body weight, lipids and BP, but not glycaemic control during the first nine years of type 2 DM between ethnic groups, but that
2. Glucose lowering treatment can be used without reference to ethnicity in this cohort.[14]

These data highlight important ethnic differences in ethnic groups in the UK, but there were no data that reviews clinical and treatment differences in an Australian context.

1.2.2 Summary

The clinical characteristics of various ethnic groups in Australia needs to be studied, so that this information can be used to subsequently determine if treatment approaches in DM need to be modified for different ethnic groups.

1.3. PHARMACEUTICAL CARE

1.3.1 Background

Drug related problems are common, contribute significantly to health care costs, and are caused by factors including inappropriate prescribing, inappropriate delivery, inappropriate patient behaviour, patient idiosyncrasy and inappropriate monitoring.[126] The process of choosing, prescribing and subsequently monitoring the most suitable drug for individual patients is becoming increasingly complex, due in part to the wide variety of drug treatments available, the aging population with multiple co-morbidities and the necessity for the patient to be actively involved in the decision making process.[127] The causes of drug related problems are multifactorial, but may also be categorised under[128]:

1. indication (e.g. unnecessary therapy)
2. effectiveness (e.g. inappropriate drug)
3. safety (e.g. adverse drug reactions)
4. compliance (e.g. poor knowledge or inappropriate patient behaviour) and
5. untreated indication (e.g. need for additional therapy).

Pharmaceutical Care (PC) aims to address all these issues by creating an environment of cooperation between patients and health care professionals (HCPs).

The PC model was established to provide a framework by which drug use could be improved to enhance patients' clinical and HRQOL outcomes. This can be achieved by a focus on active understanding and involvement of the patient in PC plans developed by a pharmacist in close partnership with the patients' physician and other HCPs.[126]

Pharmacy practice has evolved from the traditional pharmacists' roles in pharmaceutical supply to now include a strong emphasis on direct patient care at all levels of health-care service from the primary care setting to tertiary institutions. The expansion of clinical pharmacy in the 1960s, 70s and 80s has now culminated in the concept of PC which can be practised by all pharmacists as a patient-focused activity aimed at addressing drug misadventure and optimising therapeutic outcomes.[129-132]

Studies of the impact of pharmaceutical services demonstrate that pharmacists can improve the cost effectiveness of drug delivery, through face-to-face interventions, prescribing protocols, formulary compliance, drug use evaluation, therapeutic drug monitoring services,

drug administration and drug management.[128, 133, 134] Reports of the pharmacists' role in an ambulatory care setting have generally shown improvement in compliance, patient knowledge and other relevant clinical outcomes, such as international normalised ratio (INR), BP, lipids or serum drug concentration.[133-148] These services, which normally include active participation of pharmacists in decisions of drug treatment regimens, are well accepted by medical and allied health staff, and have been established in the traditional clinical pharmacy role and describe a service which, may be a part of the PC process, but may not include all nine steps as described by Hepler and Strand.[149]

The PC process involves[126, 149, 150]:

1. Developing a pharmacist-patient relationship
2. Collecting, analysing and interpreting relevant information
3. Listing and ranking drug related problems
4. Establishing pharmacotherapeutic outcomes with the patient
5. Determining feasible pharmacotherapeutic alternatives
6. Selecting the best pharmacotherapeutic solution
7. Designing a therapeutic monitoring plan
8. Implementing the individual regimen and monitoring plan
9. Follow-up.

The practical aspects of PC that need to be recognised from these steps is that it is a drug related service provided directly to the patient using a team approach. Traditional clinical pharmacy programs have been delivering this care approach for many years. However the key points that may have been over-looked in traditional clinical pharmacy programs are that it should produce definite clinical and HRQOL outcomes that are clearly established with the patient and that the pharmacist must assume personal responsibility for the outcomes.[151] It then becomes clear that establishing and monitoring the pharmacotherapeutic outcomes is the area that changes a program from a traditional clinical pharmacy program to a PC program.

There are many different models of pharmacy practice around the world, due to differing cultural, financial and organisational features of health-care systems and differing patient populations. Many articles have been written on the definition of PC and the importance of developing good models of PC.[126, 128, 139, 149-159] PC models have also been described in a

variety of settings, such as hospices and tertiary referral centres.[139, 140, 156, 160] These descriptive papers are useful for helping other HCPs to establish new services or upgrade existing services but the PC literature is lacking in large well-designed studies focusing on clinically relevant outcomes.

It has been highlighted in the literature that the quality of PC research needs to be improved, especially with respect to evaluating clinically relevant outcomes.[161-169] Studies have included analysis of drug-related problems, or pharmaceutical care issues, drug-related hospital admission, drug costs and even HRQOL but many fail to follow all the appropriate clinically relevant outcomes, for example BP, respiratory function, or glycaemic control.[136, 146, 147, 158, 160, 170-175] In addition many PC studies involve only small patient numbers[136, 158, 160, 170, 171, 173, 174, 176-180] or are not randomised controlled trials.[136, 158, 160, 170, 176, 181]

Some studies have followed clinical outcomes measures.[129-132, 143, 144, 177-184] Of these papers, only seven met all the criteria for quality PC research.[129-132, 143, 144, 182] The vital parameters for good quality research are[127];

1. Sufficiently large patient numbers
2. Randomised controlled trials and
3. Following relevant clinically important outcomes.

Despite these problems, it is clear that PC has as its core, the detection, prevention and solution of drug-related problems in a measurable form so that outcomes of care can be easily measured and reviewed and patient care is improved. Attention needs to be paid to designing PC research to include clinical outcome measurements as it is not appropriate to simply report on improving drug-related problems or pharmaceutical care issues, without proving that addressing these problems and issues is clinically relevant.[127, 168, 185]

1.3.2 Pharmaceutical Care in patients with diabetes

The need for intensive DM management is the subject of discussion and debate[103, 186-190] and it is clear that intervention programs to improve DM care and outcomes are important.[8, 13, 18, 25, 103, 191, 192] DM care is a major component of the health service and patients with DM account for 5-6% of inpatient consultant episodes and outpatient attendances and on average they stay in hospital over 50% longer.[193-195] A study in the USA determined that total

pharmacy costs were three fold higher for patients with diabetes compared with non-diabetic patients.[196] Evans and colleagues[197] found that DM patients were 1.7 times more likely to be dispensed a drug item than people without DM. Projecting these results, it was estimated that nearly 8% of the UK drug budget was accounted for by patients with diabetes (90% of this figure by patients with type 2 DM). This high use of resources provides a rational basis for good PC in these patients.

Studies have shown that intensive multifactorial intervention in patients with type 2 DM and microalbuminuria slows progression of retinopathy and autonomic neuropathy and reduces the risk of cardiovascular events by about 50% (Chapter 1; Section 1.1).[25,191] One study involved intensive intervention by the doctor, nurse and dietician addressing exercise, diet, other risk factors such as smoking and pharmacological management.[198] The addition of a pharmacist to provide PC was not undertaken in this study. Pharmacists are in an ideal position to undertake multifactorial interventions. The interventions by Gaede[25, 191] were provided through a specialist diabetes clinic with a high intensity intervention and was highly successful. Pharmacists may be able to provide this multifactorial intervention in the community setting as they are a readily accessible member of the health-care team and can establish a PC plan with patients and provide follow-up on a regular basis as part of their role.[192] PC as part of community pharmacy services for diseases such as DM can be considered disease state management (DSM), due to the chronic nature of the disease. A recent study of a DSM program that involved adherence support and compliance checks, checks of medication history and medication review, review of glycaemic control and lifestyle information, reported positive benefits for the patients.[192]

The Pharmacy Guild of Australia has also recognised the need to address diabetes care issues and commissioned the Pharmacy Diabetes Care program in 2002.[199] The project has two key elements, case detection for undiagnosed diabetes and support via community pharmacists for patients with diabetes via medication advice, home medication reviews and general support to help patients' manage and monitor their diabetes. This comprehensive program will be completed in 2004.

The home medication review (HMR) program, previously known as domiciliary medication management reviews (DMMRs)[200] is a service that exists to review all aspects of medication

use in the patient's home environment and requires a referral to an accredited pharmacist from a general practitioner. An accredited pharmacist reviews all aspects of the patient's medication in the patient's home, reports to the general practitioner and the general practitioner subsequently writes a medication management plan that is agreed to with the patient. The medication management plan is designed to be an active document to facilitate ongoing review and communication between the patient, general practitioner and pharmacist.

HMRs are now an accepted part of the pharmacists' role in Australia and are an ideal forum for PC to occur in the community, using established frameworks of communication between the general practitioner, the pharmacist, the patient, and other HCPs.[201] However, there are limitations as community pharmacies are currently under resourced in staff (and subsequently time) and there is a lack of qualified staff to deliver HMRs. There is also a perception in some pharmacies that HMRs are a time consuming expensive waste of money.[202] Subsequently, uptake of the HMR program has not been as high as originally projected.[203] As PC for diabetes patients is a time consuming process due to the chronic nature of the disease and the multiple co-morbidities associated with diabetes, these issues will need to be fully addressed so that diabetes care can be successfully incorporated into the HMR program.

There have been a number of reports in the literature reviewing the effectiveness of pharmacist involvement in the diabetes healthcare team or commenting on pharmacist involvement in such teams.[170-174, 176, 179, 181, 183, 184, 204-207] Many of the studies in the literature involving pharmacists

1. are not well designed, as they are not randomised controlled trials[170, 171, 176, 177, 181]
2. involve small patient numbers [170, 171, 173, 174, 176, 177, 179] and/or
3. do not monitor all clinically relevant patient outcomes.[170, 171, 173, 174]

Before PC was defined, Sczupak and Conrad studied the effect of patient–oriented pharmaceutical services on the treatment outcomes of ambulatory patients with diabetes.[173] This randomised controlled trial had a small sample size (n=40) and only female patients were recruited and 95% of patients had type 2 DM. The mean duration of diabetes was approximately 15 years and the majority of patients were on insulin therapy (93%). The intervention comprised most of the elements of PC[149], but it was not made clear whether treatment goals were established and subsequently reviewed with the patient. Some clinical

parameters, such as urine glucose and postprandial blood glucose levels improved over the 12-month period of the intervention. Actual data were not provided, but the differences were quoted as statistically significant. In contrast, the clinically important and relevant outcome of improvement in FPG did not show a significant improvement over the study period, but no data were provided. Patient admissions to hospital were significantly lower in the intervention group. Other important outcomes such as HRQOL and cost were not addressed. This was the first study where the addition of a pharmacist to the diabetes health-care team demonstrated clinically relevant improvements in some outcome measures.

Hawkins et el[183] published the only study in diabetic and hypertensive patients that has compared the services offered by pharmacists to the same services offered by a physician. The pharmacist intervention group showed a slight increase in scheduled service utilisation, but no decrease in non-scheduled service utilisation (e.g., emergency department visits and hospitalisation) and there were no differences in clinical outcome measures.[185] Clinical outcomes measures included FPG and BP measurements and future studies would need to add other clinical outcomes measures such as lipid levels, BMI and microalbuminuria to ascertain the clinical value of such a program. This study was completed prior to PC being defined, but reviewed traditional clinical pharmacy practice. As the pharmacist had the same impact as the physician, the pharmacy resource may be better utilised in a community setting, where physicians may be less accessible. Community pharmacists could establish a program such as this as the most accessible member of the health-care team in the community and via domicillary visits which have become an accepted part of pharmacy practice in Australia.[200]

Huff and colleagues[208] described a pharmacist-managed diabetes education service in three ambulatory care centres, established in the early 1980s. Comprehensive diabetes education was provided to the patient and short and medium term treatment goals were established and the patient was subsequently reviewed by a physician's assistant. This paper was descriptive and the group did not carry out a randomised controlled trial to establish the outcomes of the program; it merely emphasised that a pharmacist should become involved in diabetes education as they may be the most accessible health care professional in the community.

A study by Jaber and colleagues[179, 209] described a PC intervention in a group of African-American patients attending a tertiary referral outpatient clinic. This study was a randomised

controlled trial and eligible patients were randomised to either a pharmacist intervention or control group and followed over a four-month period.

Patients in the intervention group received diabetes education, medication counselling, instructions on dietary regulation, exercise, home blood glucose monitoring, and evaluation and adjustment of their hypoglycaemic regimen. Patients in the control group continued to receive standard medical care provided by their physicians. The primary outcome measures included FPG and HbA_{1c}. Secondary outcomes endpoints included BP, serum creatinine, creatinine clearance and the lipid profile. HRQOL assessments were performed in both groups at baseline and at the end of the study. Thirty-nine patients (17 intervention and 22 control) completed the study. Significant improvements in HbA_{1c} (P=0.003) and FPG (P=0.015) were achieved in the intervention group. HbA_{1c} levels fell from 11.5 ± 2.9 to 9.2 ± 2.1% in the intervention group and from 12.2 ± 3.5 to 12.1 ± 3.7% in the control group. Significant differences in the final HbA_{1c} (P=0.003) and FPG (P=0.022) concentrations were noted between the groups.

These patients were in the poorly controlled diabetic category at recruitment and also at the completion of the study, even though there was some improvement in the intervention group. Factors that may have resulted in these high HbA_{1c} levels were not explained in the report, however ethnicity may have been a factor. No significant changes in BP, lipid profile, renal function parameters, weight or HRQOL measures were noted within or between groups.

Overall this study had limitations because the small cohort had very high HbA_{1c} levels at recruitment. The relevance of this paper, which is cited as a landmark study, is questionable, because the patient group was not typical of community-based DM patients in developed countries. Patients in the UK and Australia, rarely report such high HbA_{1c} levels. Furthermore, it is notable that the follow-up to this study[209] involving only 14 intervention patients for between two and nine months, showed that the post study HbA_{1c} levels were significantly higher than at study exit, demonstrating that the intervention did not result in any long term changes. It does highlight that different ethnic groups had different levels of glycaemic control and this has been recognised in the Afro-American population.[210, 211] It also emphasizes that ethnicity specific PC programs may be important.[112, 145, 212, 213]

Baran[170] described a pharmacist run diabetes education program (n=88). This study did not include a control group, which is a major limitation, but it raised some interesting points. The pharmacists recorded patient goals, drug-and disease related adverse events, pharmacist initiated treatment interventions, patients' mastery of diabetes management skills, laboratory and physical values, patients' visits to the physician, hospital, and emergency department as well as HRQOL. Goals were established and reviewed with each patient and interventions were discussed and reviewed with the physician. Some outcomes were reported, including HRQOL, changes in visits to physicians and the emergency department, but clinically relevant parameters such as HbA_{1c}, FPG were not reported. As pharmacists may be the most accessible member of the health care team, diabetes education services such as this could be run by the community pharmacist and through domiciliary pharmacy services. The study once again highlights poor PC research due to the design, the small patient numbers and the lack of clinically relevant outcome measures.

Kelly and Rogers[177] reported on a pharmacist-managed diabetes service where the pharmacist provided a one-on-one assessment of 44 patients with HbA_{1c} levels of >8% on study entry. Assessment and intervention included dosage adjustments of medications, diabetes self-management training, continuing education and periodic assessment of treatment goals. At the end of the 7-month intervention period mean HbA_{1c} was significantly lower in the intervention group, compared with historical controls (7.5% versus 8.5%). In addition a greater proportion of patients in the intervention group had mean HbA_{1c} levels of <7%. Other outcomes measures including BP, cholesterol levels and smoking cessation did not improve over the six-month study period. Although this was not a randomised controlled trial most clinically relevant outcome measures were followed in the study.

Recently, a retrospective analysis of a physician-pharmacist collaborative drug therapy management diabetes clinic was reported, involving 87 cases in the intervention group and 85 control patients.[184] Patients were seen at approximately three-month intervals and followed for 30 months. This involved a total of 864 clinic visits for the cases and 712 visits for the control group. Patients in the intervention group, which in addition to standard physician care were reviewed by a clinical pharmacist, were 5 times more likely to achieve HbA_{1c} levels <7% at the completion of the study, which has potential clinical and economic benefits. It should be noted that HbA_{1c} levels at baseline for the cases was lower than the

controls (8.2 ± 1.9% vs 9.5 ± 2.2; P=0.014). Another disadvantage of the study was that other endpoints such as BP and lipids were not evaluated, but the study provided some evidence of the benefit of including a clinical pharmacist in drug therapy management of DM. This study is the most comprehensive retrospective study to date, demonstrating the benefit of clinical pharmacist involvement in the diabetes team.

The Asheville project[181] was not a randomised controlled trial but did attempt to monitor clinically relevant outcomes measures (glycaemic control and lipid levels) in DM patients. The study reviewed a PC program implemented in community pharmacies after the pharmacist completed a diabetes certificate program. The project followed patients for up to 5 years and found that patients maintained their improvement in glycaemic control over this period. It is notable that 187 patients were enrolled and only 11 remained in the follow-up cohort after 5 years which limits the relevance of the data.

1.3.3 Summary

The current studies of PC in patients with diabetes do not provide conclusive evidence of the benefit of PC either due to[171, 174, 176, 177, 179]; poor study design; small patient numbers and/or poor selection of outcome measures, including the selection of non-clinically relevant outcome measures.

The retrospective study by Irons and colleagues[184] does provide some low quality evidence that a clinical pharmacist may be of benefit in the diabetes team. A detailed search of the literature has failed to identify any randomised controlled trials of PC in community based patients with diabetes in an Australian population. Differences in culture, ethnicity, structure of the health care system and the availability and use of private health insurance ensures that Australian patients needs will indeed be different to that of patients from the UK and the USA.[155] The acceptability of a PC plan, or education based on a PC plan will differ according to cultural and ethnic differences and these differences must be taken into account when designing or reporting on PC projects.[155] It is also clear that diabetes care needs to be improved in the Australian setting[103, 214, 215] and that the impact of the provision of PC in the Australian context to improve this care requires investigation. PC also provides the framework to integrate and review full medication histories and monitor all aspects of pharmacotherapy including monitoring requirements of complementary medicines.

1.4. COMPLEMENTARY MEDICINES

1.4.1 Background

Complementary medicines (CMs) are being used by an increasing number of patients who typically do not advise their HCPs of concomitant use.[216-222] CMs can be defined as any non-prescription medicine, including nutritional supplements or herbal preparations purchased from a supermarket, health store, over-the-counter from a pharmacy, from a naturopath, homeopath or herbalist, by mail order, over the internet, or grown at home. CMs can be classified as nutritional supplements (for example vitamins, minerals, shark cartilage and amino acids), botanical supplements (for example Saw Palmetto, Xiaoke tea and St Johns Wort), and homeopathic medicines. For the purposes of this thesis, complementary therapies involving the using of medicines either orally, rectally, topically or by inhalation will be referred to as CMs and the use of complementary medicine practitioners will be referred to as Complementary and Alternative Medicine (CAM).

It is evident from pharmacy and supermarket shelves and the increasing number of health shops, that CMs are widely available in the community.[223] It has been established that Australians spend more than $1.2 billion on CMs annually.[224-226] CMs range from Government registered products in pharmacies and health food shops to completely uncontrolled herbal products produced in house by Chinese herbalists, homeopaths and naturopaths.[227-230]

CMs are sold as teas, foods, food supplements or in liquid, capsule, suppository, inhalation or tablet form. Many are not sold as drugs and require no proof of efficacy or warnings about side effects. The potency of these products can vary enormously and great differences in the presence of active substances have been found, depending on where the herbs were grown, how long they were allowed to stand and the soil and climatic conditions in the region where they were grown.[216] Contamination, mislabelling and misidentification of these products, can also be a problem.[216]

Many patients are not aware of what they are taking, especially products purchased from homeopaths, naturopaths or Chinese herbalists as the ingredients are not listed on the bottle, as required by law with conventional medicines.[228, 231] For example, patients who consumed the traditional Chinese medicine (TCM) Chuifong Toukuwan, developed serious side effects

including bone marrow depression, hypertension, arrythmias, and abnormal bleeding.[232] This product was purchased by mail order for the treatment of arthritis and subsequent analysis of the TCM revealed the presence of prednisolone, indomethacin and lead.[232]

Angell and Kassirer[230] state that

> *"there cannot be two kinds of medicine – conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicines that may or may not work. Alternative therapies should be subject to scientific testing no less rigorous than that required for conventional treatments".*

One of the myths that CAM encourages at the consumer level is that natural remedies are seen as somehow being simultaneously more potent and less toxic than conventional medicine.[230]

The degree of awareness of patients use of CMs varies enormously. Some community pharmacists in Australia now incorporate naturopath and iridologist consulting rooms in their pharmacies and carry an enormous range of these products. Other pharmacists may only carry a small range of mostly vitamins, minerals and common CMs, such as garlic capsules. Awareness amongst general practitioners ranges from those who warn patients not to use CMs, to those who integrate it into their practice.[231] Some general practitioners have completed naturopathy courses, prescribe TCMs or practice acupunture in their consulting rooms. Integrative medicine is a term sometimes used to describe general practitioners, pharmacists or other HCPs who incorportate complementary medicine into their practice.[233] Because of this wide spectrum amongst HCPs, there is a need for these professionals to compile full medication histories, review drug-CM and disease-CM interactions and report any suspected adverse reactions. PC provides the framework to integrate and review full medication histories and monitor all aspects of treatment including monitoring requirements of CMs.

1.4.2 Definition

There is no satisfactory definition of CMs or CAM and no appropriate name for this group of therapies that involve a wide range of heterogeneous practices.[230] Some of the names given to these practices include complementary, alternative, complementary and alternative

medicines or CAMs, integrative, herbal medicines, and natural therapies. Angell and Kassirer, consider that "what sets alternative medicine apart the most, is that it has not been scientifically tested and its advocates largely deny the need for such testing".[230]

Eisenberg and colleagues[234] defined CAM as "medical interventions not widely taught at USA medical schools or generally available at USA hospitals". However, over the last few years, many complementary practices have found their way into the medical mainstream. Some medical schools teach CAM and some hospitals offer it. Sir Charles Gardner Hospital oncology clinic in Western Australia has recently opened a facility offering many CAMs to cancer patients. Some health insurance funds in Australia now offer rebates for CAMs, such as chiropractic therapy.

The Therapeutic Goods Administration (TGA) in Australia defined CMs as traditional or alternative medicines which include vitamin, mineral, herbal, aromatherapy, and homeopathic products and allows CMs to be listed or registered.[235]

1.4.3 Regulation

Conventional medicines require comprehensive evidence of safety and efficacy by the TGA in Australia. CMs are either listed or registered by the TGA. Listed CMs are usually considered to be relatively benign, so the regulations allow for sponsors to self-assess their products and the TGA assesses for quality and safety but not efficacy. Registered CMs require comprehensive safety, quality and efficacy data. Many CM products remain in the listed category. Products that are made in-house like TCM and homeopathic remedies, usually escape regulation.

The Commonwealth Government of Australian via the TGA has recognised the growing use of CMs and established the Office of Complementary Medicines (OCM) in 1999. Under this umbrella the Complementary Medicines Evaluation Committee (CMEC) exists as a statutory committee with additional expertise on complementary healthcare products.[236]

The OCM was established to[235]:

1. Provide a government focus for the regulation of CMs and
2. To increase the transparency of CMs regulation.

The key considerations for review by the OCM included[235]:

1. Ensuring a level of regulation commensurate with the "low-risk" nature of most CMs
2. Improving market access for new products whilst maintaining public safety and health
3. Enabling involvement of the CM industry in providing expert advice to government on regulatory policies for CMs
4. Enhancing post-market vigilance, with one reform being the strengthening of the adverse drug reaction reporting system to provide easier access for the complementary healthcare sector
5. Substantiation of therapeutic claims
6. Reviewing advertising regulations to ensure they reflect current and future needs as well as community expectations and
7. Recognising that these products are often developed with an emphasis on health and wellness rather than disease.

The OCM regard CMs as "low-risk" as defined in their first key considerations for review. While many CMs are "low-risk", there are a large number of existing adverse CM reaction reports, drug-CM interactions, CM-disease interactions and even fatalities reported in the literature, leaving no doubt that CMs contain pharmacologically active substances.[237-244] The largely uncontrolled and unmonitored use of these substances, often taken without the knowledge of a HCP, and in many instances taken with prescribed and over the counter drugs, creates the potential for dangerous situations.[233] For example, three cases of heart transplant rejection have been attributed to the interaction between St John's Wort and cylcosporin.[245]

In addition, consumers also have a right to scientifically based therapies that do not make false claims. It is as important to prevent harm as to ensure the consumer receives a legitimate health product. Consumers sometimes believe that CM products are natural and therefore "low-risk", and may not be alert to potential drug-CM or disease CM interactions or adverse reactions to the CM.[230]

The fourth recommendation of the OCM identified that adverse drug reaction reporting needs to be improved for CMs. CAM practitioners, HCPs and the general public need to have available a simple way to report adverse reactions to CMs and the reports that are submitted

need to be readily accessible.[246] Pharmacists are trained in the detection, recording and prevention of adverse drug reactions and have access to the patients' full medication history and could play an active role in addressing this issue.

The last key review point of the OCM, stated that it needs to be recognised that "CMs are often developed with an emphasis on health and wellness rather than disease".[248] While this may be true in many instances, the use of CMs to treat AIDS, cancer (both in adults and children), diabetes, arthritis and other diseases is well reported in the literature and needs to be taken into consideration.[249-253] Use for specific diseases, when the patient is more than likely to be receiving other treatments or be on prescription medications potentially put the patient at risk of drug-CM and CM-disease interactions.

The Australian Expert Committee on Complementary Medicines in the Health System reported to the Commonwealth Governement in September 2003.[247] This committee was established to reassure the public after 1600 CMs were recalled as a result of the failure of one medicine manufacturer, Pan Pharmaceuticals Limited to maintain appropriate manufacturing and quality-control standards. The report re-emphasised the recommendations of the OCM but also called for increased regulation of CAM practitioners, in addition to higher standards of education and training for all those involved prescribing and supplying CMs and increased funding for research into CMs.

The Pharmaceutical Society of Australia (PSA) issued a position statement on CMs in 1997 which concurs with many of the recommendations of the OCM.[254] The PSA is currently reviewing the Expert Committee on Complementary Medicines in the Health System report.

The Australian Medical Association (AMA) issued a position statement on CMs in February 2002.[255] Overall, the AMA concurred that it was important that patients inform their general practitioner of CMs they were using and that that general practitioners should specifically ask patients about their use of CMs. The AMA also called for more research into CMs, so that their efficacy could be assessed from an evidence base. The AMA further stated that CMs should meet the same standards of safety and quality as conventional medicines and that labelling and advertising of CMs must be based on appropriate levels of evidence of efficacy. Dr Roberta Chow (an AMA representative on the CMEC)[233], stated that "the medical

profession must take the area of complementary medicines more seriously, recognising the potential importance of side-effects and interactions, irrespective of the current levels of evidence for efficacy. At a research and a clinical level this represents a new and challenging area of medicine which we must actively address as a profession." Indeed as recently as May 2003, the AMA stated in a press release that "consideration should also be given to restricting the sale of complementary drugs and herbal remedies to pharmacies. By doing this the consumer will have ready access to quality information on ingredients and any potential side effects or interactions with their prescription medication".[256] If pharmacists were to become the sole custodians of CMs several issues would need to be addressed including the review of undergraduate and postgraduate training of pharmacists with respect to CMs to ensure that pharmacists do provide "quality information on ingredients and any potential side effects or interactions with their prescription medication".[256]

1.4.3 Classification

It is difficult to assess usage surveys and CM/CAM literature because of the lack of a standardised classification system. Indeed there is no universally satisfactory classification published in the literature for CMs as such, however various countries have attempted to broadly group various CMs and CAMs.[257-259] The TGA in Australia has broadly classified CMs (Table 1.6).

Table 1.6: TGA classification of CMs[260]

Item	Ingredient
1	An amino acid
2	Charcoal
3	A choline salt
4	An essential oil
5	Plant or herbal material (or a synthetically produced substitute for material of that kind), including plant fibres, enzymes, algae, fungi, cellulose and derivatives of cellulose and chlorophyll
6	A homeopathic preparation
7	A microorganism, whole or extracted, except a vaccine
8	A mineral including mineral salt and a naturally occurring mineral
9	A mucopolysaccharide
10	Non-human animal material (or a synthetically produced substitute for material of that kind) including dried material, bone and cartilage, fats and oils and other extracts or concentrates
11	A lipid, including an essential fatty acid or phospholipid
12	A substance produced by or obtained from bees, including royal jelly, bee pollen and propolis
13	A sugar, polysaccharide or carbohydrate
14	A vitamin or provitamin

1.4.4 Adverse reactions to CMs

Known, unknown or potential drug-CM and disease-CM interactions exist.[261] There are few blinded or controlled trials in the literature to provide objective evidence of the efficacy or safety of the CMs that are widely available, however the number of rigorous trials is increasing.[262-266] Because of under-reporting and a lack of a formalised system which would make it easy for consumers and HCPs to report adverse reactions to CMs, present knowledge is limited. There is a need for general practitioners and pharmacists to raise their awareness of CMs and to report any suspected adverse effects of these products.[233] Advising patients to tell their HCPs that they are taking CMs, can allow monitoring for adverse effects. The largely uncontrolled and unmonitored use of these substances creates the potential for many dangerous situations.[233]

Certain users of CMs are at high risk of toxicity. These include those consuming large amounts or a great variety of CMs, the very young, the elderly, the sick, the malnourished or undernourished and those on long term medication or on multiple other medications, including prescription medicines, thus putting DM patients in the high-risk category.[267, 268]

Patients need clear education about the fact that CMs are pharmacologically active substances and may interfere with their disease state or other drugs they may be taking, either in a positive or a negative way. Pharmacists and general practitioners need to ask patients for information about the CMs they may be taking and then educate the patient about them in an objective fashion. Patients should not be made to feel that their use is somehow wrong, or they may continue to consume them without the HCPs knowledge. Patients need to be encouraged to bring in formulations that they are using, so that their labelling and ingredients can be reviewed. This will allow discussion on the differences between conventional medicines and CMs. Patients should be encouraged to buy their CMs from reputable sources and check the qualifications of the prescriber.

The different adverse effects have been classified below under adulteration, toxicity, mutagenicity, allergic reactions and drug-CM or disease-CM interactions. The following is intended only as a summary to high-light potential problems and issues as many reviews have been written on this subject.[237-244, 269-272]

1.4.4.1 Adulteration

Toxic ingredients including pesticides, non-declared drugs, and added chemicals are sometimes found in CMs. Heavy metals such as arsenic, mercury, lead and cadmium, as well as prescription drugs including phenylbutazone, aminopyrine, prednisolone, testosterone and diazepam have been found in CMs.[237] TCMs have been found to contain undeclared mefenamic acid and diazepam.[269] There have also been cases of lead, mercury, thallium, arsenic and cadmium poisoning due to contaminated TCMs. False authentication can be another problem with plant-derived medicines. This can happen inadvertently or be done deliberately to save money. The recent case of Pan Pharmaceuticals in Australia highlights this problem, as 1600 products manufactured by the company were recalled in April 2003 due to potiential adulteration concerns.[256, 273]

1.4.4.2 Toxicity

Just as conventional medicines can have a range of effects, CMs can be expected to have toxic effects (for example nephrotoxicity reported after ingestion of a Chinese weight loss therapy), anticholinergic effects (attributed to catnip, juniper, lobelia, wormwood and nutmeg), allergic reactions and abortifacient effects.[237, 238, 271, 272, 274, 275]

Toxic reactions to CMs have been widely reported in the literature.[237, 238, 271, 272, 274] Many medicinal plants contain flavonoids and these products are used for their antioxidant effects, however they have also been associated with haemolytic anaemia, chronic diarrhoea, nephropathy and colitis.[271, 272] For example, a review of the use or pennyroyal showed toxicity in 18 cases, two of which were fatal.[274] In France, germander was marketed as an adjuvant for weight control. More than 30 cases of acute liver failure, and one fatality were recorded and germander was subsequently withdrawn from the market.[276] MacGregor reported liver damage after taking herbal products for stress.[277] The ingredients were not precisely defined but probably included valerian, asafetida, hops, skullcap and gentian. Valerian or skullcap were the most likely hepatotoxic components, however of most concern was that at the time there were 93 products containing skullcap and 85 containing valerian available without a prescription in the UK.[237, 277]

There are numerous examples of toxicity associated with CMs that have been published in reputable journals and the subject of comprehensive authoritative review.[237, 238, 271, 272, 274] This review is not intended to be a comprehensive review of CMs and toxicity but it does serve to underline the potential problems associated with CMs.

1.4.4.3 Mutagenicity

Some CMs may be potential mutagens, such as aloe, rhubarb and senna, but this needs to be confirmed in epidemiological studies.[237, 238, 271]

1.4.4.4 Allergic reactions

Allergic reactions are possible with CMs. Reactions can vary from a transient dermatitis to anaphylactic shock.[269] Some products that have been linked to allergic reactions include arnica, cassis, dandelion, feverfew, meadowsweet and royal jelly. Royal jelly has been repeatedly linked with severe bronchospasm in atopic patients.[271] Consumers may not

attribute the allergic reaction to the CM consumed, as the premise may be that because the CM is natural it could not cause an allergy and it is therefore not reported to any HCP.

1.4.4.5 Interactions

Drug interactions with CMs and conventional medicines are probably widely under-reported and CM-disease interaction are also under-reported and frequently not recognised. There are many articles in the literature addressing this issue.[216, 237, 238, 240-243, 261, 270, 278, 279] The possibility of interaction with CM products may be even higher than with conventional medicines as CM products frequently contain multiple ingredients.

1.4.5 Global usage levels of CMs

Global usage of CMs is continually increasing.[280] Studies to determine the level of CM usage in Australia report levels of up to 64% of the population using CMs.[223, 225, 281, 282] The study showing the highest usage rate, however had the lowest response rate (44%).[282] By comparison global utilisation rates vary from as low as 10% to over 50% (Table 1.7).[234, 253, 283-304] The wide range of utilisation rates can be explained, in part, by the disparity in definitions of CM/CAM, the selection of therapies assessed and the time frame of the study. These problems can be clearly seen in Table 1.7. The articles included in Table 1.7 reflect the current state of the art as only articles from 1990 onwards were included. Articles were identified via Medline® and were included for review in Table 1.7 if they were surveys of CM or CAM use in peer reviewed journals.

Table1.7: Global usage rates of CM use, categorised by country

Article	Summary	Year	Age (years)	Response Rate	Usage rate	Critique/ Comment
Australian data						
Welch [281]	n=511 Face to face interview of hospital inpatients	2000	All ages	100%	12% were taking CMs at the time of hospital admission[1]	Usage lower because surveyed CM use at the time of data collection
Wilkinson et al [305]	n=300 Postal survey to rural areas in New South Wales	1999	Not stated	31.4%	69% during the previous twelve months (vitamins and minerals) Total CM use would be even higher, but raw data was not provided	Study discounted due to low response rate; those that consumed CMs may have been more interested in completing the survey resulting in the high usage rate seen
Clifford et al [306]	n=129 *Face to face interview of diabetic patients*	1999	>18	100%	22% were currently using CMs	*Current usage only in diabetic patients*
Kermode et al [282]	Random telephone interview in rural New South Wales	1995	>18	44%	64% current users of CM	This study has a low importance due to the low response rate; those that consumed CMs may have been more interested in completing the survey resulting in the high usage rate seen Current usage only
Kristoffersen et al [223]	n=325 Consecutive patients from an emergency department	1994	All ages	96%	52% during the previous twelve months[2] 41% during the previous three months 31% during the previous week	Only included English speaking respondents
MacLennan et al [225]	n=3004 Face to face interview	1993	>15	73%	48.5% during previous twelve months (excluding calcium, iron and prescribed vitamins)	Statistically representative sample of the Australian population after comparison with census data Good response rate
North American data						
Ryan et al [299] Canada	n=502 *Random telephone or face to face interview of diabetic patients who attended diabetes education*	Not stated	All ages	99%	30.1% used over the counter (OTC) preparations and 31.3% used CMs[3] The time-frame of usage was not stated	Year of survey not stated; published in 2001 Definition of CM different from all other surveys; after analysing the data provided in the paper, 45.8% used CMs using data as close to the definition used for this thesis as possible
Norred [307] USA	n=496 Self-reported questionnaire of a random selection of patients attending a nurse run pre-surgical day clinic	2000	Adult	99%	73.4% used CMs for the 2 weeks before surgery after being advised in the pre-surgical appointment to cease all CMs[4]	Good response rate Self-report High usage rate probably due to the inclusion of daily vitamin supplements (not normally included in studies from the USA)
Astin et al [288] USA	n=728 Random sample	2000	Elderly	51%	41% reported use of herbs, chiropractic, massage and acupuncture (breakdown of usage not provided)	Study in the elderly Low response rate

Article	Summary	Year	Age (years)	Response Rate	Usage rate	Critique/ Comment
Astin [289] USA	n=1035 Written questionnaire	Not stated	>18	69%	40% use in within previous twelve months (top four categories were chiropractic, lifestyle diet, exercise/movement and relaxation)[5] Actual % who used "medicines" not reported Exercise/movement has not generally been used in the definition of CAMs in other surveys	Year of survey not stated; published in 1999 Medium response rate Cohort had an under representation of of younger, less educated and poor persons, compared to census data *Diabetes was in the top ten of reported health problems, but the exact % of patients who reported diabetes was not given. Of those with diabetes lifestyle diet, exercise and "other" were the most common CAMs* *Having diabetes did not predict CAM use, but other chronic diseases did*
Ni et al [301] USA	n=30 801 Face to face interview	1999	>18	70%	19.9% use of CAM within previous twelve months[6]	Used data from the 1999 National Health Interview Survey (covers non institutionalised civilians); nationally representative sample
Leung et al [290] USA	n=2560 Self-administered questionnaire to consecutive elective pre-surgical patients	1999	>18	60%	39.2% were currently using at least one over the counter CM product (herbal medicine, minerals, vitamins and other dietary supplements)	English, Spanish, Russian and Chinese respondents. Help was provided to respondents who could not read and/or write Medium response rate
Palinkas, L et al [302] USA	n=541 Face to face interview of patients attending a family practice doctors clinic	1999	>18	89%	21% reported using one or more CAMs in conjunction with the most important health problem underlying their visit to the doctor within the previous twelve months[7]	Good response rate *9.4% of all users had an "endocrine" diagnosis compared with 7.5% of non-users; definition of endocrine not provided*
Kessler et al [253] USA	n=2049 Random digit dialing telephone survey of patients with self-reported anxiety or depression	1997-1998	>18	60%	6.8% used at least 1 oral therapy for anxiety and 8.7% for depression during the previous twelve months[8]	English speaking respondents only Medium response rate Reviewing use of CMs in self-defined anxiety and depression only; 9.4% reported anxiety and 7.2% reported severe depression in previous twelve months Nationally representative sample
Eisenberg et al [234] USA	n=2055 Random digit dialing telephone survey	1997	>18	60%	25.2% during previous twelve months (herbal medicines, mega-vitamins, folk remedies, homeopathy)[9]	1997 survey used a financial incentive Only included English speaking respondents Medium response rate although considered representative due to comparison with national population statistics If daily vitamin supplements were included this figure would be considerably higher and more comparable to the Australian data
Elder et al [292] USA	n=113 English speaking	Not stated	Not stated	87%	50% had used or were using some type of CAM (included chiropractic, massage, herbal medicines, megavitamins, meditation, homeopathy, nathuropathy and acupuncture); 30% had used herbal medicines, 24% had used megavitamins	Life-time use Year of survey not stated; published in 1997 Small numbers but important because survey of general practice clinics; respondents were therefore consulting mainstream doctors and using complementary therapies High usage rate seen because questioned as to whether they had ever used complementary therapies

Article	Summary	Year	Age (years)	Response Rate	Usage rate	Critique/ Comment
Burg et al [284] USA	n=1012 Random digit dialing telephone survey	1996	>18	54%	32% during life-time (herbal medicines, megavitamins, homeopathy)	Life-time use Medium response rate No definition of CMs provided to the respondent, in particular "home remedies"
Druss et al [293] USA	n=16 068 House-hold survey	1996	>18	78%	8.3% visited a CAM practitioner within previous twelve months[10]	The survey asked about "visits" to CAM practitioners and did not include "self-administration" of CAMs Not directly comparable to other studies (Eisenberg, Kristoffersen Maclennan); similar to the survey by Egede Interviews were conducted in English or Spanish
Egede et al [287] USA	n=21 571 Face to face interview	1996	All ages	78%	*5.8% of diabetic patients and 2.8% of the non-diabetic population during the previous twelve months (consulted a CAM practitioner for nutritional advice, herbal remedies, homeopathy, traditional medicine)* *Diabetes was an independent predictor of CAM use in the general population and in patients with diabetes*	*Usage rates for CAM use based on visits to a CAM practitioner; excludes treatments obtained by individuals without consultation with a CAM practitioner* *Not comparable to other studies (Eisenberg, Kristoffersen Maclennan)* *Nationally representative sample of theUSA population with over sampling of Hispanics and blacks* *Study in diabetic patients; 1.6 times more likely to use CAM than individuals without diabetes*
Millar [295] Canada	n=17 626 Face to face interview	1994-1995	>15	Consecutive patients	15% used a CAM practitioner within the previous twelve months; no data provided on use of CMs	National Population Health Survey Surveying the use of CAM practitioners eg., acupuncturist, naturopath, homeopath or massage therapist *9% of persons free of chronic disease consulted an CAM practitioner compared with 16% of those with one chronic disease and 20% of those with two chronic diseases*
Paramore [286] USA	n=3450 Telephone interview	1994	All ages	75%	9.4% visited at least one CAM practitioner in the previous twelve months (chiropractic, therapeutic massage, relaxation techniques, acupuncture)	Survey of CAM therapies only not CMs Statistically representative sample of the USA population Interviews were conducted in English or Spanish
Eisenberg et al [308] USA	n=1539 Random digit dialing telephone survey	1991	>18	67%	5.8% during previous twelve months (herbal medicines, mega-vitamins, folk remedies, homeopathy)	1991: no financial incentive Only included English speaking respondents Medium response rate although considered representative due to comparison with national population statistics If daily vitamin supplements were included this figure would be considerably higher.

Article	Summary	Year	Age (years)	Response Rate	Usage rate	Critique/ Comment
Other countries						
Nilsson et al [294] Sweden	n=5794 Self-administered questionnaire to randomly selected patients invited to participate in screening for cardiovascular risk factors	1999	25-74	72%	30.5% reported taking a CM product in the previous 2 weeks (vitamins, minerals and other substances not prescribed by a physician including biological remedies, herbs and homeopathics)	Completed as part of the Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) Project; a population based project
Dello Buono et al [309] Italy	n=655 Face to face interview with elderly patients	1996-1997	>65	65%	*29.5% reported use of CMs within the previous twelve months; of those taking CMs and conventional medicines, 4% reported diabetes and of those taking conventional medicines only 6% reported diabetes. No patients taking CMs only reported diabetes.*[11]	Respondents statistically comparable to the national elderly population from census data Definition of CMs not provided; details of what the patient was asked was not provided Medium response rate
Mahabir et al [296] Caribbean	n=627 Face to face interview by nutritionist (consecutive patients)	Not stated	Unknown	99%	42% current bush medicine use; 81% collected their own bush medicines *58% of those taking bush medicines reported use for diabetes*	Year of survey not recorded; published in 1997 Inclusion criteria for age not recorded
Mantyranta et al [283] Finland	n=2134 Telephone interview Random "representative sample"	1992	15-74	85%	39% during the previous twelve months[12]	Definition of CM unclear
Wandell et al [285] Swedish	n=12 717 *Face to face interview N=361 (diabetic patients)*	1988	16-84	80%	*31.5% use in general population of "herbal products" and vitamins over the past 2 weeks; 27.3% in diabetic patients over the past 2 weeks*	Statistically representative sample of the Swedish population Definition of "herbal products" unclear
Rasmussen et al [297] Danish	n=4753	1987	>16	100%	3.6% use of "natural medicine" e.g., homeopathy within previous twelve months 3% report use of "herbal medicine" in past 2 weeks	Use defined as "whether the interviewees had paid for treatment" Definition of "natural medicine", and "herbal medicine" not stated Was not stated whether vitamin use was included in the statistics under "natural medicine". *Use of any CAM therapy in past 12 months; 10% Use of any CAM therapy among patients with diabetes; 9.5% - this figure was not further broken down into individual "therapies" Use in patients without a specific disease; 7%*
UK data						
Thomas et al [310] UK	n=5010 Postal survey	Not stated	>18	59%	28.3% use of herbal and homeopathic remedies in previous twelve months	Medium response rate Year of survey not recorded; published in 2001 Postal survey assumes literacy and language competency

Article	Summary	Year	Age (years)	Response Rate	Usage rate	Critique/ Comment
Ernst et al [311]	n=1204 Telephone survey	August 1999	>18	No record kept of numbers who refused participation	20% used CAM in the previous 12 months; CM use not investigated separately (herbal medicines used by 7% - but no definition provided)	CAM use only
Leese et al [300] UK	n=246 *Face to face interview of patients attending a diabetes clinic*	Not stated	>16	75%	*17% life-time use in diabetes patients; 4% current use*[13] *Of users 9% used to improve glycaemic control*	Year of survey not recorded; published in 1997 Definition of CMs very unclear Inner city population of lower socio-economic diabetic patients
Cappucio et al [312] UK	n=1577 Face to face interview	1994-1996	40-59	64%	10.4% regular users (>80% of days in the previous month) of non-prescribed vitamin supplements, cod liver oil, primrose oil and garlic	Medium response rate
Thomas et al [298] UK	1. n=1575 therapists 2. n=3082 patients	1987-1988	All ages	1. 72% (therapists) 2. 80% (patients)	Using therapists own workload figures, one person consults one of these therapists for every 55 patient consultations with a general practitioner in the National Health System The main reported reason for consulting a therapist was for musculoskeletal problems (78.2%) 36% sought help directly from the therapist without any contact with their GP	Survey of patients attending CAM therapists including acupuncture, chiropractic, homeopathy, naturopathy, medical herbalism, osteopathy Therapists had to be qualified, non-medical practitioners belonging to national associations that regulate the practice of their members This survey had two parts; 1. Survey of qualified CAM therapists 2. Survey of patients attending the CAM therapist

Footnotes for Table 1.7

Entries in italics include data relevant to DM patients

[1]included herbal medications, vitamins/minerals, homeopathic remedies, aromatherapy, Chinese or Asian remedies and any "other"

[2]herbal medicines were defined as per the TGA; products from animal sources such as cod liver oil were also included (excluded homeopathic remedies but included vitamin use)

[3] Over the counter (OTC) medications defined as vitamins, folic acid, iron and calcium (authors included aspirin, but this was subtracted from the data); CMs defined as herbs and unconventional medicines

[4]included herbs, vitamins, dietary supplements or homeopathic remedies

[5]CMs listed were acupuncture, homeopathy, herbal therapies, chiropractic, massage, exercise/movement, high-dose megavitamins, spiritual healing, lifestyle diet, relaxation, imagery, energy healing, folk remedies, biofeedback, hypnosis, psychotherapy, and art/music therapy (did not list daily vitamins)

[6]included herbal medicine, lifestyle diet, homeopathy and "other". Did not provide enough raw data to determine which exactly which of the CAMs involved CMs (19.9% is the closest estimate of CM use) but excluded daily supplemental vitamin intake

[7]included CMs (herbal remedies, naturopathy, homeopathy, traditional folk remedies, multivitamin supplements, dietary intervention) and CAMs (faith healing, biofeedback, energy healing, prayer/meditation, acupuncture, massage therapy, chiropractic and "other"); from the raw data, it was not possible to separate the two

[8]oral therapy included herbal medicine, megavitamins, homeopathy and naturopathy

[9]mega-vitamins included high dose vitamins only; daily vitamin and mineral supplements not included. Folk remedies were included but not defined

[10]CMs listed were acupuncture, nutritional advice or lifestyle diet, massage therapy, herbal remedies, biofeedback, meditation, imagery, relaxation, homeopathy, spiritual healing, hypnosis, traditional medicine and "other" (did not list daily vitamin or mega-vitamin therapy)

[11]no definition of CMs was provided; an example of the CMs/CAMs included were herbs, phytotherapeutic agents (e.g., hawthorn, ginseng), homeopathics, acupuncture and relaxation techniques. Details of what the patient was asked about were not included

[12]all drugs not tested by scientific methods or licensed as medicinal products (included herbs, homeopathic remedies, herbal teas, food supplements)

[13]definition of CM unclear; appears to be a report of CAM as it seems to include acupuncture, homeopathy, herbal therapy, reflexology, aromatherapy, hyponotherapy, cellular nutrition, chiropractor and "others"

Note: references were identified after a full literature search using search terms that included complementary medicine(s), herb(s), herbal, traditional medicine(s), prevalence, usage, diabetes mellitus, alternative medicine(s)

1.4.5.1 Australian usage levels of CMs

The South Australian Omnibus Survey (MacLennan and colleagues) reviewed CM usage of over 3000 people in Australia for the first time in 1993 (Table 1.7).[225] Almost half the sample (48.5%) had consumed at least one non-prescribed CM, over the previous twelve months. Almost 20% of the sample used two or more CMs. The median expenditure reported was $10/month (range $1-$500). Extrapolation of the costs to the Australian population gives an expenditure on CMs in 1993 of $621 million. By comparison, $360 million was spent on pharmaceutical drugs in the same time.[224, 225] The amount of money spent on CMs is very large, considering the limited scientific information supporting the use of many of these preparations.[263, 313, 314] In addition one in five South Australians visited a CAM practitioner in 1993. The median expenditure on CAM practitioners was $120 per month (range $1-$3000) and the age-sex standardised expenditure for the Australian population was $309 million.[225]

The usage rate of 48.5% in this landmark population based Australian study, is higher than the figures seen in the landmark USA study by Eisenberg and colleagues in 1990 and 1997.[234, 308] However, if Eisenberg had included vitamins other than mega-vitamins (as has been included in the MacLennan study[225]), the percentage use of CMs could have been much higher.

Characteristics of users in the Australian survey included[225]:

1. Being female (females were 1.7 times more likely to use CMs than males)
2. Being younger (persons aged 15-54 were nearly twice as likely to use CMs than persons over 55 but 36% of persons over 55 years had also used a CM in the previous year)
3. Being Australian born (persons born in Australian were 1.3 times more likely to consume CMs)
4. Having a higher household income (persons with an income over $20 000 were more than 1.5 times more likely to consume CMs)
5. Being better educated (persons with post secondary school education were 1.3 times more likely to consume CMs).

This is consistent with other landmark surveys.[234]

The second major survey into CM use in Australia was completed by Kristoffersen and colleagues, in the emergency department of a tertiary referral hospital in Sydney in 1994.[223]

Data from 325 consecutive patients about CM usage over the previous twelve months was collected and 52% had used CMs during that time (Table 1.7). Females were more likely to be consuming CMs, however there were no differences between users and non-users in terms of age, ethnicity, language spoken at home or education. By choosing only English speaking subjects, recent immigrants were excluded and they might be very likely to use traditional medicines.

The Australian studies by MacLennan and Kristoffersen were very similar, were carried out at a similar time and used almost identical definitions of CMs. From these studies it can be concluded that approximately 50% of the Australian population had used CMs in the previous twelve months in the mid 1990s.

Welch completed a survey of 511 patients attending a tertiary hospital in Australia in 2000 and found that 12% were consuming CMs at the time of admission.[281] This figure is much lower than found in Australia with previous surveys, however it was current use and not use over the preceeding twelve months. Interestingly Welch found that 18% of patients were consuming CMs that could potentially interact with concomitant medicines. This was the first Australian study that reviewed potential drug-CM interactions.

In addition to the MacLennan survey[225], the prevalence of CAM use has been reported in Australia by Adams and colleagues.[315] This survey did not specifically report on CM use. CAM users were defined as "consulting an alternative health practitioner in the previous twelve months" and approximately 25% of the study population (which was females only) were CAM users. This compares to approximately 20% of the general population who were CAM users in 1993.[225] This survey is the only Australian survey that has reviewed HRQOL in CAM users versus non-users and CAM users score lower than non-users in all dimensions of HRQOL as measured by the Short-Form 36 (SF-36) QOL survey.[316] This is explained in part by the poorer overall health of CAM users compared to non-users in this survey. This survey also determined that CAM users were more likely to be consuming prescription and non-prescription medicine, but did not investigate which medicines. This survey adds to the body of knowledge of CAM use in Australia and provides important HRQOL data. HRQOL data in CM users has yet to be reviewed in an Australian context.

1.4.5.2 USA usage levels

Many studies in CM/CAM use have been carried out in the USA (Table 1.7).[234, 253, 284, 286-290, 292, 293, 308, 317] Eisenberg completed the landmark survey of alternative therapy use in the USA in 1990 and repeated this survey in 1997.[234, 308] Eisenberg reviewed 16 alternative therapies, including chiropractic, homeopathy, folk remedies, relaxation techniques and herbal medicine. When considering those groups of alternative therapies that involve medicines or oral therapies (CMs), usage in 1990 was 5.8% and 25.2% in 1997. Eisenberg excluded daily vitamin and mineral consumption of standard dosage vitamins and minerals, so these data are not directly comparable to Australian data that collected total vitamin consumption.

Eisenberg found that over the 1990 to 1997 time frame, use of herbal remedies in the USA increased by 38% and use of mega-vitamins increased by 13%. One in five persons taking prescription medicines was taking herbal medicines or mega-vitamins or both. This again raises the possibility of drug-herb and drug-megavitamin interactions. Extrapolations to the total US population suggest that an estimated 5 million adults were at risk of potential adverse drug interactions, between these therapies. Eisenberg called for greater post-marketing surveillance of potential interactions.[234]

The study did not provide a demographic breakdown of information for the subset of therapies that involved medication consumption (CMs) but for all CAM therapies the trends were;

1. women were more frequent users than men (49% of women versus 38% of men)
2. use was less common in African Americans (33% of African Americans versus 45% of Anglo-Celts)
3. use was more common in the 35-49 year old age group (50%)
4. use was higher in those who had completed a university degree (50% versus 36.4%) and
5. use was more common in people who earned >$50 000 (48% versus 43%).

The trend of being female, of higher socio-economic status and better educated were consistent with trends seen in Australian surveys.[225]

Leung and colleagues[290] completed a survey in pre-surgical hospital patients in the USA and found a current usage rate in 1999 of almost 40% (response rate, 60%; Table 1.7). This

survey used a similar definition of CMs to Australian data and found a similar usage rate to studies by MacLennan and Kristoffersen.[223, 225] Predictors of use in the Leung survey were[290]:

1. female sex
2. age (35-49 years)
3. higher income levels
4. Caucasian race
5. higher levels of education
6. problems with sleep
7. problems with joint or back pain, or allergies
8. problems with addiction, and
9. a history of general surgery.

In contrast, DM and use of antithrombotic medications were associated with lower odds of the use of herbal medicines. Further steps to elucidate whether these CMs had an effect on the clinical outcome of the patient were not undertaken. This would have been a useful addition to this paper as some CMs can affect blood glucose levels and this can have an impact during surgery and other CMs can affect bleeding times.[303, 318] The trend of being female, of higher socio-economic status, better educated and Caucasian were consistent with Australian surveys.

Egede and colleagues[287] reviewed the use of CAMs in patients with chronic disease, including diabetes (n=21 571) (Table 1.7). This study only reported on CM use provided by a CAM practitioner and it excluded treatments obtained by individuals from other sources. As a result, the rate of use was lower than those seen in other important studies.[223, 225, 234] Interestingly 8% of patients with diabetes had consulted a CAM practitioner compared with 5% of the general population in the previous twelve months. Additionally, 5.8% of patients with diabetes used a CM within the last twelve months compared with 2.8% of the non-diabetic population. To obtain the data quoted above (which were not actually calculated in the paper), the groupings herbal remedies, traditional medicine, homeopathic therapy and nutritional advice were included. Nutritional advice included non-conventional diets such as the Pritikin diet which may or may not have recommended intake of various supplements and Ayuverdic diets, naturopathic or homeopathic nutrition/diets, and orthomolecular therapies such as magnesium, melatonin, or megadoses of vitamins. The high use of nutritional advice,

is logical for a diabetic population, the majority of whom would have type 2 DM. The interesting feature is that the nutritional advice was sought from CAM practitioners, not conventional dietitians.

CAM practitioners were being used in the USA at a rate of around 10% in the mid 1990s[286,293], which is lower than that reported in Australian studies.[225, 315]

1.4.5.3 European usage levels

One of the first studies on CM use in Europe was a Danish study which demonstrated use of natural medicine in 3.6% of the surveyed population of 4753 people (Table 1.7).[297] The use of complementary therapies has been increasing in Denmark, consistent with global trends.[319,234] In the paper by Rasmussen, the use of CMs was included in the study, if the interviewee had to pay for the therapy, as other health care in the Dannish community was free at that point. The definition of natural medicine was not made and it was not clear whether vitamin use was included in the statistics. Interestingly, 9.5% of the diabetic population had used some form of CAM (e.g., reflexology, acupuncture, natural medicine) in the past twelve months. Of those who did not have a specific disease, 7% had used some form of CAM over the previous twelve months. This concurs with data found in the US, where patients with diabetes accessed CAM at a higher rate than the general population. [287]

A Finnish study demonstrated use of alternative drugs in 39% of patients (Table 1.7).[283] The definition of CMs in this survey was not clear, but it appeared that the definition was similar to that used in Australian studies and this would make usage rates similar in these two countries. The study included natural and homeopathic remedies, herbal teas, anthroposophic remedies, any alternative drugs and health food products. It was unclear as to their definition of health food products and no examples were provided. Health food product consumption was over a six-month period and the remainder over twelve months, however the discussion combined results from the two periods, adding to the ambiguity of results and emphasising the methodological differences that exist with CM surveys. The characteristics of users in this study were:

1. Being female
2. Being well-educated and

3. Having a healthier lifestyle (more non-smokers and regular exercisers were likely to use CMs).

The study also found that in general CM users also consume prescription medicines and are not using CMs as a substitute for conventional drugs and this again raises the issue of potential drug-CM interactions.

In a more recent Swedish study by Nilsson and colleagues[294] conducted in 1999 approximately one third of respondents had used a vitamin, mineral, non-prescribed medicine, or biological product within the previous 2 weeks (response rate 72%) (n=5794). This study used a similar definition of CMs to Australian studies, however utilised a different time frame. The characteristics of users in this study were:

1. Being female and
2. Being well-educated.

There was no relationship between age and CM use. The pattern of CM use was nearly identical in people with and without a history of cardiovascular disease or diabetes. Of all people taking any CM product, 30.4% reported a history of cardiovascular disease or diabetes. This survey has been repeated periodically and had previously been completed in 1990 and 1994. The prevalence of CM use in men increased from 17.2% to 21.4% and the use in women increased from 32.5% to 42%. This increase in CM use is consistent with world-wide trends.

1.4.5.4 UK usage levels

Usage figures of CMs have not been accurately determined in the UK and vary from around 10% for specific nutritional supplements to 30% for the use of herbal and homeopathic remedies in the previous 12 months (Table 1.7).[300, 310, 312, 320]

Thomas and colleagues[298] reviewed visits to CAM practitioners in the UK in 1991 and 10.6% of respondents had visited a CAM practitioner in the previous 12 months. This compares to a figure of 20% from a survey carried out by Ernst and colleagues in 1999.[311] These figures show that the usage of CAM practitioners is also increasing in the UK, however these surveys did not address the specific use of CMs.

1.4.5.5 Conclusion on usage

The only consistent trend seen in all the studies on CM use was that usage is increasing. The ability to review the data effectively is difficult, largely because of methodological differences. Some of these difficulties are noted below:

1. Many studies combined CM consumption and CAM use but then failed to adequately define CM or CAM
2. Many studies were not population based
3. Response rates were sometimes low
4. Time frames were different in many of the studies and
5. The studies were mostly cross-sectional and not longitudinal (Table 1.7).

The large CM/CAM surveys consistently found that women were more likely to use CM/CAMs, however it was generally proportional to the gender balance of people seeking all forms of treatment. Women are the greater users of health care generally and tend to report more chronic illnesses.[321] CM/CAM users were also found to be predominantly in higher-income brackets, better educated and of middle age, however this was not found in all surveys (Table 1.7).

There is no doubt that people have been turning increasingly toward CAM/CM in the past decade (Table 1.7), however further studies are needed in certain patient groups including:

1. different ethnic groups
2. low income groups and
3. the elderly.[322]

There are no studies in Australia that have addressed these areas.

1.4.6 Usage in patients with diabetes

Use of CMs and CAMs in patients with diabetes has also been reported in the literature.[285, 287, 290, 294, 299, 300, 306, 309, 323] Egede reported that patients with diabetes were 1.6 times more likely to access CAM practitioners in the USA, than patients without diabetes.[287] In a similar study from Denmark, patients with diabetes accessed CAM practitioners at a higher rate than the general population (9.5% versus 7%).[294] These studies did not address the specific use of CMs, but indicated that patients with diabetes may access all forms of CAM more frequently than non-diabetic patients.

The following studies have addressed the use of CMs by DM patients and are summarised below and in Table 1.7:

1. Leung and colleagues[290] found that having DM was associated with a lower odds ratio (OR) of the use of herbal medicines (OR 0.55, 95% confidence intervals (CI) 0.36-0.86). This study was carried out in the USA and involved 2560 elective pre-surgical patients. Overall 39.2% of respondents were current users of CMs.
2. In a cohort of community based patients with diabetes (n=502), 46% were using CMs; the defintion of CMs was unclear in this survey and the time frame of usage was not reported, making comparison with other surveys impossible.[299]
3. Wandell and colleagues questioned 361 Swedish patients with diabetes about their use of all medicines over the previous 2 weeks (table 1.7).[285] Whilst the use of herbal products and vitamins was documented in 27.3% of the patients, details regarding the specific types of medicines defined as herbal products were not provided. Of the non-diabetic population 31.5% reported use of herbal products and vitamins over the same time frame. Of the patients with diabetes, 92.5% were on some type of medication, increasing the possibility of drug-CM interactions in this cohort and this compared to 48.1% of the healthy non-diabetic population who were on some form of medication.
4. A population based study from Sweden (n=5794), found that the pattern of CM use was nearly identical in people with and without a history of diabetes.[294]
5. A study in an elderly Italian population (n=655) reported use of CMs in approximately 10% of patients with diabetes within the previous 12 months; the definition of CMs was unclear in this paper.[309]
6. A UK study reviewed the prevalence of CM use in a diabetes clinic (n=246) and 17% reported use of CMs at some stage in their life, with 4% reporting current usage. Of the users, 9% used CMs to improve glycaemic control. The definition of CM in this survey was very unclear and the delineation of CAMs that involved taking CMs was not made.[300]

Usage rates in patients with diabetes in these studies varied between 10 and 46%, however the studies had methodological differences. Whether these CMs have any impact on diabetes control or co-morbidities associated with diabetes has yet to be elucidated. However there have been reports in the literature of CMs causing serious harm to patients[218] and there is a clear need for further research into this area.

1.5. OBJECTIVES AND HYPOTHESES OF THIS RESEARCH

The literature suggests a paucity of data, particularly Australian, about ethnic differences in the treatment of DM. PC may provide a model to improve the treatment of DM in an Australian context. In order to assess some of these gaps in current knowledge this research attempts to evaluate:

1. Ethnic differences in the treatment of DM in an Australian context and
2. The impact of a prospective PC program on the treatment outcomes of DM.

In addition, the following hypotheses will be tested:

1. There are major differences between ethnic groups in the use of hypoglycaemic medication
2. Clinical outcomes can be improved by PC programs and
3. Complementary medicines are widely used in the type 2 DM population.

The variables targeted for review were chosen, as they have not been reviewed in an Australian context and have the potential to answer questions that may result in effective strategies to reduce the known complications of DM.

CHAPTER 2

ETHNICITY AND DIABETES MELLITUS

2.1 INTRODUCTION

Different ethnic groups have differences in the prevalence of diabetes, glycaemic control, and development of diabetes complications.[45, 93-97] A large Australian study concluded that diabetic complications were not well managed in the multi-ethnic Australian population and that clinical care and education programs which recognise and target the different needs of specific ethnic groups may be the key to reducing diabetes complications.[324] The Australian Aboriginal population has been widely studied with respect to complications and treatment of DM,[106, 109] but there is a paucity of information on DM treatment in relation to other ethnic groups in Australia.

The Fremantle Diabetes Study (FDS) was a community-based prospective observational study of diabetes care, control and complications in a postcode-defined region of 120 097 people surrounding the port city of Fremantle in Western Australia, and provided a unique opportunity to review medication use and ethnicity in type 2 DM. It was intended that the initial review of the FDS database at study entry to the FDS and prospectively, would provide important local information in order to design and implement a prospective PC program.

2.2 AIM

To retrospectively assess the relationship between ethnicity, glycaemic control, and the use of hypoglycaemics, in patients with type 2 DM from the FDS. The ethnic groups reviewed were SE and AC patients, as these were the two largest ethnic groups that attended the FDS.

2.3 METHODS

2.3.1 FDS STUDY DESIGN

The first phase of the FDS was essentially a census and survey of people with diabetes in the Fremantle Hospital and Health Service (FHHS) primary catchment area. The second phase of the FDS was a prospective cohort study, following each patient who returned voluntarily for an annual assessment, until the patient chose to withdraw, moved out of the area or died.

2.3.2 FDS APPROVAL AND ETHICAL CONSIDERATIONS

The Human Rights Committee, FHHS, approved the FDS protocol and all patients gave informed consent to participate. Patients were told that all information would remain strictly confidential and that they could refuse to answer individual questions or undergo specific tests if they chose, that they would have full access to their own results and could discuss these results or any aspect of the study with the principal investigator of the FDS (Professor TME Davis), or his representative at any time. Study data were made available to the patient's general practitioner and other relevant HCPs only with the patient's express permission. All hard and computer copies of the data were coded using a unique code number for each patient and data analysis was subsequently carried out using the coded data, to ensure patient confidentiality. FHHS confidentiality guidelines were respected at all times. Patients were told that they could withdraw from the study at any time without prejudice to their continuing medical care.

2.3.3 FDS PERSONNEL

A full-time research nurse and research officer managed the FDS on a day-to-day basis. The principal investigator of the FDS or other experienced staff from FHHS performed the clinical examinations. FHHS interpreters assisted with patient interviews if necessary. Other staff participated on an as required basis.

2.3.4 FDS PATIENTS

Identification of patients to the FDS was through hospital inpatient and outpatient lists, general practitioners, specialist physicians, allied health services, advertisements in pharmacies and local media, and word of mouth. Criteria for recruitment included:

1. diagnosis of diabetes by a general practitioner or hospital clinic; and
2. residence in the catchment area.

2.3.5 FDS SURVEY METHODS

2.3.5.1 Initial assessment

Epidemiological data were first obtained from all eligible, consenting patients using a questionnaire developed specifically for the FDS. The FDS interview, consisted of the following sections (Appendix 1);

1. Demographic data: Name, address, date of birth, name of general practitioner, name of the specialist (where applicable), occupation, marital status, details of first degree relatives, country of birth and country(ies) of parents' birth, self-description of ethnic background, language normally spoken at home, fluency in English, educational achievement level, employment status and annual household income bracket. With respect to ethnicity, the algorithm used for defining ethnic background incorporated the following elements:
    a. Self-described ethnic background by choosing one of six offered categories
        i. Northern European (principally ACs);
        ii. SE (family origins in Italy, Spain, Portugal or Greece);
        iii. Asian;
        iv. African;
        v. Aboriginal/Torres Strait Islander; and
        vi. Other (including mixed ethnicity).
    b. Country of birth
    c. Country of father's birth and country of mother's birth and
    d. Language spoken at home.
2. Diabetes-related data: Date of diagnosis, method of diagnosis, symptoms at the time of diagnosis, family history of diabetes, full dietary, treatment and medication history, method and frequency of blood/urine glucose monitoring, symptoms and treatment of diabetes complications, frequency of diabetes-related attendance for routine oupatient/general practitioner care.
3. Availability of diabetes care: Ease of access and transport to general practitioner/hospital clinic, need and provisions for an interpreter during consultation, availability of domiciliary support for diabetes-related problems where necessary, financial constraints on consultations/treatment/aids for monitoring of glycaemia.

4. Knowledge of diabetes: Sources of knowledge of diabetes and their relative contributions, simple test of current knowledge of diabetes
5. General medical information: Past and concurrent illness and medications, smoking history, history of alcohol intake, drug allergies, family history of illness
6. Current health status: Assessed from general and diabetes-specific indices.[325-327]

After the FDS interview was completed, each patient underwent clinical and laboratory assessment:

1. Biochemical tests: performed fasting and included serum urea, creatinine and electrolyte concentrations, FPG and HbA_{1c}, serum lipid profile, serum uric acid, dipstick urinalysis, urinary microalbumin and creatinine concentrations.
2. Cardiovascular status: pulse, supine and erect SBP and DBP, jugular venous pressure, presence/absence of carotid bruits, heart sounds, lung bases, sacral/peripheral oedema, peripheral pulses, Doppler studies, foot care, resting 12-lead electrocardiogram.
3. Respiratory assessment: spirometry, chest auscultation, sputum examination if applicable.
4. Neurological assessment: sensory testing of feet, including bio-thesiometry, ankle jerks.
5. Ophthalmic assessment: visual acuity (corrected/uncorrected, with/without pinhole), direct and indirect ophthalmoscopy through dilated pupils.
6. Measures of obesity: height, weight and calculated BMI (kg/m^2).

An endocrinologist reviewed and commented on the results of the initial assessment, and a summary was sent to the patient, the patient's general practitioner and any other relevant HCPs, if patient consent was obtained.

2.3.5.2 Annual assessment

All patients recruited during the first three years of the study were offered annual reassessments. Reassessments involved updating the FDS interview data together with identical screening for metabolic control and complications, as described in Section 2.3.5. An endocrinologist also reviewed and commented on the results of each annual assessment, and a summary was sent to the patient, the patient's general practitioner and any other relevant HCPs, if patient consent was obtained.

2.3.6 THE PRESENT STUDY

For the purposes of this retrospective review of the FDS database, demographic parameters (including ethnicity) and hypoglycaemic therapy were obtained from the FDS database and analysed at study entry for the full cohort and then reviewed over time for the subset of patients that returned for 4 subsequent FDS annual assessments.

2.3.7 DATA MANAGEMENT AND ANALYSIS

From January to April 1993, a comprehensive database (the FDS database) with adequate provision for strict confidentiality was developed by the FDS team using the commercial software DbaseIV (Ashton Tate)®.

For the present study, the FDS database was reviewed and statistical analysis was performed primarily using SPSS for Windows, Version 11 (SPSS Inc, Chicago, IL). Data are reported as mean±standard deviation (sd) (for normally distributed data), geometric mean [sd range] or median and interquartile range (IQR) (for non-normally distributed data), or percentage (%). Two-sample comparisons for normally distributed variables were by Student's *t*-test. Comparisons of proportions were by Chi-square tests and Fishers' Exact test. Non parametric tests included the Mann Whitney test and the Kruskal Wallis test. The Cochran-Armitage test for trend (using SAS® Statistical Software) was used to compare proportion across ordinal categories. A logistic regression model was used to assess the factors determining current therapy at recruitment to the study. Time to requirement for insulin following recruitment in those patients not taking insulin at recruitment was assessed using a Kaplan-Meier survival model, and relative risks calculated from a discrete proportional hazards model. A level of $P < 0.05$ was taken as significant throughout.

2.4 RESULTS

2.4.1 DEMOGRAPHICS

During the 3-year period April 1993 to April 1996, 2277 eligible subjects were identified in the FHHS catchment area and 1426 of these (64%) were recruited to the FDS. There were no significant differences in mean age, gender, country of birth or type of diabetes between FDS recruits and those patients who were not recruited to the study.[328-330]

Of the 1426 FDS recruits, 1294 (91%) had clinically defined type 2 DM of whom 819 (63%) were of AC ethnicity and 238 (18%) were of SE ethnicity. All of these patients (1057) completed the initial assessment. A total of 516 patients (49%) (409 AC patients and 107 SE patients) had data both at the initial assessment (FDS study entry) and for four consecutive annual assessments (Figure 2.1).

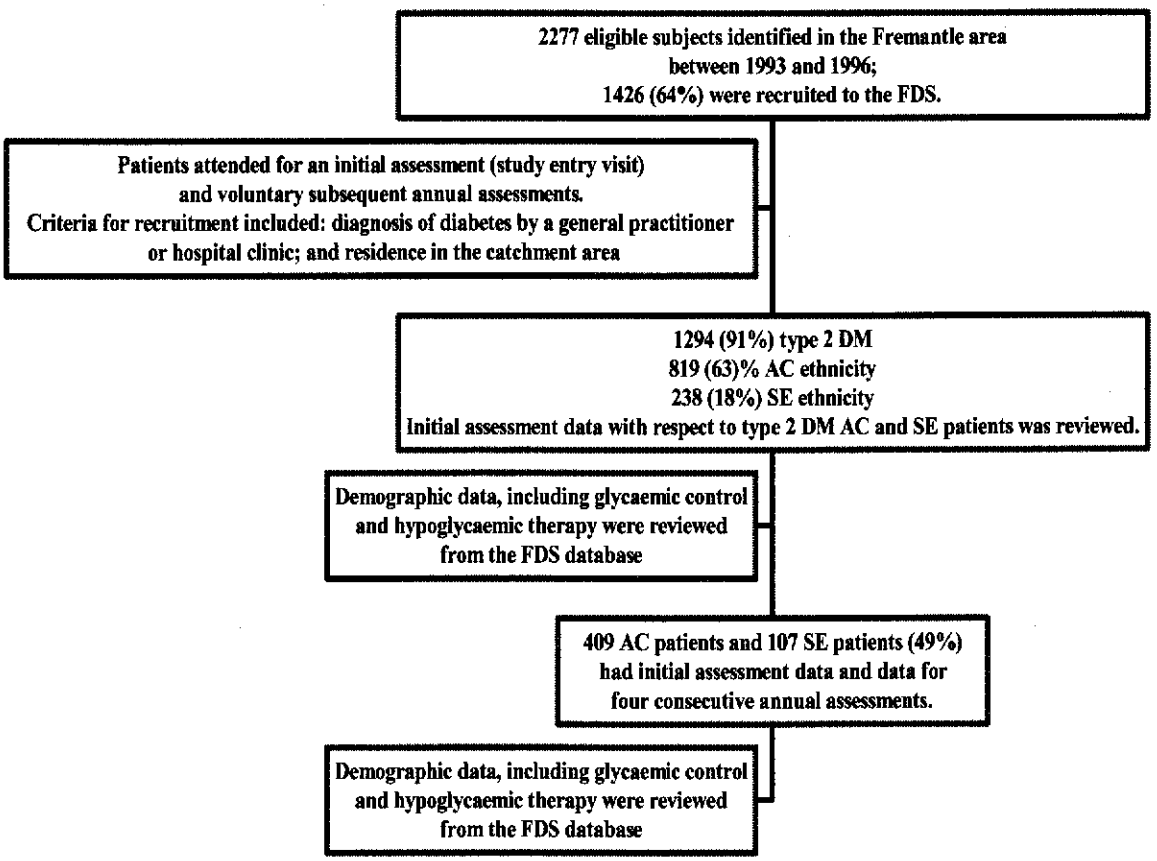


Figure 2.1: Consort diagram showing patient numbers at key time-points in the FDS

2.4.1.1 Initial assessment (study entry) data

Details of the patients in the two ethnic groups at study entry are shown in Table 2.1. The SE patients had a significantly longer duration of diabetes prior at their study entry visit and were younger at diagnosis. The SE patients also had significantly higher BMI, FPG and HbA_{1c} at recruitment. There was a significantly higher percent of SE patients in the poorly controlled glycaemic range as measured by HbA_{1c} (38% vs 28%); P=0.004; Table 2.2).

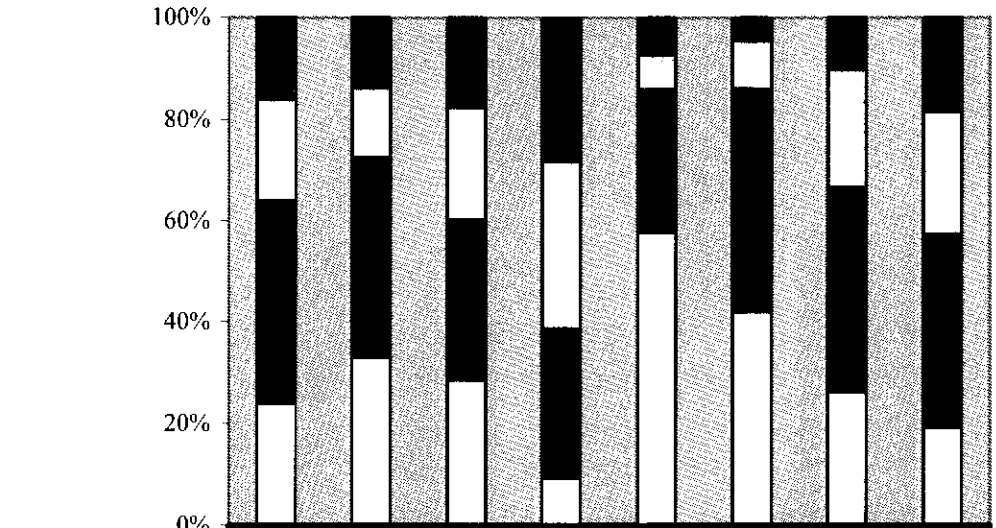
Table 2.1: Study entry characteristics of SE and AC type 2 DM patients. Data are mean±sd, median (IQR), geometric mean [sd range] or percentage (%).

	SE	**AC**	***P***
Number (%)	238 (22)	819 (78)	
Male (%)	46	49	0.32
Duration of diabetes at study entry (years)	5 [2,11]	4 [1,8]	<0.0001
Age at study entry (years)	64±10	65±11	0.14
Age at diagnosis of diabetes (years)	56±10	59±12	0.001
BMI (kg/m^2)	30.3± 4.7	29.6±5.6	0.01
FPG (mmol/L)	9.0 (7.3, 11.3)	8.2 (6.7, 10.6)	0.004
HbA_{1c} (%)	7.8 (6.3, 9.6)	7.5 (5.9, 9.4)	0.002
Waist (cm)	100±12	100±13	0.67
Waist:hip ratio	0.9±0.1	0.9±0.1	0.54
Insulin dose (units/kg)	0.55 (0.41, 0.76)	0.53 (0.47, 0.69)	0.99
	n=46	n=77	

Table 2.2: HbA_{1c} (%) categories at study entry

HbA_{1c} category (%)	**SE**	**AC**	***P***
<6.5	21	28	0.03
6.5-7.49	21	25	0.17
7.5-8.5	19	18	0.63
>8.5	38	28	0.004

Figure 2.2 shows the proportion of patients using different diabetic therapies at study entry according to FPG categories. Note that the actual categories used were <6.5, 6.5-8.49, 8.5-10.5 and >10.5mmol/L respectively. There was a significant difference in the trend across the categories with more SE patients having FPG > 10.5 mmol/L than AC patients (32% vs 27%; P=0.004). Both SE and AC patients with higher levels of FPG were more likely to be using combinations of oral hypoglycaemic agents (OHAs), OHAs plus insulin, or insulin regimens than those with lower FPG levels. Insulin use was more common overall in patients of SE origin compared with the AC group (17.8% versus 7.3%; P=0.002) irrespective of the level of glycaemia.

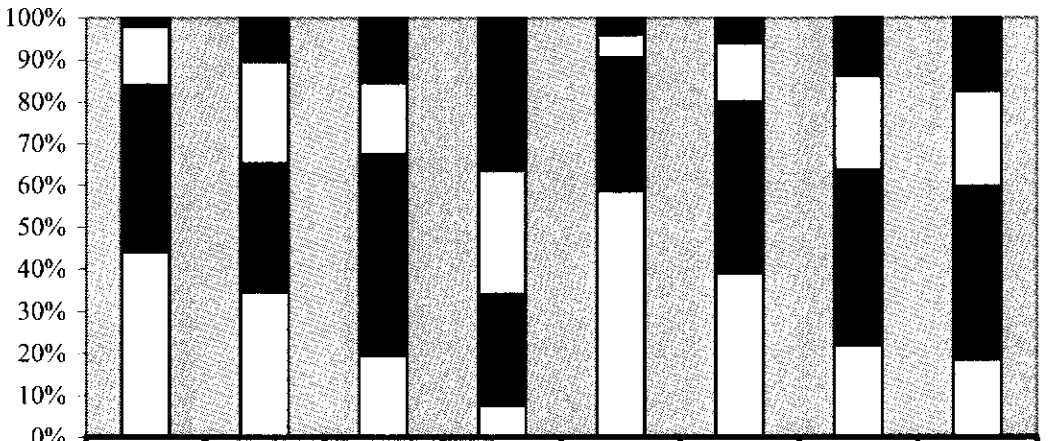


	SE				AC			
Insulin only	12	9.6	14.3	25.3	6.7	3.4	6	13.8
Meds plus insulin	4	4.1	3.2	2.7	0.6	1.1	4.2	4.6
Two medications	20	13.7	22.2	33.3	6.7	9.5	23.2	24.3
One medication	40	39.7	31.7	29.3	28	43.9	40.5	38.1
No medications	24	32.9	28.6	9.3	57.3	42	26.2	19.3

Figure 2.2: FPG (mmol/L) categories (x axis) versus medication progression. Results are % of total.

Figure 2.3 shows the relationship between treatment and HbA_{1c} levels (%) in both ethnic groups. Note that the actual categories used were <6.5, 6.5-7.49, 7.5-8.5 and >8.5%. The data parallel those seen in Figure 2.2. As with FPG, there was a significant difference in the trend across categories and significantly fewer SE patients had HbA_{1c} levels < 7.5% than AC patients (42% vs 54%; P=0.004). In those patients taking insulin, dose/kg was not

significantly different, between the two ethnic groups (AC 0.53 vs SE 0.55 units/kg: P=0.99) or between categories of glycaemic control as measured by HbA_{1c} (P=0.40) The biggest difference in insulin usage occurred in the poorly controlled HbA_{1c} range (>8.5%), where 36.3% of the SE cohort compared with 17.3% of the AC cohort self-administered insulin (Figure 2.3). The units/kg of insulin used were the same in both groups (Table 2.1).



	SE				AC			
■ Insulin only	2	10.2	13	28.6	3.5	4.4	10.3	12.1
■ Meds plus insulin	0	0	2.2	7.7	0.4	1.5	3.4	5.2
□ Two medications	14	24.5	17.4	29.7	5.6	14.1	22.6	22.9
■ One medication	40	30.6	47.8	26.4	31.6	41	41.8	41.1
□ No medications	44	34.7	19.6	7.7	58.4	39	21.9	18.6

Figure 2.3: HbA_{1c} (%) categories (x axis) versus medication progression. Results are % of total.

A logistic regression model was developed to determine factors that might influence insulin use. The model included age at diagnosis, age at recruitment, ethnicity, sex, duration of diabetes, BMI, waist or waist:hip ratio, and FPG and HbA_{1c} at recruitment (Table 2.3). SE patients were more likely than ACs to be treated with insulin independent of other variables in the model (OR (95% CI) 2.09 (1.30 to 3.36)).

Table 2.3: Factors influencing insulin therapy at study entry

Study entry variable	OR (95%CI)	*P*
Sex (female versus male)	1.17 (0.67,2.04)	0.59
Age at study entry (years)	0.99 (0.97,1.02)	<0.0001
BMI (kg/m^2)	0.97 (0.88,1.07)	0.54
FPG (lnmmol/L)	1.16 (0.49,2.71)	0.74
HbA_{1c} (ln%)	8.95 (2.28,35.1)	0.002
Duration of diabetes at study entry (years)	1.16 (1.12,3.36)	<0.0001
Ethnicity (SE/AC)	2.09 (1.30,3.36)	0.002

2.4.1.1 Initial assessment – the FDS interview

To assess factors that might influence insulin use, relevant questions from the initial FDS interview data were reviewed. There were no significant differences in self-reported levels of compliance with hypoglycaemic medication between ethnic groups (Table 2.4). SE patients accessed general practitioners at a higher rate than ACs ($P<0.0001$), but both groups accessed medical specialists or attended diabetes outpatient clinics at a similar rate. SE patients were more likely to have seen a dietitian before study entry ($P=0.01$), and less likely to have attended a diabetes education course ($P<0.0001$). There were no differences in self-reported levels of self-monitoring of blood glucose (SMBG) (Table 2.5).

Table 2.4: Self-reported compliance with anti-diabetic medication. Data are %.

	SE N=238	AC n=819	*P*
Always take medicines as prescribed	82.4	80.6	0.79
Occasionally miss a dose of prescribed medicine	15.4	16.3	
Regularly miss doses of prescribed medication	2.2	3.1	

Table 2.5: Access to various diabetes services. Data are median (IQR) or %.

	SE n=238	AC n=819	*P*
General practitioner visits in the 2 years before study entry	8 (4, 12)	6 (3, 10)	<0.0001
Medical specialist (for diabetes) or diabetes outpatient clinic in 2 years before study entry	1 (0, 4)	0 (0, 2)	0.12
Visit to a dietitian before study entry (%Yes)	45	33	0.001
Attendance at a diabetes course before study entry (% Yes)	58	72	<0.0001
Frequency of SMBG (for those who do self monitor)/week	4 (2, 7)	4 (2, 7)	0.51

2.4.1.2 Four year follow-up data

Data from 107 SE and 409 AC patients who attended for an initial assessment and four consecutive annual assessments were analysed separately. In comparison to those who did not have four follow-up visits, patients in this cohort were more likely to be male (53% vs. 45%; P=0.01), significantly younger at diagnosis (58±10 vs 59±12 years; P=0.05) and at study entry (63±9 vs 66±12 years; P<0.0001) and had a lower HbA_{1c} (7 (6, 8)% vs 8 (7, 9)% mmol/L; P=0.008).

The characteristics of the prospective cohort are shown in Table 2.6. Differences between SE and AC were similar to the full group. The SE patients were significantly younger at diagnosis of diabetes and had longer duration of diabetes at recruitment. Their FPG was significantly higher with no difference in HbA_{1c} or measures of obesity.

Table 2.6: Characteristics of SE and AC type 2 DM patients in the FDS cohort who attended a study entry visit (initial assessment) and four consecutive annual assessments. Data are mean±sd, median (IQR), geometric mean [sd range] or percentage (%).

	SE	AC	*P*
Number (%)	107 (20.7)	409 (79.3)	
Male (%)	52	53	0.86
Duration of diabetes at study entry (years)	4 [1, 11]	3 [1, 7]	0.02
Age at study entry (years)	62±9	63±9	0.21
Age at diagnosis of diabetes (years)	55±10	58±10	0.003
BMI (kg/m^2) – mean over 4 years	30±4	29±5	0.51
FPG at study entry (mmol/L)	8.9 (7.3, 10.8)	8.1 (6.7, 10.2)	0.03
FPG (mmol/L) – geometric mean over 4 years	9.1 [8.0, 11.0]	8.8 [7.3, 10.4]	0.02
HbA_{1c} at study entry (%)	7.7 (6.4, 8.8)	7.1 (6.3, 8.3)	0.09
HbA_{1c} (%) – geometric mean over 4 years	7.3 [6.1, 8.8]	7.1 [5.9, 8.5]	0.11
Waist (cm)	99±11	100±13	0.89
Waist:hip ratio	0.9± 0.1	0.9 (0.1)	0.74
Insulin dose (units/kg)	0.54 (0.41, 0.68) n=19	0.55 (0.47, 0.69) n=46	0.66

Figure 2.4 and 2.5 show the mean±sd FPG and HbA_{1c}, at each of the five visits for all patients attending. After adjusting for age at study entry, duration of diabetes and BMI, there were no significant differences in the change in FPG over time between the ethnic groups (P=0.34) nor in mean FPG when adjusted for study entry differences (P=0.13). Similarly, when adjusted for age, duration and BMI, there was no significant difference in change in HbA_{1c} between ethnic groups (P=0.85) nor in mean HbA_{1c} (P=0.24) when adjusted for study entry difference.

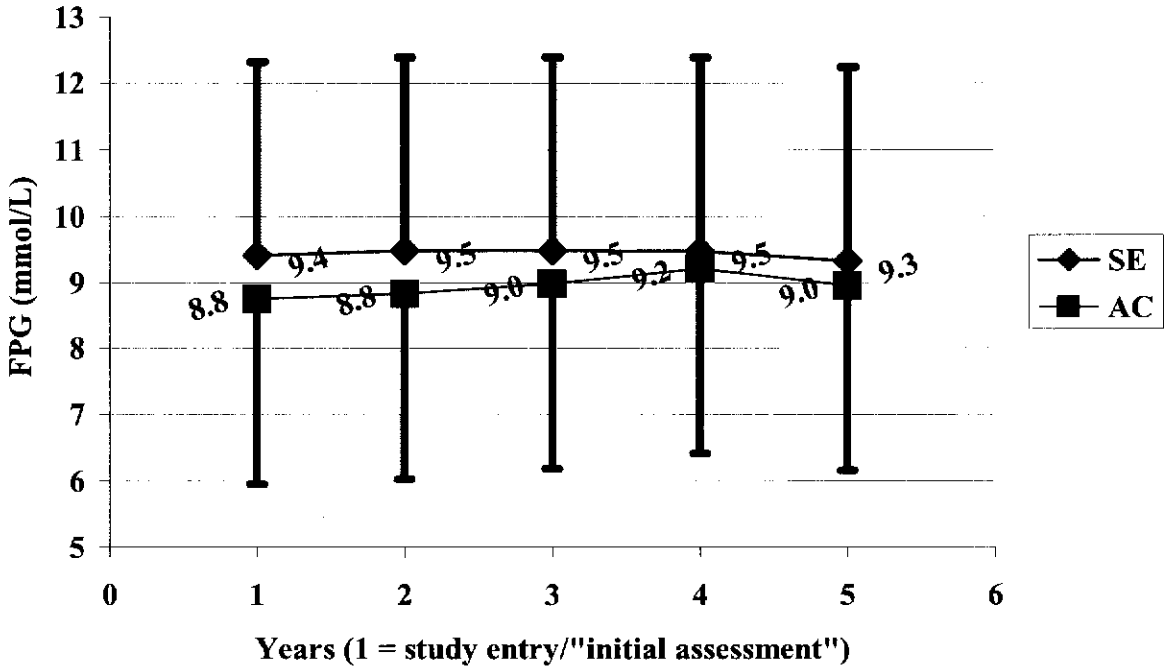


Figure 2.4: FPG (mmol/L) over time

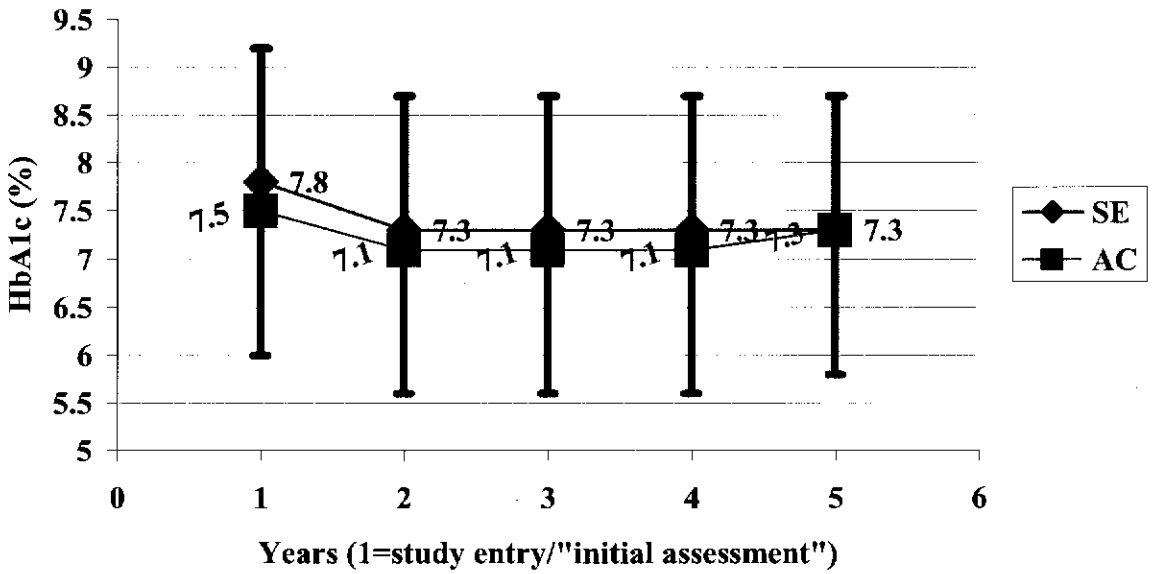
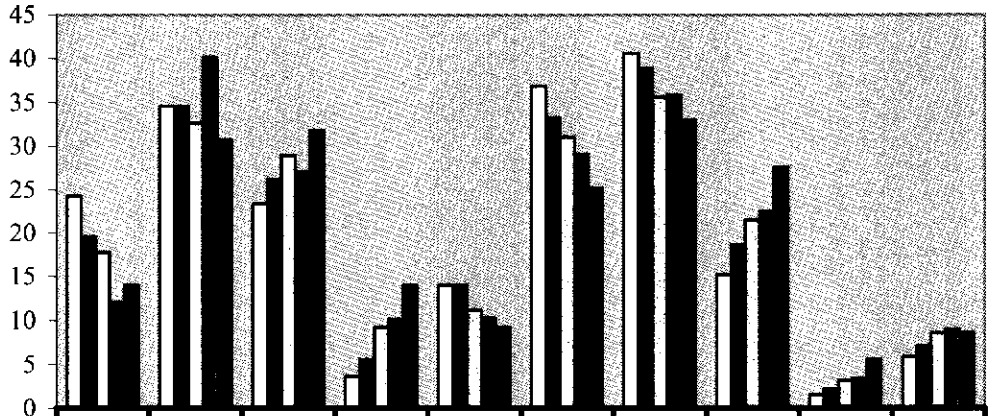


Figure 2.5: HbA_{1c} (%) over time

Figure 2.6 shows the overall medication progression in both ethnic groups over time; the left hand side of the graph shows the progression of the SEs and the right hand side shows the progression of the ACs. Table 2.7 details the percentage of patients on insulin at recruitment and at four years. There was a significant increase over time in the number of patients on insulin in both ethnic groups, however, SEs were more likely to be taking insulin with or

without OHAs at study entry (17.8% versus 7.3% of ACs; P=0.002) and at 4 years of follow-up (23.4% versus 14.2% respectively; P=0.03).



	No meds SE	1 med	2 meds	Meds + insulin	Insulin only	No meds AC	1 med	2 meds	Meds + insulin	Insulin only
□ Visit 0	24.3	34.6	23.4	3.7	14	36.9	40.6	15.2	1.5	5.9
■ Visit 1	19.6	34.6	26.2	5.6	14	33.3	38.9	18.6	2.2	7.1
□ Visit 2	17.8	32.7	29	9.3	11.2	31.1	35.7	21.5	3.2	8.6
■ Visit 3	12.1	40.2	27.1	10.2	10.3	29.1	35.9	22.5	3.4	9
■ Visit 4	14	30.8	31.8	14	9.3	25.2	33	27.6	5.6	8.6

Figure 2.6: Medication progression over time. Results are % of total.

Table 2.7: Percentage of SE and AC patients on insulin therapy who attended a study entry visit (initial assessment) and four consecutive annual assessments.

	SE Study entry n=19	**AC Study entry n=30**	***P***	**SE 4 years n=25**	**AC 4 years n=58**	***P***
Insulin therapy	17.8	7.3	0.002	23.4	14.2	0.03

2.5 DISCUSSION

Southern European patients in the FDS cohort were twice as likely to be treated with insulin than patients of AC ethnicity at study entry. This difference persisted after adjustment for confounding demographic, morphometric and diabetes specific factors in a logistic regression model. Longitudinal data showed that, although the use of insulin increased progressively in the two groups, the difference persisted after 4 years of follow-up in a subgroup of patients with complete annual assessments. Although there have been many studies of ethnic differences in glycaemic control[14,94,101,125], none have established an independent relationship between ethnicity and the type of treatment administered.

The reasons for the higher use of insulin in the SE population need to be elucidated. Patient-specific factors may be responsible for the differences seen. Such factors may include fear of, or preference for injections. Fear of injections, SMBG and hypoglycaemia in DM have been widely studied, but were beyond the scope of the present investigation.[331-333] Diabetes specific questionnaires have been developed and validated to help identify patients with fear of injections and further define this group, so that specific education can be provided to the patient.[334-336] While there were no differences in the rate of SMBG between ethnic groups, it may be that SE patients do not understand how to adjust insulin doses appropriately in response to the SMBG level obtained. SMBG has been widely reviewed in the literature,[337-340] but there have been no studies reviewing ethnic differences in the ability to self-adjust insulin doses in response to SMBG results.

Another patient-specific factor that may be important is medication compliance. It may be that different ethnic groups are more (or less) compliant with complex oral regimens. Compliance is difficult to assess accurately. However, data from the initial FDS interview, found no ethnic differences in the level of compliance with hypoglcyaemic medications. A range of different tools have been used to measure or improve compliance, and have included specially developed questionnaires that rely on patient self-report or reports by carers, electronic monitoring, medication event monitoring systems, packaging aids with microelectronic devices fitted, indirect clinical observations (for example drug assays), physiologic parameters (for example BP) and retrospective review of prescription collection.[341, 342, 343, 344] Further study into compliance between ethnic groups is warranted.

Variations in diet may also be a factor in the differences seen and have been reported in other minority groups.[345] It may be that AC patients are more diligent with diet than SE patients reducing the need to progress to more intensive therapy. An assessment of the lifestyle (diet and exercise) of both ethnic groups is warranted to determine whether lifestyle factors influence medication treatment. Studies that have reviewed diet quantitatively have found differences in intake between ethnic groups with respect to recommended levels of fat and carbohydrates.[345] This could have implications for the development of education strategies.

Physician factors, such as beliefs about the blood glucose control of various ethnic groups or pressures from patients either to initiate or not initiate insulin may also be important. SE patients did access general practitioners at a higher rate, however it is not known whether SE patients have a preference for injections which might influence general practitioner prescription of insulin. Conversely, ACs may have a fear of insulin and resist suggestions from their general practitioner to start insulin. It may be that SE have a higher rate of diabetes-related complications thus influencing GPs or specialists to start insulin in order to improve glycaemic control. These data from the FDS have yet to be reviewed. Physician factors relating to ethnicity and treatment of DM have not been addressed in Australian studies.

It is important to note that ethnicity is a key difference when reviewing treatment strategies and that SEs may need more aggressive therapy to maintain glycaemic control than in other groups. The National Health Survey[115] and the Visual Impairment Project[102], both identified that the prevalence of DM was higher in people of SE ethnicity and these data, together with the data found in the present study may mean that SE patients are in a high-risk category.

Strategies need to be developed to target high-risk ethnic groups and may include:

1. Screening of high-risk persons, according to ethnicity;
2. Development of education programs specifically for individual minority groups.[346] Most current education material requires a high level of reading ability and is not culturally sensitive;
3. Training of more ethnic minority physicians, educators and translators in the care of patients with diabetes;

4. Development of low-cost models of diabetes care, that are easily used in a variety of settings with a variety of ethnic groups;[112, 211, 347, 348]
5. Recognition of differences in risk factors in different ethnic groups to enable HCPs to more effectively target preventative and treatment programs.[347, 349-351]

The present data, from a community-based cohort of patients with diabetes living in an urban Australian setting, indicate that SE patients are twice as likely to be on insulin than AC patients. It is presently not known why more SEs progress to insulin than ACs, nor why more SEs remain in the poorly controlled range (as measured by HbA_{1c}) despite apparently more aggressive treatment. There is a paucity of information in the literature addressing patient- and physician-specific factors that may have resulted in the difference in insulin use and glycaemic control between the SEs and ACs observed in the present study.

2.6 LIMITATIONS

- The FDS was a community-based study. It attempted to recruit all known diabetic people from a local community. However, only 64% of identified patients were recruited to the FDS. There were no significant differences in mean age, gender, country of birth or type of diabetes between FDS recruits and those patients who were not recruited to the study. It could be that non-recruits were more likely to be too busy, disinterested in their health, too sick, or too frail to attend and the implications of this are unknown.
- Of those patients who attended for an initial assessment, only 49% returned for four consecutive annual assessments. These patients were younger and had better levels of glycaemic control than the full cohort. It may be that this cohort were more interested in their health as evidenced by their regular attendance over a number of years at the FDS and this has unknown implications.
- While there was a significant difference in the use of insulin identified between ethnic groups, the actual number of patients on insulin was small. A larger study, with more patients on insulin would be needed to confirm the findings of the present study.
- While information on diabetes related complications was collected as part of the FDS assessment, analysis of these data was beyond the scope of the present study. It may well be that the diabetes complications were confounders for different levels of insulin use by different ethnic groups.
- The FDS interview relied of self-reported data. Self-report of diabetes care is likely to have inaccuracies due to memory problems, patients not wanting to admit deficits in self care, and patients either over or under-estimating quantitative data.[344, 352-354] In many cases FDS patients did attend with a carer or relative and many of these persons assisted the patient during the FDS interview.

2.7 RECOMMENDATIONS

- Ethnic differences with respect to fear of injections, fear of SMBG, or preference for injections in DM have not been studied. Future studies could use existing questionnaires that address these issues and compare results between ethnic groups.
- Ethnic differences with respect to appropriate adjustment of insulin doses according to SMBG results requires further study. This may lead to the implementation of intensified, ethnicity specific education of patients.
- Further study into compliance in different ethnic groups is warranted. A range of tools should be used to thoroughly address compliance as all reported methods have limitations.
- Diet and exercise can influence glycaemic control. Quantitative differences in lifestyle need to be reviewed between ethnic groups.
- Physician factors, such as beliefs about the blood glucose control of various ethnic groups, or pressures from patients either to initiate or not initiate insulin may also be important and have not been adequately addressed in the literature. Further studies are needed in this area.

CHAPTER 3

PHARMACEUTICAL CARE IN HIGH-RISK DIABETES MELLITUS PATIENTS IN AN OUTPATIENT CLINIC

3.1 INTRODUCTION

PC is the process through which a clinical pharmacist cooperates with a patient and HCPs in designing, implementing, and monitoring a therapeutic plan that will produce specific outcomes.[149] PC studies have been completed in patients with diabetes, however all had limitations (Chapter 1, Section 1.3.2).[170-174, 176, 179, 183, 184, 204-207] There are no studies published to date reviewing PC in Australian patients with diabetes.

A pilot study was developed to review PC in patients with diabetes in Australia. The pilot study was completed in a diabetes outpatient clinic of a tertiary referral centre, as the infrastructure existed for the easy addition of a clinical pharmacist to the existing health care team.

3.2 AIM

The aim of the present study was to determine the impact of a PC program in patients with diabetes attending a hospital outpatient clinic, in Australia. The hypothesis was that a PC program would improve glycaemic control without impacting adversely on the HRQOL of the patient or their satisfaction with the health care provided. The specific outcome measures that were used to determine the impact of the program were

1. glycaemic control as assessed by HbA_{1c}
2. HRQOL as measured by a diabetes-specific questionnaire
3. identification and resolution of actual and potential drug related problems and
4. patient satisfaction with HCPs as measured by a questionnaire developed for the present study.

3.3 METHODS

3.3.1 APPROVAL

The study was undertaken in the Diabetes Outpatient clinic at FHHS, a 499-bed university teaching hospital in Fremantle, Western Australia. The Human Rights Committee, FHHS and the Human Research Ethics Committee, Curtin University, approved the study. All patients gave informed consent to participate after verbal and written explanations of the study were provided.

3.3.2 IMPLEMENTATION

Adult patients aged over 18 years with either type 1 or type 2 DM and at least one of the following features indicating the patient was high-risk for the development of DM complications were recruited to the present study[11, 20, 56, 85, 324, 355, 356]:

1. Random blood glucose levels >11 mmol/L on at least two occasions in a tertiary care setting in the previous twelve months
2. HbA_{1c} > 8% on at least two occasions in the previous twelve months
3. Hypertension (SBP >160mmHg and/or DBP >90mmHg) and/or requiring drug therapy
4. Dyslipidaemia (total serum cholesterol >5.5 mmol/L and/or serum triglycerides > 4.0 mmol/L) or
5. Polypharmacy (> 3 drugs)

Patients were excluded under the following conditions:

1. Patients who did not provide informed consent and
2. Inadequate fluency in English because interpreter services were not available for this study.

During the recruitment phase (October 1998 – April 1999), the medical records of all scheduled outpatients were reviewed for eligibility one week prior to the clinic appointment. Patients who met the inclusion criteria were then telephoned to determine their willingness to participate in the study and asked to attend their scheduled outpatient appointment 45 minutes early. All patients who were telephoned agreed to participate in the study. At this time patients were then allocated to case or control groups using a 2:1 computer-generated randomisation schedule. On the day of enrolment patients were provided with a written patient information sheet explaining the study, with a verbal explanation from the investigator and subsequently

signed an informed consent form. Demographic information and data relating to glycaemic control over the previous six months were obtained from each patient's hospital case notes. Patients were followed for six months from recruitment.

All patients completed a modified version of the Diabetes Quality of Life (DQOL) instrument developed for the Diabetic Control and Complications Trial (DCCT) (Appendix 2).[12, 327] In view of the duration of each clinic visit and given the age and clinical state of the patients, questions with least relevance to adult patients were omitted (questions 5, 6, 8, 12 and 14 for "satisfaction"; 1, 2, 3, 6, 7, 10, 12, 14, 17, 20 for "impact of diabetes; 1, 2, 5 for "worry" – social and vocational; 2 and 4 for "worry" - Diabetes-related). Such an approach has been used previously for type 2 DM patients.[357] The modified DQOL survey was divided into three sections:

1. ten questions related to the patients' general self-satisfaction ("satisfaction")
2. ten questions related to how often the patients' diabetes interfered with their life ("impact" of diabetes) and
3. six questions related to how often the patient worried about their diabetes ("worry").

Responses to DQOL questions were rated on a Likert scale from 1 to 5, with higher scores indicating greater "dissatisfaction", "impact" or "worry" regarding their diabetes. For each subscale and the total, individual item scores were averaged.

The patient satisfaction survey consisted of twenty questions related to patient satisfaction with the hospital physician and clinical pharmacist, including satisfaction with the information provided by the clinical pharmacist relating to drug therapy (Appendix 3). The patient satisfaction survey was developed for the present study. It was pre-tested on a random sample of twenty-five patients from the FHHS pharmacy outpatient section to ensure the survey was easy to administer and complete. Patients were asked to rate their satisfaction with the hospital physician, clinical pharmacist and the hospital drug information provided on a scale from 1 to 4 (very dissatisfied through to very satisfied). Recall error at the end of the study was avoided by administering the survey on the final day of the study after the patient's clinic visit with the investigator. An independent person administered the survey in each case.

All patients randomised to the PC program attended appointments at six-weekly intervals for six months with the investigating pharmacist, who had completed a comprehensive, self-

directed revision of diabetes management prior to the study. The investigator saw each patient at every visit, eliminating bias that may have arisen from using different clinical pharmacists. A comprehensive list of questions relating to pharmacotherapy and diabetes, including use of prescription and non-prescription medicines (including the use of complementary medicines), was covered during the patient's appointment (Appendix 4). Treatment goals were established at recruitment and discussed, reviewed and modified during the intervention according to the individual needs of the patient. The PC program was carried out in close co-operation with the diabetes physicians and other members of the diabetes health care team, who were aware of the PC program/control allocation for patients. The control patients received standard outpatient care for their diabetes but no intervention from the investigator. These patients completed the HRQOL survey but not the patient satisfaction survey. All patients had their HbA_{1c} measured at the beginning and end of the study.

Based on a previous study[179], it had been determined that 17 PC patients and 17 controls were required to demonstrate a 20% difference in the HbA_{1c} at the end of the study (power>80%, α=0.05). To account for potential withdrawals, particularly from the PC group, and to increase the power of the study, the target was 50 PC patients and 25 controls.

3.3.3 DATA ANALYSIS

Data are reported as mean±sd (for normally distributed data) and geometric mean [sd range] or median (IQR) (for non-normally distributed data). Statistical analyses were performed using the Statistical Package for Social Sciences, (SPSS), version 11. Statistical differences in continuous outcome measures between the two groups were assessed using Student's *t*-test for independent samples. Study entry and endpoint outcome measures were compared using the paired *t*-test. Categorical data were assessed by Chi-square tests or Fishers' exact test. HRQOL and patient satisfaction scores were similarly analysed. Non parametric tests included the Mann Whitney test and the Kruskal Wallis test. A significance level of $P<0.05$ was used.

3.4 RESULTS

3.4.1 DEMOGRAPHICS

In this pilot study, seventy-three patients were recruited, from the FHHS Diabetes Outpatient clinic, comprising 48 cases and 25 controls (Figure 3.1). There were no significant differences between cases and controls for any of the demographic variables that were documented. The sample was predominantly elderly type 2 DM patients (Table 3.1).

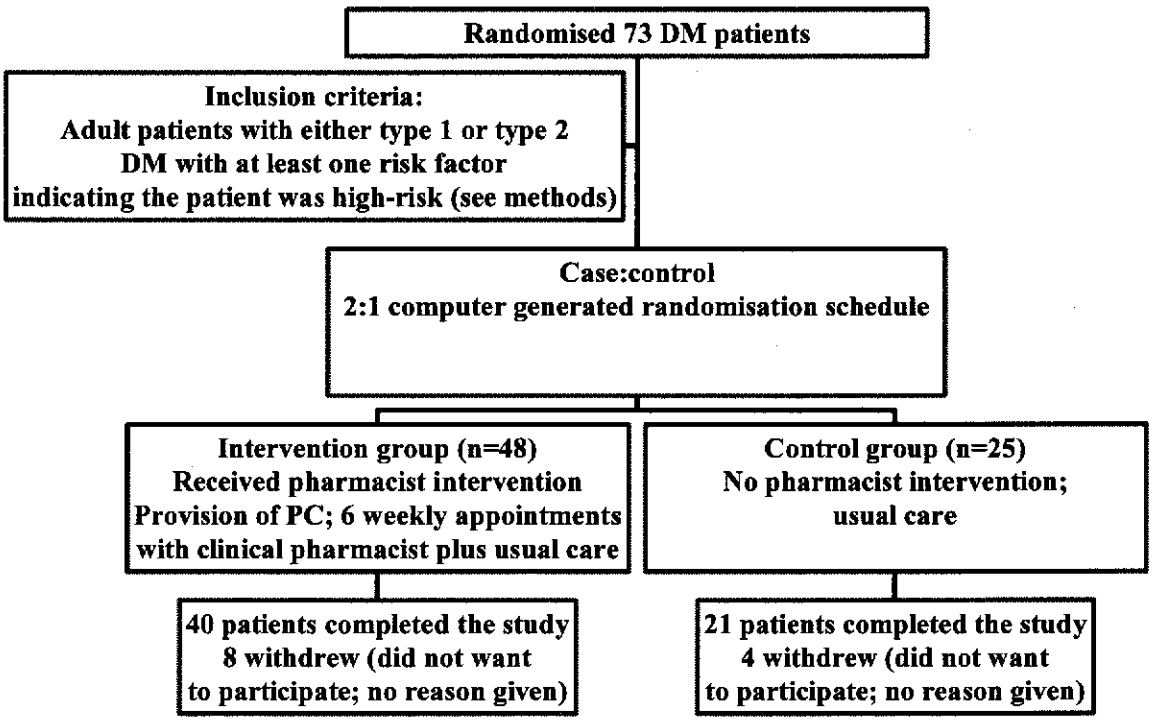


Figure 3.1: Consort diagram showing patient numbers at key time-points in the study between recruitment and close-out

Table 3.1: Patient demographics for patients enrolled in the intervention study

	Cases	Controls	*P*
Total number	48	25	
Type 2 DM (%)	34 (71)	20 (80)	0.41
Age (years)	60±12	61±12	0.45
Male (%)	28 (58%)	12 (48%)	0.34

3.4.2 GLYCAEMIC CONTROL

During the study period, the median (IQR) HbA_{1c} levels did not change significantly in either the cases or controls at the beginning and end of the study (P>0.42 across time and between groups) (Table 3.2).

Table 3.2: HbA_{1c} (%) levels over time. Data are median (IQR).

	Study entry	**6 months**	***P***
Cases (n=48)	8.1 (7.2, 9.0)	7.8 (7.3, 8.9)	0.59
Control (n=25)	8.5 (7.2, 9.7)	8.2 (7.3, 8.9)	0.59
P	0.67	0.42	

3.4.3 HEALTH-RELATED QUALITY OF LIFE

Responses to DQOL questions were rated on a Likert scale from 1 to 5, with higher scores indicating greater dissatisfaction (reported as "satisfaction"), impact (reported as "impact") worry (reported as "worry") regarding their diabetes. There were no significant differences in DQOL within or between groups during the course of the study (P>0.11) (Table 3.3). As there were no significant differences in HRQOL in the univariate statistics, multivariate analysis was not undertaken.

Table 3.3– DQOL for cases and controls at study entry and at 6 months. Data are median (IQR).

	Case n=48 Control n=25	**Study entry**	***P* Case vs control**	**6 months**	*P* **Case vs control**	*P* **Study entry – 6 months**
Satisfaction	Case	1.9 (1,4, 2.5)	0.46	2.2 (1.9, 2.8)	0.19	0.68
	Control	1.6 (1.4, 2.4)		1.8 (1.2, 2.4)		0.67
Impact	Case	2.2 (1.8, 2.4)	0.86	2.2 (2.1, 2.8)	0.90	0.63
	Control	2.2 (2.0, 2.6)		2.3 (1.8, 2.5)		0.28
Worry	Case	1.7 (1.3, 2.3)	0.21	2.0 (1.6, 2.6)	0.81	0.15
	Control	1.8 (0.9, 2.6)		1.9 (1.4, 2.5)		0.46
Total	Case	1.9 (1.6, 2.3)	0.73	2.1 (1.9, 2.6)	0.90	0.11
	Control	2.0 (1.5, 2.3)		2.1 (1.5, 2.4)		0.38

3.4.4 PATIENT SATISFACTION

Patients were asked to rate the questions from strongly disagree, disagree, agree, to strongly agree (rated as one, two, three and four). A higher score indicated a higher degree of satisfaction. Whilst the study entry score for the pharmacist was lower than that for the physician, there was a significantly higher satisfaction with the clinical pharmacist at the end of the study than at the beginning (P=0.01) as well as a greater patient satisfaction with drug information (P=0.04) (Table 3.4).

In the group of questions relating to medical practitioners, the respondents generally agreed with the statements relating to the care given by their medical practitioner (rating three). In the group of questions relating to satisfaction with their pharmacist and satisfaction with the drug information provided, there was a shift from disagreeing about the statements regarding the level of care of the pharmacist to agreeing (rating scale two to rating scale three).

Table 3.4: Results of the patient satisfaction survey. Data are mean±sd.

	Study entry	**Six months**	***P***
Hospital physician satisfaction	3.1±0.6	3.3±0.8	0.21
Clinical pharmacist satisfaction	2.9±0.6	3.3±0.8	0.01
Drug information satisfaction	2.9±0.5	3.1±0.5	0.04

3.4.5 DRUG THERAPY INTERVENTIONS

Thirty-nine drug therapy interventions were made in the cases after a full medication review and subsequent discussion with the hospital physician (Table 3.5). All drug therapy suggestions that were discussed with the hospital physician were implemented. No interventions were made in the control group as there was no medication review in this group by the investigator.

Table 3.5: Categories of interventions

Intervention	n (%)	Example:
Addition of a drug	16 (41)	Addition of metformin to a poorly controlled obese type 2 DM patient on insulin therapy
Cessation of a drug	8 (20)	Patient with contraindications to the use of NSAIDS – change to regular paracetamol dosing
Adverse drug reaction	1 (3)	Rash to cerivastatin
Drug/food interaction	9 (23)	OHAs – advice with respect to timing of doses and meals
Compliance	2 (5)	Patient had discontinued low dose aspirin – advised to restart
Dose increase	3 (8)	Lipid levels remaining high; increase simvastatin dose

3.4.6 COMPLEMENTARY MEDICINES

During the study it was determined that 16% of patients were taking at least one CM, usually without the knowledge of the hospital physician. Fourteen different CMs were being consumed and 9 of these (64%) had the potential to interfere with another medication or affect an existing disease state in the individual patient (Table 3.6). Details of the potential monitoring requirements can be seen in Table 3.7.

Cases: = 48	**Controls = 25**
Number of patients taking CMs = 8 (16.7%)	**Number of patients taking CMs = 4 (16%)**
Number of CMs = 8	**Number of CMs = 6**
Omega – 3 fish oil	Herbalax ®
Chromium	Linseed and ***Garlic***
Gingko biloba	Grape seed Extract
Gotu-cola	***Fish Oil and glucosamine***
Glucosamine	
Cod liver oil	
Thiamine	
Thiamine	

*CMs in italics had the **potential** to interfere with another medication or influence an existing disease state in the individual patient.*

Table 3.7: Potential monitoring requirements for CMs

CM	Number and (%) of CM users	Main active constituents	Main/purported actions	Main adverse effects	Potential monitoring in a diabetic patient
Fish-Oil/omega-3 fatty acids[358]	3 (25)	Omega-3 fatty acids including eicosapentaenoic acid and docosaheaenoic acid	Lowers triglycerides LDL levels may increase Anti-inflammatory Anti-platelet Hypotensive	Worsening of glycaemic control possible in type 2 patients Prolonged bleeding time Vitamin A and D toxicity	INR (anticoagulant potentiation) Glycaemic control (decreases and increases in blood glucose levels have been reported) Serum triglycerides Serum LDL Vitamin A and D levels (with high doses) BP
Glucosamine[359, 360]	2 (17)	An amino sugar comprising an amino acid and a sugar molecule	Osteoarthritis	Nausea, flatulence, diarrhoea, leg oedema, "heavy" legs and skin reactions Avoid in patients with seafood allergy	Glycaemic control (theoretically increases blood glucose levels)
Garlic[361, 362]	1 (8)	Constituents of garlic include alliin, allicin, diallyl disulphide and ajoene	Antispasmodic Antiviral Hypotensive Hypocholesterolemic Hypoglycaemic	Prolonged bleeding time at high doses	INR (anticoagulant potentiation) Glycaemic control (potential to decrease blood glucose levels) Lipid levels BP
Chromium[252]	1 (8)	Chromium is an essential trace element involved in glucose metabolism	Introduction of chromium to a stable diabetic regimen may result in decreased insulin requirements and changes to oral hypoglycaemic requirements	Gastrointestinal disturbances, anaemia and renal failure	Glycaemic control (may decrease blood glucose levels)
Ginkgo biloba [363]	1 (8)	Plant extract	Cerebral insufficiency Peripheral vascular disease	Prolonged bleeding time Gastrointestinal disorders	INR (anticoagulant potentiation)
Gotu-cola [364]	1 (8)	Plant extract	Improvement in mental function Mild tranquilliser; antianxiety ability	Increases in serum cholesterol reported Possible worsening of glycaemic control	Glycaemic control (may increase blood glucose levels) Lipid levels

3.5 DISCUSSION

The overall level of glycaemic control in the majority of the present patients was suboptimal.[1] It is well documented that good glycaemic control with HbA_{1c} levels of less than 7.0% results in health and cost benefits in the diabetic patient.[188, 355, 365-368] As diabetes progresses, the level of glycaemic control generally worsens and it may have been that these patients had a long duration of diabetes, making attainment of good glycaemic control more difficult.[18]

In the context of this small-scale pilot study, it may be that more regular patient contact either by more frequent clinic appointments or via the telephone would have been an important factor in influencing glycaemic control. Asking patients to attend more regularly may have had an impact on their HRQOL[12], however more regular contact via the telephone may prove effective.[348] Other educational strategies, such as a regular newsletter addressing different aspects of maintaining good glycaemic control may also have been of benefit.[158, 208, 211, 369] A longer study, may also have been important to see changes in glycaemic control.

HRQOL is a widely accepted endpoint in intervention studies. HRQOL endpoints that are related to health care have been used to adjust measures of effectiveness for clinical decision-making and resource allocation, and to evaluate drugs and health-care programs in many areas.[370, 371] In the present study, the DQOL did not change in any dimension over the six-month period in cases or controls.

The DQOL was developed for the DCCT.[12] It was postulated that HRQOL might be worse in the DCCT intervention group, due to the increased incidence of hypoglycaemia and the increased demands of intensive therapy. However, there was no intervention-specific difference in HRQOL mean and total scores. The present study was more demanding for the patient as they had to attend the outpatient clinic more regularly. This did not worsen the individual "satisfaction" scores. While the DQOL is a diabetes-specific HRQOL tool[12], it would have been useful to have used a general health related QOL tool such as the SF-36.[316] Multiple indexes of HRQOL are preferable because no single standard measure exists for assessing the effects of clinical interventions in diabetes.[17]

The patient satisfaction survey was administered to cases only as a measure of their satisfaction with their hospital physician, pharmacist and the drug information provided to them during the study. It is important to note that the investigator did not administer the survey to minimise the influence of the investigator's presence. The survey was administered by an independent person, who reported (anecdotally) a high level of positive comments regarding the study. Some cases rang the investigator after the conclusion of the study to offer positive comments and their thanks. The survey was reported by the independent monitor to be easy to administer and patients did not report any difficulty understanding the questions.

The survey results showed an improvement in the mean patient satisfaction scores for the pharmacist and the drug related information, both being rated more highly at the end of the study. The satisfaction with the pharmacist had the greatest improvement. This is an important result in terms of the pharmacists' role. Patient satisfaction with the delivery of health care services has become recognised as an increasingly important outcome of care and an indicator of the quality of those services.[372-374] There are a plethora of patient satisfaction surveys in the literature, however few are standardised and most measure patient satisfaction by different methods.[374, 375] The various methods that have been used include self-administered questionnaires, phone surveys, face-to-face interviews, mail surveys and comment cards. Various scales, rating methods and types of questions have also been used and have included visual analog scales, Likert scales, open-ended questions, closed-ended questions and positive or negative questions.[372-374] Although it is important to observe improvement in patient satisfaction, if this is not accompanied by improvement in other outcome measures such as HRQOL and clinical parameters, then the benefit of the patient satisfaction score is diminished.

Drug therapy interventions were a result of the PC process.[126] During the process, drug-related problems were identified, discussed with the patient and the physician and changes to the patients medications were then considered. These types of interventions are well described in the literature.[129, 130, 158, 165, 376] As only one measure of clinical outcome was followed in the present study, it can be concluded that the drug therapy interventions did not result in improvement in glycaemic control. If multiple clinical outcomes had been measured

and followed (e.g., lipids, BP, BMI), the effect of these drug therapy interventions may have been seen.

The use of CMs in patients with diabetes has been described, but the surveys all have methodological differences, making comparison difficult.[281, 285, 299, 300] It is clear that the present patient group was consuming CMs and some of these CMs may have the potential for CM-drug interactions or CM–disease interactions. This would increase certain monitoring requirements in a diabetic patient. The importance of a complete patient medication history as part of the PC process becomes paramount.

3.6 SUMMARY

A PC program was successfully accommodated in an outpatient clinic setting and was well received by patients and hospital physicians. The PC program did not adversely affect the patient's HRQOL and it significantly improved patient satisfaction both with the role of the clinical pharmacist and with the provision of drug-related information. The PC program was not associated with any improvement in glycaemic control within the 6-month study period as assessed by HbA_{1c}. A longer time frame and increased intensity of intervention may be required to show a clinical improvement in glycaemic control in a tertiary care setting.

High-risk patients were targeted on the basis that they would have the greatest potential for clinical benefit from the PC program.[179] It is also possible that the multiple problems and complexities of care facing these patients blunted the impact of the PC program. In addition these patients are usually reviewed by up to five different HCPs, including a hospital physician after referral by their general practitioner to the clinic. Even with this level of care, HbA_{1c} levels below 8% were not achieved in most of the case and control subjects. The value of adding a pharmacist in this setting appears to be related to the medication review process. The medication review process is an important part of the management of the diabetic patient, and showed benefits in highlighting the use of CMs and drug therapy changes.

There has been a small-scale study of a PC program in a diabetes outpatient clinic involving 39 urban African-American patients.[179] A range of interventions was implemented in addition to medication counselling. The mean HbA_{1c} at the beginning of the study was >12% and 9.2% at the end, a level that is still substantially higher than that seen in the patients recruited to the present study. Given the very high initial HbA_{1c} levels in the patients recruited, it is not surprising that a positive result was achieved. Recent evidence suggests that there is no threshold HbA_{1c} level for vascular benefit in diabetes.[377] Although the data from the restricted sample in the present study, did not show a significant reduction in HbA_{1c} even a small improvement as a result of a PC program may prove cost effective.

Thirty-nine interventions were implemented in the case group. These interventions involved a wide range of medications, not just hypoglycaemics. While these interventions did not result

in a significant improvement in glycaemic control over a six-month period, it may be that additional vascular risk factors, such as blood lipids and BP may have improved. These secondary endpoints were not considered in the present study.

During the process of medication review, one in six patients was found to be consuming one and two CMs. Of these CMs, 64% had the potential to interact with prescribed medicines or have a potential effect on an existing disease state in the patient. The use of CMs in type 2 DM warrants further investigation and in particular the clinical impact of these CMs requires review.

The present study highlights the value of the pharmacist as an information resource for patients with diabetes. This extends to CMs where potential interactions with conventional therapy may be neither suspected nor recognised. The present data and those of others suggest that a larger evaluation of a PC program for diabetes in the primary care setting may be valuable. The service was offered by a single dedicated clinical pharmacist who had completed self-directed diabetes care training. When reviewing the ability of this service to be adapted to the wider community, diabetes training of the service provider must be included as part of the study design.

3.7 LIMITATIONS AND RECOMMENDATIONS

- Future studies need to collect further demographic information including duration of diabetes, presence of complications (such as cardiovascular disease), and ethnicity. This information may have helped to explain the poor level of glycaemic control seen in this group of patients and if collected enable the pharmacist to provide more targeted PC.
- Future studies need to follow all pertinent end points relevant to diabetes care including lipid levels, BP, microalbuminuria and body mass index (BMI). While some of these parameters were inclusion criteria, they were not followed as part of the present pilot study and this is a major limitation. It may well be that even though glycaemic control did not improve in the present study, these other important endpoints that were not followed, may have improved.
- A larger cohort and longer study would have been necessary to see statistically significant changes in the various parameters. This study was carried out over a six-month period. It may be that with this cohort of poorly controlled patients with diabetes, a longer time frame may have been necessary. A longer time frame would have allowed for further educational strategies to be implemented and for more contact with the patient.
- While the DQOL is a diabetes specific HRQOL tool[12], it would have been useful to add a health related QOL tool, such as the SF-36.[316] Multiple indexes of HRQOL are preferable, as one tool does not assess all aspects of HRQOL.
- This study identified for the first time a high usage of CMs in high-risk diabetes patients. A larger detailed study of CM usage in patients with diabetes would provide valuable data to further address this issue.
- The patient satisfaction survey was developed for the present study and as such was a non validated tool. A larger cohort and more studies would be needed to fully validate the instrument.
- A single pharmacist with diabetes specific training completed the intervention. For this intervention to be able to be widely used in the community, pharmacists would have to complete a diabetes related training course.

CHAPTER 4

PHARMACEUTICAL CARE IN COMMUNITY-BASED DIABETES MELLITUS PATIENTS

4.1 INTRODUCTION

The PC model was established to provide a framework by which drug use could be improved to enhance patients' clinical and HRQOL outcomes.[149] PC must not end in the tertiary referral centre but must continue into the community.[153, 378] As such, communication mechanisms need to be established with the general practitioner other HCPs in the community. (Chapter 1, Section 1.3).[379]

Following the pilot study carried out in the tertiary referral centre (Chapter 3), the methodology used was reviewed and modified to enable a larger, more comprehensive study to be carried out in a community-based group of patients with diabetes. As ethnicity was found to be an important factor in the treatment schedule for SE and AC patients attending the FDS (Chapter 2), the PC program recruited patients from the these two ethnic groups to further define treatment differences between them.

4.2 AIM

The aim of the present study was to determine the impact of a PC program in type 2 DM patients attending the Fremantle Diabetes Study (FDS), in Western Australia. The hypothesis was that a PC program would improve glycaemic control, BP, lipid profile, BMI and microalbuminuria without impacting adversely on the HRQOL of the patient. The specific outcome measures that were used to determine the impact of the program were:

1. glycaemic control as assessed by FPG and HbA_{1c}
2. BP as measured by SBP and DBP measurements using a sphygnomanometer
3. lipid profile as measured by total plasma cholesterol, plasma HDL-cholesterol and plasma triglycerides
4. BMI calculated from weight and height measurements
5. HRQOL as measured by a diabetes-specific QOL questionnaire (the DQOL) and a general health QOL questionnaire (the SF-36).

4.3 METHODS

4.3.1 APPROVAL

The study was undertaken in the Diabetes Research Unit, in the University Department of Medicine at FHHS, Western Australia. All patients were recruited from the FDS (Chapter 2; Section 2.3). The Human Rights Committee, FHHS approved the FDS and the Human Research Ethics Committee, Curtin University, approved the present sub-study. All patients gave informed consent to participate.

4.3.2 IMPLEMENTATION

4.3.2.1 Patients

Adult patients from the FDS, with type 2 DM of SE or AC ethnicity, on one or more medications at recruitment, were entered into the study. During the recruitment phase (February 2001 – November 2001), all patients attending the FDS for their annual assessment were assessed for eligibility. Type 2 patients with diabetes were included as these patients generally have more co-morbidities and diabetes related complications and are on more medications than type 1 patients and may therefore benefit more from a pharmaceutical care program. Type 2 patients with diabetes are also more commonly seen in the community due to the higher prevalence of this form of diabetes. Patients who met the inclusion criteria were randomised as cases or controls by consecutive case: control allocation. All eligible patients agreed to participate. In the present study FDS patients were followed for twelve months from recruitment. Exclusion criteria were:

1. type 1 DM patients
2. patients not of SE or AC ethnicity and
3. patients on no medications at recruitment.

4.3.3.2 Methods

All patients that were recruited to the present study completed the annual FDS assessment (Chapter 2; Section 2.3.5 and Appendix 1). Demographic information, past medical history, self-care characteristics and relevant clinical data were obtained from each patient's FDS records. The FDS records included the initial assessment (Chapter 2, Section 2.3.5.1) and each annual assessment (Chapter 2, Section 2.3.5.2). The FDS interview was administered by the investigator for patients recruited to the present study.

Specific outcomes included change in HbA_{1c}, FPG, BP, lipid profile, BMI, presence of microalbuminuria (urine albumin;urine creatinine ratio (ACR) ≥ 3mg/mmol), 10-year vascular risk and HRQOL. HRQOL was assessed using a diabetes specific tool, the modified DQOL (Chapter 3; Section 3.3.2) and a general health QOL tool, the SF-36.[316]

At the annual FDS assessment, an experienced clinical pharmacist (the investigator) assessed all patients randomised to the PC program. The same clinical pharmacist, who had completed a comprehensive, self-directed revision of diabetes management prior to the study, saw each patient at every visit, eliminating bias that may have arisen from using different clinical pharmacists. A comprehensive list of questions relating to pharmacotherapy and diabetes, including use of prescription and non-prescription medicines, was covered during the patient's appointment with the clinical pharmacist (Appendix 4). A medication profile was subsequently provided to individual patients, along with their test results from their assessments. The medication profile listed all the patients' medications (prescription and non-prescription), important or relevant side effects and treatment goals. This was also sent to the patient's general practitioner and any other relevant HCPs. The control patients underwent the standard FDS assessment and the results were forwarded to their general practitioner; no medication profile was provided. All patients (cases and controls) attended the FDS for a six-month interim review of relevant clinical indicators and these results were forwarded to the general practitioner.

For patients in the PC arm, treatment goals were prioritised and the patient was telephoned at approximately six weekly intervals for twelve months and each treatment goal (in order of perceived importance by the investigator) was discussed over the intervention period. When necessary the medication profile and treatment goals were revised and a new copy was posted to the patient, their general practitioner and any other relevant HCPs. Patients were encouraged to discuss treatment goals with their general practitioner and other relevant HCPs. Topics that were discussed via telephone and at the interview included medication compliance, individual medications, BP reduction, glycaemic control, lipid level reduction, diet, exercise and other topics to meet the needs of the individual patient (as assessed by the clinical pharmacist). In addition to the regular contact by telephone, all patients received a bimonthly newsletter on important topics for patients with diabetes, such as glycaemic control, maintaining a balanced diet, BP and exercise. The clinical pharmacist wrote four

newsletters for distribution to the PC program patients after specific issues were identified in many patients via patient interview. Topics included the use of low-dose aspirin in type 2 DM, the importance of exercise and the importance of regular monitoring of HbA_{1c}. Other educational pamphlets were provided from the Heart Foundation of Australia and Diabetes Australia and included topics such as eating a balanced diet and the importance of BP reduction.

Regular examinations and tests are an accepted and necessary part of diabetes care.[198] The minimum recommended frequency of various tests and examinations can be seen in Table 4.1. This was developed from various literature sources[1, 103, 198, 215] and then used as a guide when reviewing treatment goals and standards in the PC program patients. Treatment goals were modified according to individual patient's needs.

Table 4.1: Tests and examinations for patients with diabetes

Test/Examination	**Minimum frequency**	**Goal**
Eye examination	Annual	
BP	Annual	<135/85 mmHg
Neurological examination	Annual	
Total cholesterol	Annual	<5 mmol/L
Triglycerides	Annual	<1.7 mmol/L
HDL – cholesterol	Annual	>1.1 mmol/L
HbA_{1c}	6 monthly	<7%
FPG	6 monthly	<6.7 mmol/L
Serum creatinine	Annual	
Condition of feet – podiatrist	Annual	
General practitioner consult	4 monthly	
Dietetic consult	Annual	
Diabetes education	Annual	
Complete physical	Annual	
BMI	6 monthly	BMI < 27 kg/m^2
Influenza vaccination (seasonal)	Annual	
Urine analysis (test for presence of protein)	Annual	ACR<3mg/mmol
Medication profile review and update including:	4 monthly	
Review of hypoglycaemics		
Review of lipid lowering drugs		
Review of BP lowering drugs		
Review of CMs		
Aspirin therapy where indicated		
Other as required		

4.3.3 DATA ANALYSIS

Based on previous studies[179], (Chapter 3) it was determined that approximately 80 PC patients and 80 controls were required to demonstrate a 10% difference in the HbA_{1c} at the end of the study (power>80%, α=0.05). To account for potential withdrawals, the target cohort was 100 PC program patients and 100 controls.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 11. Results are expressed as mean±sd (for normally distributed data), and geometric mean [sd range] or median (IQR) (for non-normally distributed data). Statistical differences in continuous outcome measures between the two groups were assessed using Student's *t*-test for independent samples. Study entry and endpoint outcome measures were compared using the paired *t*-test. Categorical data were assessed by Chi-square tests or Fishers' exact test. Non parametric tests included the Mann Whitney test and the Kruskal Wallis test. Multiple linear regression analysis was used to determine whether PC group membership was an independent predictor of response after adjusting for key variables. Repeated measures general linear modelling was applied to determine factors associated with DQOL. A significance level of <0.05 was used.

4.4 RESULTS

4.4.1 DEMOGRAPHICS

4.4.1.1 FDS patients

During the 3-year period April 1993 to April 1996, 2277 eligible subjects were identified from the Fremantle postcode area, and 1426 of these (63%) were recruited to the FDS. There were no significant differences in mean age, gender, country of birth or type of diabetes between FDS recruits and those patients who were not recruited to the study.[328, 329]

4.4.1.2 PC patients

Of 489 type 2 DM patients who attended for an FDS assessment during the recruitment period, 202 met the selection criteria and were recruited to the study with an equal allocation of cases and controls. There were no gender or age differences between these subjects and FDS patients who were not recruited, however study participants had a shorter mean duration of diabetes at their baseline FDS visit (3.0 [0.5, 6.0] vs 4.0 [1.0, 10.0] years; $P<0.001$). Patients recruited to the study were more like to be of AC ethnicity (87% vs 60%; $P<0.001$). Of the 202 recruited patients, 185 completed the 12-month study (Figure 4.1). There were no significant differences in mean age, gender distribution, mean duration of diabetes or clinical variables between those who completed the study and those who withdrew.

In the present study, patients in the case group had a longer duration of diabetes than the controls at randomisation (10 [7, 16] years vs 9 [5, 15]; $P=0.01$), were on more medications (7 (5,9) vs 5 (3,7); $P=0.003$) and a higher percentage had microalbuminuria (53% vs 26%; $P=0.001$). There were no other significant differences between cases and controls for any other demographic variables (Table 4.2). Other than duration of diabetes there were no ethnic differences in any of the study entry demographic variables.

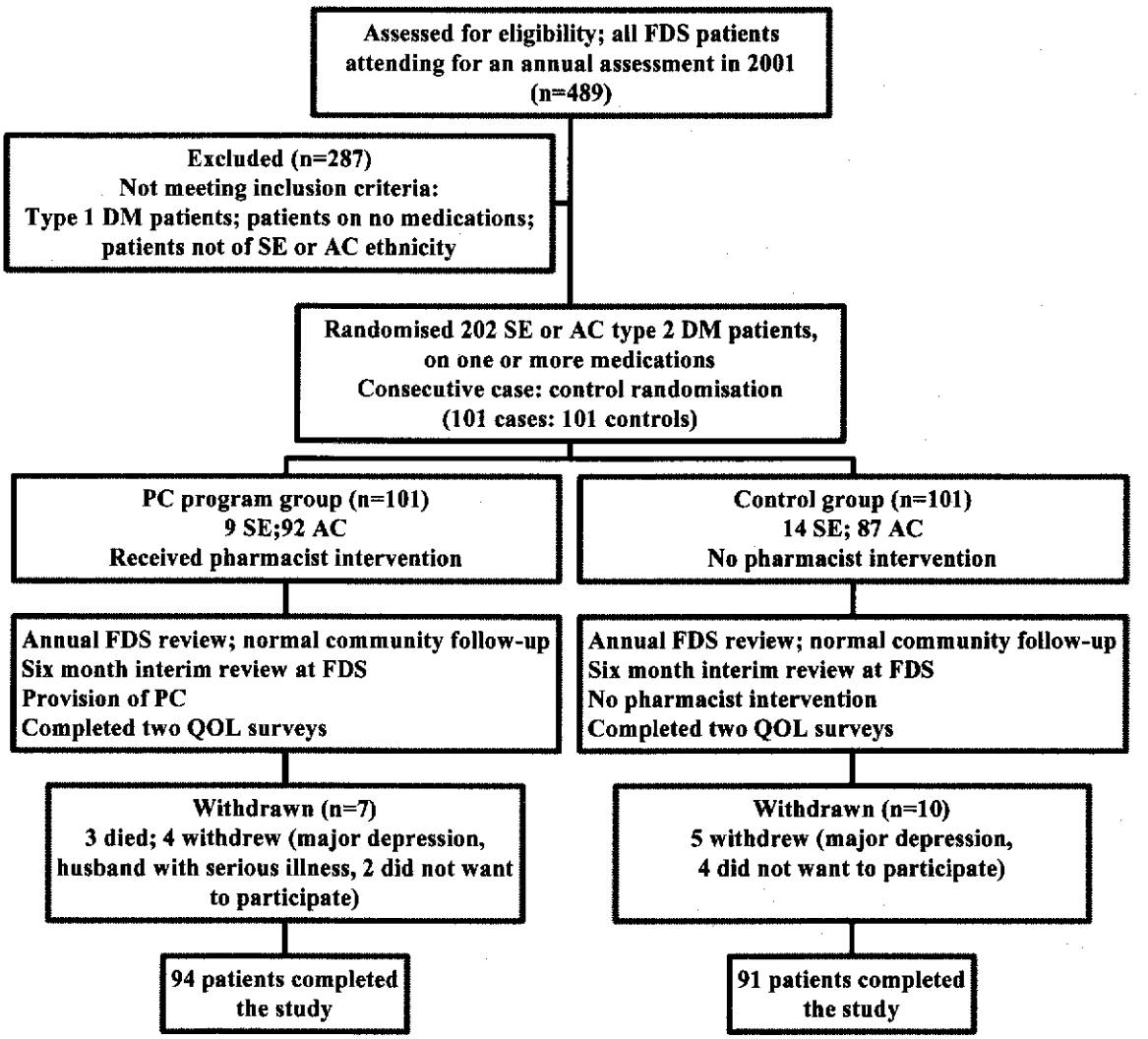


Figure 4.1: Consort diagram showing patient numbers at key time-points in the study between recruitment and close-out

Table 4.2 – Baseline characteristics of patients who completed the study. Data are mean±sd, geometric mean [sd range], median (IQR), or percentage (%)

	Case	**Control**	***P***
n	94	91	
Age (years)	71±7	70±8	0.70
Male (%)	48	57	0.24
Duration (years)	10 [7,16]	9 [5,15]	0.01
BMI (kg/m^2)	30±4	30±4	0.97
FPG (mmol/L)	8.8 (7.3, 10.5)	8.1 (6.7, 9.7)	0.12
HbA_{1c} (%)	7.5 (6.9, 8.0)	7.1 (6.3, 8.1)	0.20
SBP (mmHg)	158±22	156±25	0.63
DBP (mmHg)	77±10	77±11	0.95
Plasma total cholesterol (mmol/L)	5.0±1.1	4.9±0.8	0.50
Plasma HDL-cholesterol (mmol/L)	1.22±0.36	1.19±0.32	0.63
Plasma triglyceride (mmol/L)	1.6 [0.9, 3.0]	1.5 [1.0, 2.5]	0.45
ACR (mg/mmol)	2.9 [0.6, 14.1]	1.7 [0.4, 8.2]	0.02
Microalbuminuric (%)	53	26	0.001
Known IHD/CVD* (self-report)	54	41	0.08
Number of medications	7 (5,9)	5 (3,7)	0.003

*IHD (ischaemic heart disease); CVD (cerebrovascular disease)

4.4.2 CLINICAL OUTCOME MEASURES

BMI, SBP, DBP, FPG, HbA_{1c}, triglycerides and total cholesterol all decreased in the case group over the 12-month period of the intervention (Table 4.3). The percentage of patients who were microalbuminuric decreased in the case group over time and increased in the control group (53% vs 40% for the cases; $P<0.0001$ and 26% vs 35% for the controls; $P=0.05$). Table 4.4 shows the unadjusted mean (95% CIs) for changes in variables over the intervention period. There were no ethnic differences in any clinical outcome measure.

Multiple linear regression analysis that adjusted for age, gender, duration of diabetes at baseline, BMI, the associated baseline variable and change in exercise over the study period (model 1), confirmed that changes in glycaemic control (as measured by FPG and HbA_{1c}), BP (as measured by SBP and DBP) and ACR remained significant (Table 4.5). Model 2 reviewed dosage intensification in addition to the parameters in model 1. For changes in glycaemic control model 2 included dose decrease, no change, increase in dosages of hypoglycaemics, addition of one OHA, addition of two OHAs and progression to insulin. Using model 2 changes in glycaemic control remained significant. For changes in blood pressure, ACR and lipids model 2 included dose decrease, no change and addition of the relevant medication (for example addition of an antihypertensive or a lipid lowering medication). Using model 2 changes in SBP, DBP and ACR remained significant. Changes in the lipid profile did not remain significant in the multiple linear regression analysis.

The 10-year risk of having a new CHD event or stroke was calculated using the UKPDS risk engine, which is only valid for patients without a previous event.[380, 381] The risk of having a new event in this subset of patients decreased in the case group over time (Table 4.6), while the risk for the controls increased. The 10-year risk of stroke stayed the same in the case group, but increased in the control group.

Table 4.3: Clinical outcomes measures for patients who completed the PC study. Data are mean±sd, geometric mean [sd range], median (IQR), or percentage (%).

	Case Study entry n =94	**Case 12 months n=94**	***P* Case**	**Control Study entry n=91**	**Control 12 months n=91**	***P* Control**	***P* Case vs control 12 months**
BMI (kg/m^2)	29.8±4.4	29.2±4.4	0.001	29.9±4.5	30.0±4.8	0.51	0.20
SBP (mmHg)	158±22	143±21	<0.0001	156±25	147±21	0.002	0.19
DBP (mmHg)	77±10	71±10	<0.0001	77±11	74±10	0.14	0.03
FPG (mmol/L)	8.8 (7.3, 10.5)	7.9 (6.7, 9.4)	0.001	8.1 (6.7, 9.7)	8.2 (6.9, 10.4)	0.18	0.21
HbA_{1c} (%)	7.5 (6.9, 8.0)	7.0 (6.5, 7.5)	<0.0001	7.1 (6.3, 7.8)	7.2 (6.5, 8.2)	0.55	0.07
Total cholesterol (mmol/L)	5.0±1.1	4.6±0.8	<0.0001	4.9±0.8	4.7±1.0	0.06	0.60
HDL-cholesterol (mmol/L)	1.2±0.4	1.2±0.4	0.12	1.2±0.3	1.2±0.3	0.39	0.32
Triglycerides (mmol/L)	1.6 [0.9, 3.0]	1.4 [0.9, 2.4]	0.004	1.5 [1.0, 2.5]	1.5 [0.9, 2.5]	0.88	0.59
ACR mg/mmol	2.9 [0.6, 14.1]	2.3 [0.7, 8.2]	0.28	1.7 [0.4, 8.2]	2.6 [0.5, 12.0]	<0.0001	0.73

Table 4.4: Unadjusted mean (95% CIs) for changes in variables over the intervention period.

	Case	**Control**	***P***
	12 months – Study entry	**12 months – Study entry**	**Case vs control**
	n=94	**n=91**	
ΔBMI (kg/m^2)	-0.6 (-0.3 to –0.9)	0.1 (-0.5 to 0.2)	0.004
Δ SBP (mmHg)	-14 (-10 to -19)	-7 (-3 to -12)	0.03
Δ DBP (mmHg)	-6 (-3 to -8)	-2 (-5 to 1)	0.05
ΔFPG (mmol/L)	-0.8 (-0.3 to -1.3)	0.3 (-0.2 to 0.9)	0.002
ΔHbA_{1c} (%)	-0.5 (-0.3 to -0.6)	0.0 (-0.2 to 0.2)	0.001
ΔTotal cholesterol (mmol/L)	-0.3 (-0.1 to –0.5)	-0.1 (-0.3 to 0.0)	0.14
ΔHDL-cholesterol (mmol/L)	0.0 (0.0 to 0.1)	0.0 (-0.1 to 0.0)	0.08
ΔTriglycerides (mmol/L)	-0.6 (-1.2 to 0.1)	0.0 (-0.1 to 0.2)	0.08
ΔACR (mg/mmol)	-2.5 (-5.7 to 0.5)	1.6 (-3.2 to 6.4)	0.14

Table 4.5: Multiple linear regression analysis adjusting for key variables

	Model 1	***P***	**Model 2**	***P***
	Regression coefficient for case		**Regression coefficient for case**	
ΔBMI (kg/m^2)*	-0.8	0.003		
ΔSBP (mmHg)	-6	0.02	-6	0.03
ΔDBP (mmHg)	-3	0.02	-3	0.022
ΔFPG (mmol/L)	-1.0	0.004	-0.9	0.01
ΔHbA_{1c} (%)	-0.3	0.01	-0.3	0.03
ΔTotal serum cholesterol (mmol/L)	-0.1	0.23	-0.1	0.26
ΔSerum HDL-cholesterol (mmol/L)	0.0	0.08	0.0	0.08
ΔSerum triglycerides (mmol/L)	-0.2	0.19	-0.2	0.20
ΔACR (mg/mmol)	-6	0.003	-5	0.01

Model 1 – adjustment for age, gender, duration of diabetes at baseline, baseline value for the associated variable and change in exercise over the study period

Model 2 – model 1 and adjustment for relevant intensified pharmacotherapy (*exception, BMI: not adjusted for weight reducing medication)

Table 4.6: 10 year vascular risk assessment in patients with no history of CHD or stroke. Data are mean±sd.

	Case Study entry n=47	**Case 12 months**	***P***	**Control Study entry n=59**	**Control 12 months**	***P***	***P* Case vs Control 12 months**
CHD risk	41.4±18.4	36.8±17.9	<0.0001	38.8±17.1	39.1±15.3	0.23	0.51
Stroke risk	26.0±17.1	26.0±16.9	0.12	25.0±15.6	25.4±14.6	<0.0001	0.86

4.4.3 MEDICATIONS

There was an increase in insulin use over the study period in the case group (Table 4.7). The number of cases on ACE inhibitors or ARII blockers, insulin and anti-platelet agents increased over the study period. More cases were on ACE inhibitors or ARII blockers and anti-platelet agents than controls at 12 months.

Table 4.7: Medication changes over time during the intervention (%)

Medication	**Case Study entry n= 94**	**Case 12 months**	***P***	**Control Study entry n=91**	**Control 12 months**	***P***	***P* Case vs Control 12 months**
ACE inhibitors or ARII blockers	55	74	0.002	54	57	0.57	0.01
Lipid lowering agents	69	75	0.77	64	65	0.18	0.15
OHA only	71	73	0.10	66	64	0.43	0.21
Insulin (+/- OHA)	7	17	0.05	16	17	1.00	1.00
Antihypertensives[#]	74	87	0.06	76	81	0.52	0.31
Anti-platelet agents	62	80	0.004	43	48	0.83	<0.0001
Anti-platelet agents (for patients with a self-reported history of IHD/CVD)	82	92	<0.0001	68	73	0.001	0.02
Aspirin only	54	75	<0.0001	40	42	0.60	<0.0001

[#]includes ACE inhibitor or ARII blockers, diuretics, beta-blockers, calcium channel blockers, alpha-blockers

4.4.4 THE FDS INTERVIEW

A comprehensive questionnaire related to diabetes self-care and management was administered at each annual FDS assessment (Chapter 2, Section 2.3.5). This FDS interview was administered by the investigator for the PC program patients at study entry and at 12 months. There were few differences between cases and controls either at study entry or at 12 months. PC program patients reported better levels of glycaemic control as measured by fasting SMBG, at 12 months (Table 4.8). There were no differences in self-care characteristics between ethnic groups.

Table 4.8: Self-care characteristics – the FDS interview. Data are mean±sd, median (IQR), or percentage (%).

All self-report questions administered during annual FDS assessment	**Case Study entry n=94**	**Case 12 months**	***P***	**Control Study entry n=91**	**Control 12 months**	***P***	***P*** **Case vs control 12 months**
Patients who performed SMBG in the last month (%)	82	70	0.003	77	68	0.002	0.85
Frequency SMBG in the last month (of those who performed SMBG)	4 (2, 8)	6 (3, 9)	0.43	4 (2, 8.5)	4 (2, 10)	0.99	0.22
Frequency of SMBG in the last month for patients on insulin	3 (0.3, 10)	6 (3, 14)	0.56	5 (3, 14)	7 (4, 14)	0.10	0.24
Lowest FPG in the last week with SMBG (mmol/L)	5.7±2.0	5.4±1.6	0.32	5.5±1.8	6.1±2.2	0.31	0.03
Highest FPG in the last week with SMBG (mmol/L)	9.2±3.5	8.5±2.3	0.16	9.0±2.8	9.6±3.2	0.08	0.03
Diary of blood glucose monitoring (%)	65	64	0.39	60	54	0.66	0.23
Dietitian in last year (%)	15	18	1.00	12	11	0.22	0.29
How well do you follow a recommended diet							
1. Only eat food recommended	8	14		10	11		
2. Occasionally eat food that isn't recommended.	85	73	0.70	76	74	0.60	0.18
3. Regularly eat food that isn't recommended.	4	13		4	11		
4. No advice to follow	3	0		10	4		
Visits to general practitioner in past 12 months	4 (2, 8.5)	4 (2, 8)	0.50	4(2, 6)	3 (2, 6)	0.90	0.13
Patients who attended any outpatient clinic (OPC) or medical specialist (MS) in past 12 months (%)	36	16	0.56	41	11	0.52	0.56
Frequency of attendance at any OPC or MS in past 12 month (for those who attended these services)s	2 (2,4)	2 (1, 2)	0.16	2 (2,4)	2 (1,3)	0.50	0.38
Attended a diabetes OPC in the last year (%)	12	7	1.00	15	3	0.35	0.50
Eye examination in the last year (%)	71	70	0.81	71	61	0.47	0.21
Blood pressure measurement in the last year (%)	95	99	1.00	95	97	1.00	0.37
Neurological examination in the last year (%)	22	27	1.00	21	16	0.15	0.09
Cardiac auscultation in the last year (%)	69	72	0.80	74	53	0.05	0.01
Blood test in the last year (%)	84	82	1.00	86	83	1.00	0.85
ECG in the last year (%)	32	27	1.00	28	30	1.00	0.73
Diabetes course in the last year (%)	18	27	0.75	18	28	0.77	1.00
Foot care in the last year (%)	44	42	0.29	39	40	0.66	0.88
Weigh regularly (>/= 1/month) (%)	98	68	0.53	95	59	0.40	0.22
Frequency of weighing of those who weigh regularly/month	4 (2, 14)	4 (2, 8)	0.22	4 (2, 8)	4 (1, 6)	0.23	0.13
Exercise in the last 2 weeks (%)	76	71	0.28	71	64	0.20	0.43

4.4.5 QUALITY OF LFE

Two HRQOL tools were used to determine whether there were HRQOL differences between cases and controls. A diabetes specific tool was used (modified DQOL; Chapter 3, Section 3.3.2) and a general health QOL tool, the SF-36.[12, 316, 330, 382]

4.4.5.1 DQOL scores

Responses to DQOL questions were rated on a Likert scale from 1 to 5, with higher scores indicating greater dissatisfaction, or poorer HRQOL. The dimensions were labelled "satisfaction", "worry" and "impact". There were significant changes in HRQOL over time for both the cases and the controls, as measured by the DQOL. Both the case and control groups saw an improvement in HRQOL for aspects relating to "how often diabetes interferes with their life", reported as "impact" (P=0.01 and P=0.02 respectively). There were no other improvements in HRQOL in any other dimension for cases and the total HRQOL for the cases remained the same. Controls however reported an improvement in HRQOL in the dimension of "worry" and also in the total DQOL (Table 4.9).

Table 4.9: DQOL in PC study groups. Data are median (IQR). Cases n=94; controls n=91.

		Study entry	***P*** **Case vs control**	**12 months**	***P*** **Case vs control**	***P*** **Study entry – 12 months**
Satisfaction	Case	1.5 (1.2, 2.1)	0.52	1.4 (1.1, 2.1)	0.18	0.91
	Control	1.6 (1.3, 2.1)		1.6 (1.2, 2.0)		0.11
Impact	Case	2.1 (1.8, 2.4)	0.14	1.9 (1.6, 2.4)	0.38	0.01
	Control	2.2 (1.8, 2.2)		1.8 (1.5, 2.2)		0.02
Worry	Case	1.5 (1.2, 2.2)	0.36	1.4 (1.0, 2.2)	0.76	0.47
	Control	1.7 (1.2, 2.3)		1.3 (1.0, 2.0)		<0.0001
Total	Case	1.8 (2.1, 2.4)	0.77	1.7 (1.4, 2.1)	0.60	0.32
	Control	1.8 (1.5, 2.2)		1.7 (1.4, 2.0)		<0.0001

The DQOL scores for each dimension were totalled for all dimensions, giving a "sum" DQOL (Table 4.10). The possible range of scores was from 26 to 130, with a higher score indicating a worse DQOL. There were no differences between cases and control at study entry or 12 months, however the control "sum" DQOL improved over time (P<0.001), while the "sum" DQOL for the cases remained the same

Using a general linear model, which adjusted for age, sex and ethnicity, it was found that the repeated DQOL measures could be accounted for by gender and ethnicity, but not the PC study, after controlling for the age of the patients (Table 4.11).

The significant ethnic differences in DQOL have been further analysed in Table 4.12. SE patients had a worse total DQOL than AC patients at study entry and at twelve months in the dimensions of "satisfaction" and "impact", which was reflected in a higher total DQOL. AC patients also showed an improvement in the dimension of "impact" over time, which was reflected in a significant improvement in the total DQOL ($P<0.0001$), when reviewed according to ethnicity.

Table 4.10: "Sum" DQOL. Data are gemometric mean [sd range]

	Study entry	**12 months**	***P*** **Study entry – 12 months**
Case (n=94)	44 [35, 55]	41 [31, 55]	0.07
Control (n=91)	46 [36, 58]	39 [30, 52]	<0.001
P Case vs Control	0.17	0.47	

Table 4.11 General linear modelling reviewing factors affecting DQOL

Factors	*P*
Case – control (being enrolled in the PC study)	0.73
Age	0.67
Gender	0.04
Ethnicity	<0.0001

Table 4.12: DQOL in ethnic groups (n=164 AC; n=21 SE). Data are median (IQR).

	Ethnic group	Study entry	*P* AC vs SE	12 months	*P* AC vs SE	*P* Study entry – 12 months
Satisfaction	AC	1.5 (1.2, 2.0)	0.05	1.4 (1.1, 2.0)	0.001	0.13
	SE	1.9 (1.5, 2.8)		2.0 (1.6, 2.6)		0.47
Impact	AC	2.1 (1.8, 2.4)	0.05	1.8 (1,5, 2.3)	0.01	<0.0001
	SE	2.3 (2.0, 2.8)		2.3 (2.0, 2.8)		0.83
Worry	AC	1.6 (1.2, 2.2)	0.50	1.3 (1.0, 2.0)	0.40	0.43
	SE	1.7 (1.3, 2.7)		1.7 (1.2, 3.0)		0.25
Total	AC	1.8 (1.5, 2.2)	0.02	1.6 (1,3, 2.0)	0.001	<0.0001
	SE	2.0 (1.6, 2.6)		2.0 (1.7, 3.0)		0.97

After adjusting for gender, age and ethnicity, there was no difference in HRQOL as measured by the DQOL between cases and controls. The apparent improvement in HRQOL in the control group is due to changes in the ethnic mix over the time frame of the study because of patient withdrawals. The ethnic differences in DQOL warrant further investigation.

4.4.5.2 SF-36 scores

There were no significant differences in HRQOL as measured by the SF-36 in any dimension between intervention groups or across time (Table 4.13). In view of the lack of difference between cases and controls within groups and across time, multivariate analysis was not performed.

When reviewing ethnicity, SE patients had a worse HRQOL in the dimension of mental health and general health that persisted over time. (Table 4.14)

Table 4.13: SF-36 scores for PC study. Data are mean±sd

	Case Study entry n=94	**Case 12 months**	***P* Study entry – 12 months**	**Control Study entry n=91**	**Control 12 months**	***P* Study entry – 12 months**	***P* Study entry Case vs control**	***P* 12 months Case vs control**	**Norms for DM[316]**
Physical functioning	56±27	58±29	0.88	62±28	62±27	0.26	0.12	0.38	68
Role emotional	72±40	72±41	0.87	70±39	69±42	0.54	0.82	0.65	76
Role physical	53±44	50±43	0.09	54±43	57±42	0.85	0.96	0.30	57
Social functioning	82±21	84±23	0.57	84±20	86±19	0.13	0.50	0.40	82
Mental health	74±17	76±16	0.41	75±16	76±17	0.94	0.63	0.94	77
Energy and vitality	56±20	55±22	0.27	57±20	59±20	0.76	0.82	0.20	56
Bodily pain	66±27	64±26	0.31	67±26	68±28	0.75	0.75	0.31	69
General health	59±22	58±21	0.26	58±19	62±19	0.63	0.93	0.14	56

Table 4.14: SF-36 scores for ethnic groups (n=164 AC; n=21 SE). Data are mean±sd

	SE Study entry	**SE 12 months**	***P* Study entry – 12 months**	**AC Study entry**	**AC 12 months**	***P* Study entry – 12 months**	***P* Study entry SE vs AC**	***P* 12 months SE vs AC**
Physical functioning	52±33	55±25	0.45	60±27	60±28	0.65	0.17	0.43
Role emotional	70±40	57±47	0.23	71±40	72±41	0.90	0.87	0.12
Role physical	58±46	59±45	0.81	53±43	53±42	0.31	0.59	0.54
Social functioning	75±24	78±26	0.61	84±20	86±21	0.18	0.06	0.12
Mental health	66±18	63±19	0.55	76±16	78±16	0.31	0.01	<0.0001
Energy/vitality	54±21	51±25	0.44	57±20	57±20	0.76	0.46	0.25
Bodily pain	59±30	59±29	0.30	68±26	67±27	0.47	0.17	0.24
General health	46±21	48±22	0.96	60±20	61±19	0.49	0.002	0.004

4.5 DISCUSSION

4.5.1 GENERAL

The present study has demonstrated that a community-based PC program with type 2 DM patients was associated with beneficial reductions in modifiable vascular risk factors. There were significant improvements in glycaemic control and BP and these improvements persisted after adjustment for key demographic variables and intensification of pharmacotherapy. In addition, the PC program was associated with a significant reduction in the 10-year risk of having a new CHD event for patients without a history of cardiovascular disease.

Glycaemic control (as measured by HbA_{1c} and FPG) improved over the study period, in the cases. The UKPDS determined that, for each 1% reduction in HbA_{1c}, there was a reduction in risk of 21% for any endpoint related to diabetes and 14% for myocardial infarction, with no threshold of risk observed.[9, 377] In the present study, there was an increase in the number of cases on insulin. However, a multiple linear regression model that adjusted for key demographic variables and treatment intensification with hypoglycaemic therapy found that the beneficial effects remained significant. This confirmed that the PC program was an independent predictor of response and that the PC program had benefits for non-drug determinants of risk.

Blood pressure as measured by SBP and DBP decreased in the case group over time. While the proportion of patients on anti-hypertensive therapy did not increase in the case group, improvements in BP observed in the PC group were possibly due to more appropriate doses of these medications and/or lifestyle change, both of which were specifically targeted in the PC program. The multifactorial nature of the PC program was highlighted by the results of the multiple linear regression analysis, which showed that the beneficial changes seen with BP reduction persisted after adjusting for key variables including treatment intensification with antihypertensive medication. It may well be that the improvement in BP control was the results of improved adherence, however this was not assessed in the present study. BP education was specifically targeted in the study group at a one-on-one level and via Diabetes Australia and National Heart Foundation pamphlets. BP treatment goals were recorded on

the patients' medication profile as well as the patients' BP on the day of their FDS assessment. This information was also forwarded to the patient's general practitioner.

Other changes in medications that resulted in clinically relevant improvements in key parameters, included the increase in the number of cases on ACE inhibitors or ARII blockers, with a resultant decrease in the proportion of patients with microalbuminuria. Systolic BP and DBP decreased in the PC study patients and this may have been due to the addition of ACE inhibitors or ARII blockers, dosage modification of existing antihypertensives (the percentage of antihypertensive therapy did not change within groups or across time) or lifestyle changes. ACE inhibitors and ARII blockers have been shown to slow the progression of nephropathy in patients with type 2 DM and to be vasculoprotective.[34, 37-40] The results of the present study have clinically significant ramifications in improving both renal and vascular outcomes in the PC study group.

While there was a significant decrease in total cholesterol and triglycerides in the PC study patients over the intervention period, these changes did not persist after adjusting for key variables in multiple linear regression analysis. Despite the lack of impact of the PC program on lipids there was still an absolute reduction of CHD risk of almost 5% in the PC group. Treatment of dyslipidaemia should be based on an assessment of absolute vascular risk rather than lipid levels alone.[383] It is well-established that aggressive treatment of dyslipidaemia in DM is essential and should be targeted in intervention programs.[78, 79] Plasma cholesterol is an independent risk factor for CHD and the risk is higher in people with DM than in the non-diabetic population.[1] Both the Multiple Risk Factor Intervention Trial (MRFIT)[124] and the UKPDS[10] have confirmed that for every 1 mmol/L increase in low-density lipoprotein cholesterol, the relative risk of CHD increases by over 50%. Patients in the present study were educated about the meaning and consequences of elevated cholesterol and the importance of lifestyle changes, such as dietary modification and exercise. Emphasis was placed on weight reduction, exercise and restriction of saturated fat, cholesterol, sugar, sodium chloride and alcohol. Current evidence suggests that all DM patients should be considered for treatment with statins[384] and this could be targeted as part of future PC programs.

The PC program did not result in significant increases in HDL-cholesterol. The main lipid lowering medications used in patients attending the FDS were statins. While statins have proven benefits in reducing total cholesterol[384], they only have minimal effects on HDL, raising levels by approximately 5%.[385] Combination therapy may need to be considered to further increase the HDL cholesterol. Education of general practitioners and patients should address this issue.

There is considerable evidence of the benefit of regular low-dose aspirin therapy in the prevention of further cardiovascular events.[386-389] Populations, in whom regular low-dose aspirin therapy has been advised based on the Hypertension Optimal Treatment (HOT) study[387], included hypertensive patients, current smokers, those with dyslipidaemia and people with diabetes.

The ADA recommendations for the use of aspirin were first published in 1997[386] and updated in 2003[390] and recommended aspirin for:

1. Secondary prevention of cardiovascular disease and
2. Primary prevention of cardiovascular disease where there are one or more of the following risk factors
    a. Family history of CHD
    b. Current smokers
    c. Hypertension (>160mmHg or on antihypertensives)
    d. Obesity (>120% desirable weight)
    e. Albuminuria (micro or macro)
    f. Dyslipidaemia
    g. Age >30 years old

    (where no contra-indications existed).

If no contra-indications to the use of aspirin exist, the use of aspirin in the current study should be 100%, according to the ADA recommendations as all of the patients were over 30 years old. Reviewing the recommendation (but excluding family history of CHD), 99% of cases and 94% of controls had at least one risk factor (other than age) for primary prevention.

When reviewing recruitment data for the entire FDS cohort, only 22% of the 1294 patients were taking regular aspirin.[391] More than twice the proportion of users (76% vs 30% of non-

users) had experienced a prior event. Of those with a prior event only 41% were taking aspirin. The importance of low dose aspirin in DM has been well documented since 1997[386-390] and it is clear that the use of aspirin in the community-based FDS population was increasing. It was also clear that ongoing education of patients and general practitioners is necessary to maintain high levels of use of aspirin. There is a need for measures to increase general practitioner and patient awareness of the value of adjunctive aspirin therapy in patients with type 2 DM. A specific leaflet was produced for the PC program patients to explain the importance of low-dose aspirin in the patient groups recommended by the ADA[386, 390] and patients were encouraged to discuss the contents of this newsletter with their general practitioner. This intervention was successful in increasing the level of aspirin usage over time.

Large well-designed, multi-centre trials have confirmed the importance of targeting risk factors to reduce vascular risk in type 2 patients with diabetes.[4, 9, 392, 393] The most intensive interventions resulted in the largest improvement in metabolic parameters. However these programs were time consuming and involved large financial commitments. Programs that are simple to run and can be implemented in the community setting, such as the PC program outlined in this study are needed to ensure the known benefits of improving metabolic parameters in the diabetic patient are realised across large numbers of patients.[394] In the Australian context, programs that are adaptable to rural and remote areas are also important and other studies have involved rural community pharmacists targeting cardiovascular risk factors.[395] PC services that target DM, such as the one used in the present study could be implemented in rural and remote areas.

The beneficial outcomes found in the present study were associated with the addition of a pharmacist to the care of community-based type 2 DM patients. The service was offered by a single dedicated clinical pharmacist who had completed self-directed diabetes care training. When reviewing the ability of this service to be adapted to the wider community, diabetes training of the service provider must be included as part of the study design. With this in mind the strategy was to develop a simple program that would provide maximum benefit to the patient, with minimum impact on their daily lives. A major factor that contributed to this goal was the provision of a patient-specific medication profile, which was updated on a regular basis according to the needs of the patient. The medication profile listed all the

patients' medications (prescription and non-prescription), important and/or relevant side effects and treatment goals. Patients were encouraged to carry their profiles with them and discuss them with their general practitioner (who was also sent a copy) and other relevant HCPs. The medication profile was designed to give the patient clear instructions and guidelines on the use of their medications, with the goal of improving compliance and reducing confusion over medications. Each medication listed on the profile was explained to the patient in the face-to-face counselling sessions at recruitment, at six-months and at close-out and over the telephone when necessary. The relevant treatment goals were listed on the profile, with the aim of reminding patients to try and achieve their treatment goals. Importantly, the profile served as a communication tool between the pharmacist, patient and other relevant HCPs. This may have been especially relevant for patients who had a hospital admission, during the intervention period as one of the aims of the medication profile was to reduce confusion surrounding current medications at the point of admission.

A second key factor was the use of the telephone as a means of communication, so that diabetes care issues could be addressed without undue disruption for the patient. This simple, inexpensive means of regular patient contact meant that the patients only had to attend for two visits in the 12-month intervention period. The telephone has been successfully used as an adjunct in the management of diabetes[348] and other conditions[396] and proved to be a useful communication tool in the current study.

Another important factor was the provision of individualised patient education and counselling, which was followed up with written education to reinforce the relevant messages. Diabetes Australia and National Heart Foundation pamphlets that were easily accessible were used along with a regular newsletter (written by the clinical pharmacist) that targeted issues raised by many patients during individualised telephone education sessions.

This simple program could be easily used in the context of a modified HMR program.[200] In Australia, this service exists to review all aspects of medication use in the patient's home environment and requires a referral to an accredited pharmacist from a general practitioner. The HMR program only allows one review per year, except where there are significant changes to the patients' drug therapy, a situation which may commonly apply to DM patients due to the chronic and progressive nature of the disease. However, the HMR process results

in a medication management plan and it is intended that this "plan" should be an active document which is reviewed on an ongoing basis by both the community pharmacist and the general practitioner. Based on the present study and other PC studies in patients with diabetes,[209, 397] patients with diabetes do need more frequent follow up to maintain improvements in metabolic parameters as the disease progresses. There are several issues that need to be addressed to increase the uptake of the HMR program and to ensure it adequately meets the needs of DM patients:

1. Education of general practitioners to recognise the benefits of the HMR program. More than 25,000 HMRs have been conducted to date, but this has involved only 6% of general practitioners.[398] The Australian Division of General Practice supports the HMR program, but recognises that more education of general practitioners about the benefits of the program is important. The education of general practitioners must also proceed via recognised pharmacy bodies but more importantly via communication mechanisms established in the local community between general practitioners, community pharmacists and accredited pharmacists.
2. Currently only 75% of community pharmacies are accredited to complete HMRs.[398] For DM to be adequately targeted in the community all pharmacies need to be accredited.
3. Continuing education of general practitioners and pharmacists about DM to ensure DM care issues are adequately addressed in the community.
4. Ensuring that the medication management plan is an active document that is routinely and regularly reviewed by the community pharmacist and the general practitioner.

The positive clinical outcomes seen in the present study, prove that a PC program can have benefits for DM patients. Pharmacists can provide this multifactorial intervention in a community setting as they are the most accessible member of the health-care team. This will require collaboration between pharmacists, general practitioners and other relevant HCPs and the development of easy to follow guidelines for the care of DM patients, supported by ongoing education.

4.5.2 THE FDS INTERVIEW

Self-report of diabetes care is likely to have inaccuracies due to memory problems, patients not wanting to admit deficits in self care, and patients either over exaggerating or under

exaggerating.[344, 352-354] However, self-reported data did provide some interesting points for review. The fact that cases and controls had similar responses is encouraging as vast discrepancies could indicate any one of the above problems.

4.5.2.1 Self monitoring of blood glucose

In the present group of type 2 DM patients, SMBG was performed approximately once a week. The benefits or otherwise of SMBG have been widely discussed in the literature.[337-340, 399, 400] Franciosi and colleagues, in their study involving nearly 3000 patients, showed that SMBG performed ≥ 1/day resulted in an increase in distress and worry in non-insulin treated patients and no improvements in glycaemic control.[339] These authors also showed that advanced age was associated with a low probability of performing SMBG. The level of testing seen in the present study may also be due to the older age of the patients.

There are no universal guidelines that have been agreed to with respect to SMBG and this area warrants further investigation. Additional research is needed to identify subgroups of patients and the frequency they need to monitor their blood glucose and to set up more effective clinical practice guidelines on this aspect of diabetes care. The guidelines should be differentiated according to diabetes type and treatment.[337, 338]

4.5.2.2 Fasting plasma glucose levels

There were differences in the self-reported data relating to FPG levels. This difference is to be expected as the PC program patients saw an improvement in glycaemic control (as measured by HbA_{1c}) of 0.5% and the control group HbA_{1c} level stayed the same. The cases also saw a decrease in laboratory measured FPG, while the controls saw an increase. This has been reflected in a statistically significant difference in the both the lowest and the highest self-reported FPG data (from SMBG) between cases and controls at 12 months. This gives some strength to the self-reported data as it concurs with the laboratory tests from the study with respect to glycaemic control.

4.5.2.3 Use of health care professionals

Only a small proportion of patients had attended a dietitian during the previous twelve months and there were no differences between groups or over time. Most patients commented that they had a consultation with a dietitian when they were diagnosed with diabetes but had not had a follow-up. On questioning, during the FDS interview many patients were confused with aspects of a healthy diet and in particular the meaning of the

glycaemic index. Information on diet needs to be reinforced over the years and follow-up visits to the dietitian should be considered as diabetes progresses. Information sheets were provided to patients on various aspects of a healthy diet and the glycaemic index, as part of the educational strategies of the PC program. Patients in the case group were encouraged to attend a dietitian if they were confused about aspects of their diet, however this did not result in a statistically significant increase in the number of patients who attended a dietitian over the intervention period.

There were no significant differences in patient numbers in either group who attended an outpatient clinic or a medical specialist. This question related to any medical specialist or outpatient clinic. For example, patients may have been under the care of a cardiologist, oncologist or endocrinologist and may have attended a diabetes outpatient clinic or a pain clinic. Specific details were not requested (a limitation of the study), except in the case of the diabetes outpatient clinic where a subsequent question asked "have you attended a Diabetic Outpatient Clinic in the last 12 months?" There were no differences between groups or over time with this question.

As part of the PC program, patients with poor diabetes control were encouraged to attend the FHHS diabetes outpatient clinic or a diabetes specialist. Some patients took this advice, however as would be expected over the year, other patients who may have attended an outpatient clinic or medical specialist in the previous year, may have had no reason to visit them during the intervention year. The numbers of patients attending diabetes outpatient clinics or diabetes specialists will fluctuate greatly according to need and the results from the present study confirmed this. It would have been useful to find out exactly what outpatient clinics and medical specialists were visited over the intervention year, however these data was not collected.

Few patients had attended a diabetes education course. However, most commented that they had attended a course at diagnosis but had not attended since. Some expressed an interest in attending again, however there was not a statistically significant increase in the number of patients who did attend a diabetes course over time or between groups. Diabetes education needs to be an ongoing process as the disease progresses and treatments change. Pharmacists could continue this education process using the HMR program as one of the most accessible

member of the health care team[401] and encourage patients to attend local diabetes education courses where appropriate.

It was notable that most patients were attending their general practitioner for a review at 3 monthly intervals, however many of the examinations and tests were not being carried out at an acceptable minimum frequency (Chapter 4; Section 4.3.3.2).

4.5.2.4 Regular examinations and tests

Goals were reviewed and revised according to Table 4.1. The guidelines for tests and examinations were poorly followed in the present patients. The patterns in the present data were also seen in the comprehensive review of Medicare occasions of service.[103] The Overland study[103] provided an overview of the pattern and standard of diabetes care from 1993-1997. The Royal College of General Practice has tried to improve standards of diabetes care by formally adopting consensus guidelines for the management of diabetes.[215] This consensus statement recommended that HbA_{1c} levels be measured 2-4 times per year and was widely publicised in the mid 1990s.[215] In the late 1990s, HbA_{1c} was still not performed on an annual basis in over 40% of patients with diabetes. Other tests that were suggested in the guidelines that were not followed in the Overland study, which was completed in 1997 included[103]:

- microalbuminuria (tested in only 12%)
- HDL-cholesterol (tested in only 19%) and
- lipid studies (tested in only 52%).

This rate of compliance with recommendations was low. Without information regarding patients' microalbuminuria and lipid status the commencement of timely treatment of various risk factors may be delayed with obvious long-term negative effects. Admittedly the overwhelming evidence on the preferred and necessary treatment for microalbuminuria did not appear in the literature until the late 1990s[4] and this information may take longer to disseminate to GPs.

The low level of compliance in the present study may be due in part due to the fact that the general practitioners in the Fremantle area are well aware of the FDS and the tests that are performed for their patients, as an annual report is forwarded to the appropriate general practitioner. However it is clear that these guidelines tend to be poorly followed in Australia and the FDS has now concluded.[215] This issue must be addressed both in educational

strategies directed at the patient and at the general practitioner. Again the pharmacist is in an ideal position to facilitate this education, both to general practitioners and to patients.

4.5.3 HEALTH-RELATED QUALITY OF LIFE

While patients in the PC program did not see an improvement in their HRQOL (as measured by the SF-36 or DQOL), it is important to note that the program did not have a deleterious effect on their overall HRQOL or their diabetes specific QOL. The UKPDS 37, aimed to determine the effects on HRQOL of intensive therapeutic policies and found that long-term intensive policies did not have a deleterious effects on HRQOL.[17]

The results from the present study highlight that DM patients represent a vulnerable population that merits special attention from HCPs, because of their low HRQOL scores. In the present study, the SF-36 dimensions were lower than the published type 2 DM norms for six of eight dimensions and equal for two dimensions.[316] The published norms are for younger patients than the cohort in the PC study group and HRQOL does decrease with age. However this finding remains important, given that low HRQOL can be a risk factor for subsequent cardiovascular events or complications, and DM patients are already at a higher risk for these complications.[402]

Ethnic differences were seen in the HRQOL as measured by SF-36 and DQOL. There are no Australian studies that have reviewed HRQOL in different ethnic groups and the reasons for the lower HRQOL in SE in this sample remain unclear. It may indicate that SE patients need prolonged extra support throughout the course of their disease. Further research with larger patient numbers is needed to determine the clinical implications of this data.

4.5 LIMITATIONS

- PC studies should consist of three elements[127]
    - Review of appropriate clinical outcomes
    - Review of HRQOL outcomes
    - Review of the economic outcomes

  The present study reviewed points one and two in detail, but no economic analysis was performed, as it was beyond the scope of the present study.
- Surviving FDS patients who voluntarily returned for their annual diabetes review were included, and these were younger, had shorter duration of disease and were more likely to be AC than those in the full FDS cohort. Ethnic differences in the treatment of diabetes were elucidated in Chapter 2 and these differences were to be explored in this PC study, however fewer SE patients attended the FDS in 2001 than during the recruitment phase. As a consequence the number of SE patients was too small to see any statistically significant differences in the care and control of their diabetes. HRQOL differences were elucidated. Future studies could specifically target SE patients to review this subset of patients more thoroughly. This research is necessary to determine appropriate treatment options in different ethnic groups in a multicultural environment.
- FDS patients who attended voluntarily in 2001, and were willing to be enrolled in the PC program may be more interested in their health and more likely to respond to intervention to improve diabetes care and control. Despite this, case patients saw significant improvements in modifiable risk factors and control patients did not.
- Self-reported data have limitations due to memory problems, patients not wanting to admit deficits in self care, and patients either over exaggerating or under exaggerating.[352-354] It was notable that the self-report data related to FPG were reflected in laboratory measures of glycaemic control, indicating that aspects of the self-report data may be reliable. Quantitative data should be sought to compare with self-reported data wherever possible.
- Despite clear prior instructions, some patients did not bring their medications to the interview for review. Follow-up phone calls were made in the event of any uncertainty, but there remains some risk that the medication records were incomplete, for a small number of patients.

- Diabetes is a chronic disease and while the present intervention was successful over a 12-month period, it is necessary to determine whether a program such as this has longer-term benefits and whether the HMR program can be modified to include the frequent reviews required by DM patients.
- A single pharmacist with diabetes specific training completed the intervention. For this intervention to be able to be widely used in the community, pharmacists would have to complete a diabetes related training course.

4.6 RECOMMENDATIONS

- This simple program could be easily used in the context of a modified HMR program.[200] In Australia, the HMR program exists to review all aspects of medication use in patients and requires a referral to an accredited pharmacist from a general practitioner. While the HMR program only allows one review per year, the medication management plan is an active document and should be reviewed regularly by the general practitioner and the community pharmacist. Based on the present study and other PC studies in patients with diabetes,[209, 397] patients with diabetes do need frequent follow up to maintain improvements in metabolic parameters as the disease progresses. Issues that need to be addressed before DM care issues can be adequately developed as part of the HMR program include uptake of the HMR program by GPs and pharmacists and education of the community-based practitioners with respect to DM care issues.
- The telephone was used as a means of patient contact, so that DM care issues could be addressed without undue disruption for the patient. This simple, inexpensive means of regular patient contact meant that the patients only had to attend for two visits in the 12-month intervention period. This method of communication also provides a unique opportunity to extend PC services for DM patients into rural and remote areas, in collaboration with rural community pharmacists and general practitioners and this should be the focus of future studies.
- Treatment and HRQOL differences do exist between ethnic groups. Subsequent studies should include over-sampling of specific ethnic groups, to further investigate these differences.

- The present study highlighted a fairly "ad hoc" approach to SMBG, by patients in the present study. There are no universal guidelines that have been agreed to with respect to SMBG. Additional research is needed to identify subgroups of patients that need to closely monitor their blood glucose and set up more effective clinical practice guidelines on this aspect of diabetes care. The guidelines should be differentiated according to diabetes type and treatment.[337, 338]
- Guidelines for regular testing and examination of DM patients were poorly followed in this group of patients for a number of reasons. This problem has been identified in other studies[103] and could be addressed with specific educational strategies as part of a modified HMR program.
- Ongoing education of general practitioners, accredited pharmacists, community pharmacists and patients is required to ensure all DM patients in whom regular aspirin therapy is indicted is used.

CHAPTER 5

COMPLEMENTARY MEDICINES

5.1 INTRODUCTION

Complementary medicines (CMs) are being used by an increasing number of patients who typically do not advise HCPs of their use.[216-222] In the preliminary study on PC in the tertiary referral centre, it was found that approximately one quarter of the patients with diabetes were consuming CMs (Chapter 3). While there have been studies of CM use in diabetes mellitus patients[285, 287, 299, 306, 309] there have not been any large studies in Australian patients with diabetes. In addition, there have not been any studies that have reviewed the implications of the use of these CMs on clinical parameters and patient status.

5.2 AIM

The preliminary study of PC in patients with diabetes identified that a significant number of patients with diabetes were consuming CMs (Chapter 3; Section 3.4.6). The aim of the present sub-study was to determine the level of use of CMs in a large sample of Australian DM patients from the FDS.

The specific objectives were to evaluate the use of CMs by patients with diabetes and determine what factors predict their usage and to investigate whether CMs used in patients with diabetes could potentially affect:

1. diabetes control
2. related co-morbidities and
3. existing therapeutic regimens.

5.3 METHODS

5.3.1 APPROVAL

All patients were participants in the FDS. The Human Rights Committee, FHHS approved the FDS protocol and Curtin University, Human Research Ethics Committee gave approval for the present sub-study. All patients gave informed consent to participate.

5.3.2 IMPLEMENTATION

Participants in the present study comprised a convenience sample of surviving FDS patients who were attending for an annual assessment (Chapter 2; Section 2.3.5) between February 2001 and September 2001. Patients were subsequently re-interviewed about their CM use one year later, between February 2002 and September 2002.

Each patient was informed as to the purposes of the present study, including being given a description of the type of products considered to be CMs. In addition to information obtained as part of the annual FDS assessment, each patient was asked to provide details of current (in the last week) and past (life-time) CM use. "Regular" users of CMs were defined as patients who had used CMs at least weekly for a 12-month period. An Access® database was developed to record the information collected. The questions were developed after an extensive review of the literature (Chapter 1; Section 1.4). The information collected included (Appendix 4):

1. CM brand and dose, from which the actual cost per month of the CM was calculated
2. Frequency of use
3. Length of use
4. Patient estimate of the monthly cost of CM use
5. Whether the patient made the decision to purchase CMs themselves or, if not, which primary source of advice or recommendation was used
6. Place of purchase
7. Primary reason for use
8. Whether the patient consults with CAM practitioners and the frequency and cost of consultations.

For the purposes of the present study, CMs were defined as any non-prescription medicine,

and included nutritional supplements or "herbal" preparations either purchased from a supermarket, health store, over-the-counter from a pharmacy, from a naturopath, homeopath or herbalist, by mail order or over the internet, or grown at home. CMs were classified as nutritional supplements (for example vitamins, minerals, shark cartilage and amino acids), botanical supplements (for example Saw palmetto, Xiaoke tea and St Johns Wort), and homeopathic medicine (Table 5.1). Any conventional over-the-counter medicines including "non-herbal" pain medicines, such as paracetamol, diclofenac, ibuprofen, "non-herbal" laxatives, such as di-octyl sodium succinate and any other over the counter medicines that did not meet the criteria for being a CM were excluded.

Table 5.1: Classification of CMs[403]

Classification group	Includes:	Examples:	Further definition
A. Nutritional supplements	1. Micronutrients	1. Vitamins, minerals, calcium, iron	Products that are ordinarily obtained from the diet. Although some of the products may originate from sources other than diet (for example bee pollen and shark cartilage), they still contribute to the total dietary intake of specific constituents such as vitamins, minerals, enzymes and amino acids.
	2. Food supplements	2. Lecithin, wheat germ, soy products	
	3. Dietary supplements	3. Bee pollen, food yeast, kelp, dolomite, shark cartilage	
	4. Biological supplements	4. Supplemental enzymes, amino acids, cod liver oil, probiotics	
B. Botanical supplements	1. Western herbal medicine	1. Saw palmetto, St John's wort, garlic	Products derived predominantly from medicinal herbs. In general they alter physiological responses, rather than contribute significantly to total nutrient intake. They are made from the whole plant or selected plant constituents.
	2. TCM	2. Chifong toukuwan, Xiaoke tea	
	3. Ayurvedic medicine	3. Amalaki, bitter melon, brahmi	
	4. Aboriginal medicines	4. Fever grass, soursop	
C. Homeopathic Medicine		Aconite, chamomile, rhus toxicodendron	
D. Other			Any product not on prescription and not included in A,B or C.

Following compilation of the complete list of CMs reported by the patients, a subsequent search of the literature was carried out to determine whether their use might potentially necessitate additional clinical and/or laboratory monitoring due to:

1. an adverse effect on glucose homeostasis
2. a co-morbid condition commonly associated with diabetes or
3. a potential interaction with prescription or other non-prescription items.

Search tools included Medline®, IDIS®, the World-Wide-Web and Andin®. Well known CM, World-Wide-Web web sites were used including; The Natural Pharmacist (www.tnp.com), The Longwood Herbal Task Force (www.mcp.edu/herbal), Quackwatch (www.quackwatch.com) and the Natural Medicines Comprehensive Database (www.naturaldatabase.com).

Patients were asked to complete two HRQOL surveys to determine whether there were HRQOL differences between users and non-users. A diabetes specific tool was used (modified DQOL; Chapter 3; Section 3.3.2) and a general health QOL tool, the SF-36.

5.3.3 DATA ANALYSIS

Statistical analysis was performed using SPSS for Windows, version 11 (Inc, Chicago, IL). Data are reported as mean±sd, median (IQR), or percentage (%). Two-sample comparisons for normally distributed variables were by Student's *t*-test and the Wilcoxon Mann-Whitney test was used for non-normally distributed data. Comparisons of proportions were by Chi square tests or Fishers' exact test. Multivariate unconditional logistic regression analysis was undertaken to determine factors associated with CM use. A significance level of $P<0.05$ was used throughout.

5.4 RESULTS

5.4.1 DEMOGRAPHICS

A total of 351 FDS patients were recruited (25% of the total FDS cohort). In comparison with the 746 surviving patients who did not attend during the 8-month study period, the present patients were significantly younger and had shorter duration of diabetes ($P<0.05$).

Details of the present patients at study entry, classified by CM use are shown in Table 5.2. For the purposes of the present study "regular" users were identified and analysed. Most had relatively modest household incomes, low levels of education and over 60% were retired. CM users were more likely to be female than CM non-users. CM users were significantly more likely to maintain a diary of the result of self blood glucose monitoring, but the median HbA_{1c} was similar in the two groups. Complication rates were similar in the two groups, however CM users were more likely to have never been smokers. Table 5.3 reviews the factors associated with CM use after adjustment for age and sex. It was found that people who had never smoked and people who spoke English at home were more likely to be taking CMs.

5.2 Characteristics of patients interviewed regarding the use of CMs at study entry. Data are mean±sd, median (IQR) or %.

		Regular CM Users n=83	**Non-users n=268**	***P***
Patients (%)		23.6	76.4	
Type 2 (%)		98	95	0.37
Age (years)		68±9	69±10	0.53
Gender (% male)		41	59	0.02
Ethnicity (% AC)		82	71	0.06
English ability (% fluent)		94	86	0.11
HbA_{1c} (%)		7.3 (6.4, 8.3)	7.5 (6.7, 8.2)	0.56
FPG (mmol/L)		8.2 (6.8, 10.2)	8.3 (7.0, 10.0)	0.91
BMI (kg/m^2)		30±5	29±5	0.38
Completed high school (%)		31	25	0.23
Household income <$40,000 (%)		90	93	0.46
Retired (%)		63	68	0.41
Blood glucose monitoring (times/week)		6 (3, 10)	5 (2, 8)	0.93
Diary of blood glucose monitoring (%)		75	61	0.03
Exercise in previous 2 weeks (%)		80	73	0.31
Complications	IHD (%)	37	43	0.31
	Retinopathy (%)	49	47	
	Neuropathy (%)	71	66	
Smoking status	Never smoked (%)	57	42	0.04
	Ex-smoker (%)	35	44	
	Current smoker (%)	8	14	
Alcoholic drinks/day		0.1 (0, 0.8)	0 (0, 0.8)	0.48
Chronic alcohol users (>3 standard drinks/day) (%)		8.3	7.5	1.00

Table 5.3: Factors associated with CM use after adjustment for age and sex at study entry

Variable		OR (95% CI)	*P-value*
Age			
	Current age	1	
	Age last birthday	0.97 (0.94, 1)	0.04
Sex			
	Female	1	
	Male	1.4 (0.79, 2.47)	0.25
Smoker (ever)			
	Yes	1	
	No	1.9 (1.1, 3.3)	0.03
Speaking English at home			
	No	1	
	Yes	3.5 (1.2, 10.5)	0.03

5.4.2 CM USE

Twenty-four percent (83/351) of study patients were consuming between one and eight CMs on a daily basis at study entry, and had been consuming the CM over the last 12 months on a regular basis, defining them as regular users. This increased to 30% (93/306), one year later. The median number of CMs at study entry and at one year was 1 (1,2). Flow of patients through the study can be seen in Figure 5.1.

183 different products were being used at study entry, involving more than 58 ingredients:

- 80% were classified as nutritional supplements (the most common being multivitamins)
- 19% were botanical supplements (the most common being garlic)
- 1% were homeopathic remedies.

192 different products were being used at 1 year involving more than 58 ingredients:

- 80% were classified as nutritional supplements (the most common being multivitamins)
- 19% were botanical supplements (the most common being garlic)
- 0.5 % were homeopathic remedies and
- 0.5 % were "unknown".

The CMs used at study entry and at one year can be seen in Table 5.4. CMs with a potential to interact either with other medications or diabetes control or a co-morbidity associated with DM are also shown in Table 5.4. A total of 43.1% were identified as having the potential to

interact at study entry and 43.2% at one year. Table 5.5 details potential interaction details and potential monitoring requirements.

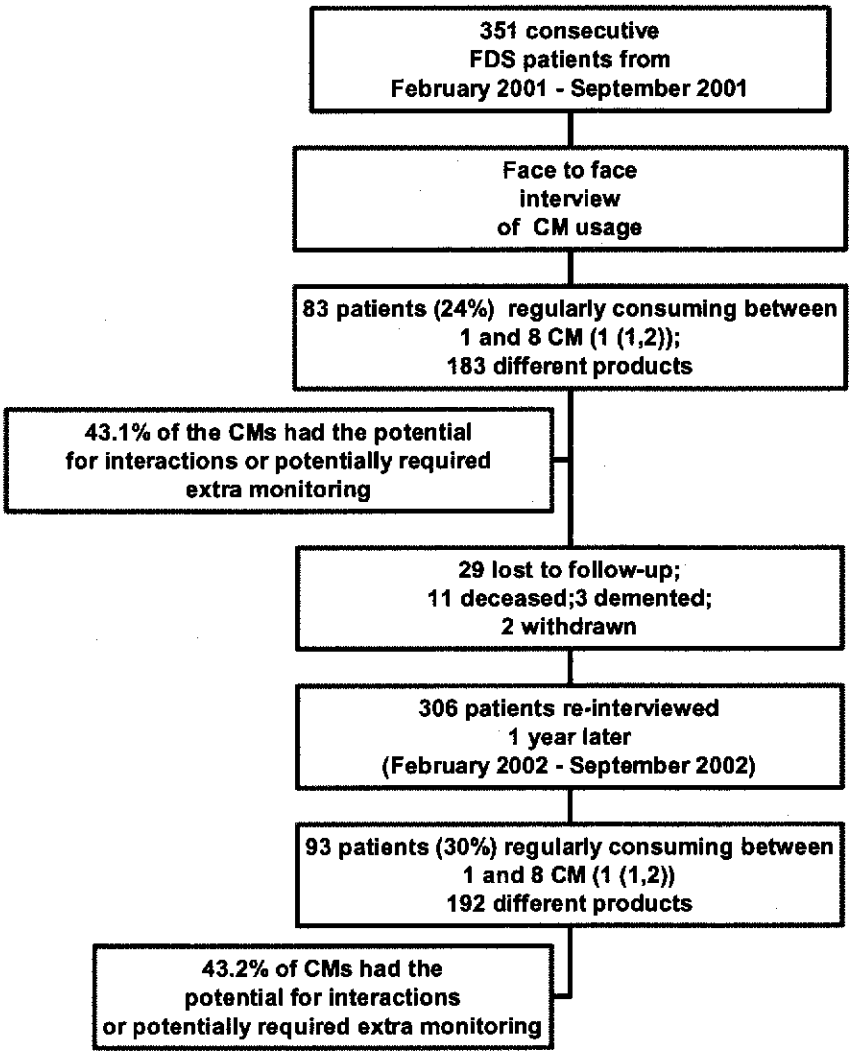


Figure 5.1: Consort diagram showing patient numbers at key time-points in the study between recruitment and close-out

Table 5.4: CMs used at study entry and at one year with potential interaction or potential increase in monitoring data.

	Study entry n=83	12 months n =93	Potential interaction or potential increase in monitoring
Multivitamins	21	21	No
Omega- 3 fatty acids	17	17	Yes
Vitamin C	15	15	No
Garlic	14	13	Yes
Vitamin E	11	11	Yes
Vitamin B	9	11	No
Calcium	8	8	No
Chromium	6	8	Yes
Glucosamine	9	8	Yes
Gingko biloba	5	5	Yes
Folic acid	3	4	No
Magnesium	3	4	No
Herbal laxatives (various)	1	4	No
Zinc	5	4	No
Evening primrose oil	4	4	No
Psyllium	0	3	Yes
Horseradish	3	3	No
Iron	3	3	No
Antioxidants	3	2	No
Lecithin	3	3	No
Amino acids	2	2	No
Celery seed oil	2	2	No
Chinese medicines	2	2	Unknown
Slippery elm	2	2	No
Fenugreek	2	2	Yes
Acidophilus	2	2	No
Ginseng	1	1	Yes
Echinacea	1	1	Yes
Homeopathic	1	1	Unknown
Linseed	1	1	Yes
Saw Palmetto	1	1	Yes
Selenium	1	1	No
St John's Wort	1	1	Yes
Valerian	1	1	No
Wheat grass juice	1	1	Yes
Gotu cola (Brahmi)	1	1	Yes
Herbal tea (unknown ingredients)	1	1	Unknown
Pumpkin seeds	1	1	No
Charcoal	1	1	Yes
Kelp	2	1	Yes
Shark cartilage	1	1	Yes
Dandelion	1	1	Yes
Eucalyptus	1	1	Yes
Potentiate bee pollen	1	1	Unknown
Cider vinegar	1	1	No
Radish	1	1	No
Carrot (concentrated juice)	1	1	No
Wheat germ	1	1	No
Barley	1	1	No
Amaranth	1	1	No
Red Clover	1	1	Yes
Tea tree oil	1	1	No
Noni juice	1	1	Yes
Ginger	0	1	Yes
Policosanol	0	1	Yes
Total	**183**	**192**	

Table 5.5: Details of CMs with potential interactions and potential monitoring requirements

CM	No. and (%) of CM users Study entry	No. and (%) of CM users 12 months	Main/purported actions	Main adverse effects	Potential monitoring in a diabetic patient
Fish-Oil/omega-3 fatty acids[358, 404, 405]	17 (20)	17 (18)	Lowers triglycerides LDL levels may increase Anti-inflammatory Anti-platelet Hypotensive	Worsening of glycaemic control possible in type 2 DM patients Prolonged bleeding time Vitamin A and D toxicity (in high doses)	INR (anticoagulant potentiation) Glycaemic control (decreases and increases in blood glucose levels have been reported) Serum triglycerides Serum LDL Vitamin A and D levels (with high doses) BP
Garlic[361, 362]	14 (17)	13 (14)	Antispasmodic Antiviral Hypotensive Hypocholesterolaemic Hypoglycaemic	Prolonged bleeding time at high doses	INR (anticoagulant potentiation) Glycaemic control (decreases blood glucose levels) Lipid levels BP
Vitamin E[89, 406, 407]	11 (13)	11 (12)	Antioxidant	Anti-platelet (high doses); prolonged bleeding time	INR (anticoagulant potentiation)
Glucosamine[359, 360]	9 (11)	8 (9)	Osteo-arthritis	Nausea, flatulence, diarrhoea, leg oedema, "heavy" legs and skin reactions Avoid in patients with seafood allergy	Glycaemic control (theoretically increases blood glucose levels) Question patient regarding seafood allergy
Chromium [251, 252, 408-411]	6 (7)	8 (9)	Introduction of chromium to a stable diabetic regimen may result in decreased insulin requirements and changes to OHA requirements	Gastrointestinal disturbances, anaemia and renal failure	Glycaemic control (may decrease blood glucose levels)
Ginkgo biloba[363, 412-414]	5 (6)	5 (5)	Cerebral insufficiency Peripheral vascular disease	Prolonged bleeding time Gastrointestinal disorders	INR (anticoagulant potentiation)

CM	No. and (%) of CM users Study entry	No. and (%) of CM users 12 months	Main/purported actions	Main adverse effects	Potential monitoring in a diabetic patient
Psyllium[415-417]	0 (0)	3 (3)	Laxative Hypotensive Hypoglycaemic Hypocholesterolemic	Potential to bind other medications – take at least 2 hours apart from other medications Take with plenty of fluid to avoid intestinal obstruction Allergic reactions have been reported	Glycaemic control (may decrease blood glucose levels) BP Potential for binding other medication Lipid levels
Fenugreek[416, 418]	2 (2)	2 (2)	Hypocholesterolaemic Hypoglycaemic	Potential to bind other medications – take at least 2 hours apart from other medications	INR (anticoagulant potentiation) Lipid levels Glycaemic control (may decrease blood glucose levels) Possible interaction with monoamine oxidase inhibitors (MAOIs) Potential for binding other medication
Ginseng[416, 418]	1 (1)	1 (1)	Hypoglycaemic General health; immune stimulant effects	Hypertension Nervousness Diarrhoea Androgen effect Gynaecomastia	Glycaemic control (may decrease blood glucose levels) BP Potentiates digoxin Potential for interaction with MAOIs INR (anticoagulant potentiation)
Echinacea[417, 419]	1 (1)	1 (1)	Respiratory tract infections	Anaphylaxis Hepatotoxicity	Liver function tests (care with other hepatotoxic drugs e.g., methotrexate, ketoconazole)
Linseed (flaxseed)[420]	1 (1)	1 (1)	Laxative Hypocholesterolemic	Potential to bind other medications – take at least 2 hours apart from other medications Contain high levels of omega-3 fatty acids (see omega-3 fatty acids)	Potential for binding other medication Lipid levels INR (anticoagulant potentiation)
Saw Palmetto[416, 421]	1 (1)	1 (1)	Prostatic hypertrophy Stimulates sexual vigor Anti-androgen and oestrogenic activity	Gastrointestinal upsets Headaches Diarrhoea	Possibility of increasing the risk of intra-operative bleeding May interfere with hormonal therapies such as the contraceptive pill and hormone replacement therapy (rarely used in females though)

CM	No. and (%) of CM users Study entry	No. and (%) of CM users 12 months	Main/purported actions	Main adverse effects	Potential monitoring in a diabetic patient
St John's Wort [237-242, 245]	1 (1)	1 (1)	Depression Diuretic Insomnia	Gastrointestinal upsets Allergic reactions Photosensitivity Inhibition of sperm motility Dry mouth Dizziness Constipation	INR (anticoagulant potentiation) Many drug interactions including: MAOIs and selective serotonin reuptake inhibitors (SSRIs), known photosensitisers, digoxin, theophylline, cyclosporin, indinavir, amitriptyline, nortriptyline and many others (see references for a complete list)
Gotu cola (brahmi)[364, 416, 422]	1 (1)	1 (1)	Improves memory Anti-stress/ anti-anxiety	Photosensitivity Hyperglycaemic Hypercholesterolemic	Glycaemic control (may cause hyperglycaemia) Lipid levels
Charcoal[423]	1 (1)	1 (1)	Reduction of flatulence	Abdominal pain Nausea and vomiting Constipation Binds to other medications	Binds to medications – patients should be advised to take other medications 2 hours apart from charcoal
Kelp[424]	2 (2)	1 (1)	Thyroid disorders Obesity Arthritis Constipation	Can induce or exacerbate hyperthyroidism (high iodine content) Prolonged ingestion can reduce iron absorption High sodium content can adversely affect individuals with restricted sodium intake High potassium content	INR (anticoagulant potentiation) Can reduce the effectiveness of diuretics due to high sodium content Monitor thyroid function due to high iodine content Monitor potassium levels due to high potassium content
Shark cartilage[425, 426]	1 (1)	1 (1)	Anti-cancer Arthritis Hypertension	Gastrointestinal Hepatitis Hypercalcaemia	Liver function tests (care with other hepatotoxic drugs e.g., methotrexate, ketoconazole) Calcium levels may increase
Dandelion[416, 424]	1 (1)	1 (1)	Hypoglycaemic Diuretic Laxative Arthritis	Allergic reactions Gastric hyperacidity	Glycaemic control (may decrease blood glucose levels) INR (anticoagulant potentiation)
Eucalyptus[416]	1 (1)	1 (1)	Hypoglycaemic	Extreme caution in overdose – a dose of 3.5mL has proved fatal	Glycaemic control (may decrease blood glucose levels)

CM	No. and (%) of CM users Study entry	No. and (%) of CM users 12 months	Main/purported actions	Main adverse effects	Potential monitoring in a diabetic patient
Red clover[416, 424]	1 (1)	1 (1)	Menopausal symptoms Hypocholesterolemic	Allergic reactions – rash possible Oestrogenic properties – may cause vaginal spotting	INR (anticoagulant potentiation) Lipid levels Due to oestrogenic properties may have an additive effect with hormone replacement therapy or oral contraceptives May antagonise the anti-tuomor effects of anti-oestrogenic drugs e.g., tamoxifen Theoretical evidence of inhibition of cytochrome P450
Noni Juice[427, 428]	1 (1)	1 (1)	Hypoglycaemic Builds immunity	Hyperkalaemia Diarrhoea	Potassium levels (ma increase) Glycaemic control (may decrease blood glucose levels) Caution: some brands may be high in sugar
Wheat grass[424]	1 (1)	1 (1)	Hypoglycaemic Anti-cancer Hypertention Builds immunity		Due to the vitamin K content, wheatgrass may decrease the anticoagulant effect of warfarin
Ginger[416, 417, 424]	0 (1)	1 (1)	Anti-nauseant Gastrointestinal upsets Hypoglycaemic	Abdominal discomfort Heartburn Diarrhoea Irritant in the mouth and throat	INR (anticoagulant potentiation) Glycaemic control (may decrease blood glucose levels)
Policosanol[424]	0 (0)	1 (1)	Hypocholesterolemic	Erythema Migraines Insomnia Weight loss Nose and gum bleeding	INR (anticoagulant potentiation) Lipid levels

5.4.3 COSTS OF CMS

The median amount spent per month at study entry and at 12 months was $11.34 (Table 5.6). Costs were calculated from the amount used per month (reported by the patient) and the current price listed by the relevant company for each CM.

Tables 5.6: Costs of CMs per patient over time. Data are median (IQR).

	Study entry	Visit2	Non users
Cost ($)/month	11.34 (4.32, 25.47)	11.34 (3.98, 22.61)	0

5.4.4 SOURCES OF RECOMMENDATION AND PLACE OF PURCHASE

The sources of recommendation for the use of CMs are summarized in Table 5.7. Only a small number of patients were using CMs on the recommendation of a community pharmacist. Over 50% of patients decided to use CMs themselves or on the advice of a friend or a relative and did not seek the advice of a HCP. GPs were recommending the use of CMs in approximately 20% of users.

The places of purchase for CMs can be seen in Table 5.8. Over 50% of patients purchased their CMs from pharmacist. The next most common purchase point was health food shops.

Table 5.7: Sources of recommendation for the use of CMs

	Study entry n=83 n (%)	**12 months n =93 n (%)**
Friend/relative	24 (29)	30 (32)
Self	22 (27)	27 (29)
GP	20 (24)	17 (18)
Pharmacist	7 (8)	6 (6)
Reading material	6 (7)	5 (5)
Medical specialist	1 (1)	2 (2)
Dietitian	1 (1)	2 (2)
Radio/TV	1 (1)	2 (2)
Health food shop owner	1 (1)	1 (1)
Chiropractor	0 (0)	1 (1)
Naturopath	0 (0)	1 (1)

5.8: Purchase points for CMs

	Study entry n =83 n (%)	**12 months n =93 n (%)**
Pharmacy	47 (57)	53 (57)
Health Food Shop	19 (23)	21 (23)
Own produce	1 (1)	1 (1)
Mail order/internet	6 (7)	4 (4)
Chinese herbalist	1 (1)	-
Supermarket	7 (8)	10 (11)
Naturopath	2 (3)	3 (3)
Friend	-	1 (1)

5.4.5 REASONS FOR USE

Patients were asked the main reason that they were consuming CMs (Table 5.9). The majority were taking CMs to improve their general health (approximately 50%). The next most common reason for use was arthritis, followed by diabetes. There were no significant differences in "reasons for use" across time.

Table 5.9 Main reason for taking CMs

	Study entry n=83 n (%)	**12 months n =93 n (%)**
General health	41 (49)	51 (55)
Arthritis	7 (8)	10 (11)
Diabetes	7 (8)	6 (6)
Cholesterol lowering	2 (2)	4 (4)
Osteoporosis	4 (4)	1 (1)
Heart	2 (2)	2 (2)
Memory	2 (2)	1 (1)
Pain relief	2 (2)	2 (2)
Antispasmodic	2 (2)	2 (2)
Circulation	1 (1)	1 (1)
Laxative	1	3 (3)
Cramps	1	2 (2)
Anaemia	1	1 (1)
Thrush	1	1 (1)
Allergy	1	1 (1)
Prostate	1	1 (1)
Ulcerative colitis	1	1 (1)
Weight loss	1	1 (1)
Insomnia	1	-
Skin condition	1	1 (1)
Bowel problem	1	1 (1)
Cancer	-	1 (1)

5.4.6 REASONS FOR NOT TAKING CMS

Patients who did not consume CMs were asked whether there were reasons that they did not consume CMs on a regular basis (Table 5.10) Over two-thirds of patients at study entry and at 12 months reported "no reason" for not taking CMs. The remainder of patients did not consume CMs for a wide variety of reasons, including "taking enough medicine already", "fear" and "not believing in them". There were no significant differences across time in patients "reasons for not taking CMs".

Table 5.10: Reasons for not taking CMs (CM non users)

	Study entry (n=268) n (%)	**12 months (n=212) n (%)**
No reason	169 (63)	157 (74)
Happy with current treatment from GP	33 (12)	9 (4)
No need	22 (8)	13 (6)
Expensive	14 (5)	4 (2)
Takes enough medicine already	7 (3)	13 (6)
They don't work	7 (3)	1 (0.5)
Healthy	3 (1)	-
Don't believe in them	4 (1)	4 (2)
Fear	2 (1)	1 (0.5)
Don't like to	2 (1)	-
Unwise	1 (0.4)	-
Not sure of their role	1 (0.4)	-
Never thought about it	1 (0.4)	1 (0.5)
Interactions	1 (0.4)	4 (2)
Advised not to	1 (0.4)	1 (0.5)
Don't like medicine	-	3 (1.5)
Don't know about CMs	-	1 (0.5)

5.4.7 USE OF CAM PRACTITIONERS

Patients were asked if they regularly attend any CAM practitioners. In 2001, 3.7% were using a CAM practitioner on a monthly basis and this figure decreased to 2.6% in 2002. The most commonly used CAM practitioner was a chiropractor (Table 5.11).

Table 5.11: CAM practitioner use

	Study entry n =351 n (%)	**12 months n=305 n (%)**
Chiropractor	8 (2)	2 (0.007)
Naturopath	2 (0.01)	2 (0.007)
Accupuncturist	2 (0.01)	2 (0.007)
Relaxation therapist	1 (0.002)	1 (0.003)
Bowen therapy	1 (0.002)	0
Masseur	0	0
Homeopath	0	0
Reflexologist	0	1 (0.003)
Iridologist	0	0
Hypnotherapist	0	0
Positive imagery therapist	0	0
Aromatherapist	0	0
Herbalist	0	0

5.4.8 HEALTH-RELATED QUALITY OF LIFE AND CM USE

Two HRQOL tools were used to determine whether there were HRQOL differences between users and non-users. A diabetes specific tool was used (modified DQOL; Chapter 3; Section 3 3.2) and a general health QOL tool, the SF-36 (Table 5.12 and Table 5.13).

When reviewing the DQOL and the SF-36, there were no HRQOL differences between users and non-users. As there were no significant differences in HRQOL in the univariate statistics, multivariate analysis was not undertaken.

Table 5.12: Modified DQOL scores. Data are median (IQR).

	Users n=83	**Non-users n=268**	***P***
Satisfaction	1.7 (1.2, 2.1)	1.6 (1.3, 2.2)	0.95
Impact	2.1 (1.8, 2.4)	2.1 (1.8, 2.4)	0.77
Worry	1.7 (1.3, 2.5)	1.7 (1.3, 2.3)	0.46
Total	1.8 (1.5, 2.3)	1.8 (1.5, 2.2)	0.66

Table 5.13 SF-36 scores. Data are mean±sd.

	Users n=83	**Non users n=268**	***P***	**Norms for type 2 diabetes[316]**
Physical functioning	62±28	60±28	0.74	68
Role emotional	74±37	69±41	0.36	76
Role physical	53±43	57±43	0.53	57
Social functioning	83±22	79±24	0.21	82
Mental health	75±15	72±20	0.17	77
Energy/vitality	58±21	56±21	0.49	56
Bodily pain	65±27	66±28	0.84	69
General health	55±21	58±21	0.39	56

5.5 DISCUSSION

Consistent with previous studies performed in developed countries[223, 225, 234, 299, 308, 310] the univariate statistics showed that this group contained a disproportionately large number of females. Behavioural correlates were not explored in detail, but CM users were more likely to keep a diary of their home blood glucose test results even though the frequency of testing was similar to that amongst CM non-users. This suggests that concern about diabetes may have influenced CM use in the study sample. CM users were more likely to have never smoked, indicating that concern for their health may have influenced CM use in our sample.

Level of education and income were not predictors of CM use as seen in other large population based studies.[225, 234] The study data emphasized the unique nature of the FDS sample. Unlike other surveys (Chapter 1; Table 1.7), this study comprised elderly patients with diabetes with low levels of education and income.

Using a logistic regression model, that included all demographic and clinical characteristics and that adjusted for age and sex, people that had never smoked were twice as likely to be CM users. This was consistent with other surveys that show CM use was generally related to a more healthy lifestyle. [283, 293] However the CM users in this population were not more likely to exercise or consume less alcohol, which may be considered to be associated with a "healthier" lifestyle. People who spoke English at home were 3.5 times as likely to use CMs, which was consistent with other surveys in which English speaking patients were more likely to use CMs, in English speaking countries.[225, 290]

The results of the present study showed that approximately one quarter of patients with diabetes drawn from an urban community setting were using CMs. Nutritional supplements comprised the most frequently used CMs, and most of these were vitamins. A landmark population based study by Eisenberg and colleagues in the USA, that is widely referenced in the published literature did not include the self-prescribed use of vitamins, other than mega-vitamins, and so may have underestimated CM use.[234, 308] Australian studies that included the self-prescribed use of vitamins showed levels of usage of around 50% in younger, more educated subjects with higher annual incomes.[223, 225]

In societies with a nutritionally adequate diet, there are few data to support the regular use of vitamin supplements. Both the Heart Outcomes Prevention Evaluation Study[34, 35, 429] and the Heart Protection Study[430] found no cardiovascular benefit from the regular use of vitamin E, while the value of vitamin C supplementation remains unproven.[431, 432] Although chromium is claimed to improve glucose tolerance, there have been no randomised controlled trials that have confirmed this effect.[432] Of other commonly-used CMs in the present study, fish oil has strong evidence of potential benefit in a high vascular risk situation such as type 2 diabetes.[358, 405] While the effects of calcium supplementation on preservation of bone mass are well established[433] and glucosamine[371] may be of benefit for patients with arthritis these products were not taken specifically for diabetes or its complications. Overall, the majority of the CMs used by FDS patients were of unproven benefit.

Interactions between CMs and prescription medicines are probably under-reported and may go unrecognised, a situation that also applies for CM-disease interactions.[216, 237, 238, 240, 279] There are many reports in the literature of interactions, adverse effects and even fatalities associated with CM use.[237-245, 270, 274] Since the adverse effects of prescription medicines are more prevalent in elderly patients with multiple co-morbidities and complex drug regimens, it seems logical to expect that the elderly may be more susceptible to adverse effects from CMs.[434-437] Almost half of the patients in the present study were older than 70 years. In addition, almost half of the CMs used by FDS subjects had the potential to influence glycaemic control or other metabolic parameters. In the majority of these cases, severe problems were rare, but without a full medication profile including CMs, the prescriber may not, for example, be aware that the development of hyperkalaemia in a ramipril-treated patient was due to Noni Juice supplementation purchased over the internet; that increased falls in an elderly diabetic patient may be due to the mild hypotensive effect of garlic capsules; or that postoperative bleeding may have been worsened by Ginkgo Biloba.[361, 363, 414, 427, 428]

In the present study, it was found that this elderly cohort were spending approximately $11/month on CMs in 2001 and in 2002. Approximately 90% of this sample had incomes of less than $40000/annum. In 1992, respondents to the South Australian Omnibus Survey were spending between $1 and $500, with a median expenditure of $10/month on CMs.[225] Only 27% of the population in the MacLennan survey were over 55 and 29% were on "low incomes" (as assessed in 1993). At this time the age-sex standardised expenditure on CMs for

the Australian population was $621 million per year. This compared to $360 million for patient contributions for all classes of PBS drugs purchased in Australia in 1992/93. The 2001/2002 figure for patient contributions to the PBS was $800 million and it has been recently estimated that Australians spend $2.3 billion per annum on CMs and CAM.[438] There have been no recent Australian studies that have accurately estimated the annual cost of CM use, or reviewed expenditure in different patient groups.

The trends in advice and purchase point were similar over time and only small numbers of patients consulted general practitioners, pharmacists or medical specialists about the use of CMs. This issue needs to be addressed by educating patients to discuss the use of CMs with HCPs and educating HCPs to ask patients about CM use.

While less than 10% of patients consult community pharmacists about the use of CMs, over half of the patients purchased their CMs from a pharmacy. This unique opportunity needs to be fully utilised and community pharmacists need to take the opportunity to talk to the patients about the use of CMs, keep a full medication history, advise them on interactions (drug and disease), advise them on whether the particular product has an evidence base to justify its use and ask the patient to report back any adverse effects. This would be a very time consuming task due to the high level of CM usage in the community. Perhaps the first task could be to identify high-risk patients (such as elderly patients with diabetes on multiple prescription medicines) and begin this process with them. The HMR program in Australia[200] could provide a unique opportunity to review CM use of DM patients in their home and ask to see the products that are actually being used. Education could then be provided on the scientific basis for the use of the product, potential interactions and potential adverse reactions.

Of some concern was that patients were ordering CMs by mail or over the internet, sources that are largely unregulated and that have no requirement for provision of product information. A recent article reviewing internet marketing of herbal products concluded that "consumers may be misled by vendor's claims that herbal products can treat, prevent, diagnose, or cure specific diseases, despite regulations prohibiting such statements." [439] It is likely that with the increasing use of the internet, this source of supply will increase, although because of the small patient numbers an increase was not seen over the year of the study. It

must be remembered that the present FDS sample tend not to use technology as much as younger people with better access to computers and the internet, but even in this elderly group between 4 and 7% were using this technology. It was also of concern that approximately 10% of patients purchased their CMs from a supermarket, which again provides no opportunity for medication review.

Given these trends, one way to combat inappropriate or potentially hazardous use of CMs is for HCPs, especially general practitioners and pharmacists, to ascertain and document CM use in all patients. This would necessitate making CMs "pharmacy only", so that the consumer has some protection from adverse outcomes and misleading scientific claims. Several of the Australian OCM key considerations would be fulfilled by this strategy, including increased post-marketing surveillance and the strengthening of adverse drug reaction reporting.[235, 248] The AMA has also called for CMs to be made "pharmacy only" products.[256] If pharmacists were to be made the sole custodians of CMs, undergraduate and postgraduate training in this area would need to be reviewed to ensure pharmacists have the appropriate knowledge to take on this responsibility. Interestingly, it was evident from the present study that consumers choose pharmacists as their purchase point over 50% of the time.

Patients consume CMs for a large variety of reasons and most consume vitamin products to improve their "general health". It was not surprising that around 10% of this elderly population were consuming products for arthritis, the most common one in this study being glucosamine. There is mounting evidence that glucosamine is effective in arthritis[371] and it is a logical alternative for patients in whom NSAIDS are contraindicated.

Approximately 7% of patients were consuming products specifically for their diabetes, the most common one in this study being chromium. Chromium is an essential nutrient involved in normal carbohydrate and lipid metabolism. It has been postulated that the chromium requirement increases with increased glucose tolerance and diabetes, while insufficient dietary intake has been associated with type 2 DM.[408, 410] At present there are no standardised biochemical tests which, provide a valid assessment of chromium status. There are no randomised controlled trials in the literature and until such studies are carried out, chromium supplementation should not be recommended in patients with diabetes.[252]

The landmark population-based survey that reviewed use of CAM practitioners in Australia in 1993 reported that 20.3% of respondents had visited at least one CAM practitioner in the previous 12 months.[225] This was the first study in Australia to address CAM practitioner use in patients with diabetes. The usage rate in the present study was low, perhaps because of the large cost of attending such practitioners and the generally low incomes of the FDS sample. It also emphasised the finding that the use of CMs was generally self-initiated by the patient, or suggested by a friend or relative and not by a CAM practitioner.

There were no differences in HRQOL for any of the dimensions in either the DQOL or the SF-36. Users of CMs presumably do so to improve their health and have a positive impact on their HRQOL. This present study showed that CM users do not enjoy a better HRQOL in any dimension compared with non-users. There are studies that have looked at individual CMs to review HRQOL during treatment[440] but no other studies have been identified in the literature that address HRQOL differences between users of CMs and non-users. A recent Australian study by Adams and colleagues[315] found that CAM users have a lower HRQOL in all dimensions of the SF-36 than non-users however this study did not specifically review HRQOL in CM users and non-users.

In the present study, the SF-36 dimensions were lower than the published type 2 diabetes norms for six of eight dimensions and equal for two dimensions.[316] The norms were presented for patients with a mean age of 60 (56% female). In the present study, patients were older (68) with 55% being male. The older age may explain the poorer HRQOL as HRQOL normally decreases with age.[316]

Jacobson and colleagues[357] evaluated DQOL with the SF-36 in a group of two hundred and forty patients. The study showed that the DQOL and the SF-36 surveys both provided reliable and valid results. The DQOL seemed more sensitive to lifestyle issues, whereas SF-36 provided more information about functional health status. The study showed that the DQOL measure exhibited consistency in type 2 DM patients and confirmed that SF-36 also had internal consistency in type 1 and type 2 DM patients and that the two study tools used to compare HRQOL in users and non-users of CMs in the present study were appropriate.

Patients in the present study took CMs predominantly to improve their "general health", however their consumption was not followed with an improvement in their HRQOL. This was an important finding. There was also a lack of scientific evidence for many of the CMs that patients were consuming[432, 441-444] and the lack of improvement of HRQOL may be a reflection of the lack of efficacy of the CMs. Patients however continue to self-prescribe CMs and spend a reasonable amount of money on products that do not improve their HRQOL.

5.6 LIMITATIONS

- Surviving FDS patients who voluntarily returned for their annual diabetes review were included, and these were younger and had shorter duration of disease than those in the full FDS cohort, and were more likely to be AC. Even though there was no independent effect of age or diabetes duration on CM use, it was possible that the higher proportion of AC patients led to an overestimate of CM use.
- Despite clear prior instructions, less than one quarter of the patients brought in their CMs to their interview and recall bias may have influenced the findings. Follow-up phone calls were made in the event of any uncertainty, but there remains some risk that the medication records were incomplete.
- The logistic regression model included all relevant demographic and clinical characteristics that were identified in data collection and that seemed relevant to the current study after a review of the literature. There may be other factors that are important as "predictors" or factors associated with CM use that were not collected in the present study. Examples may include the consumption of tea or coffee or the type of diet followed by the patient. It was not possible to collect every patient detail, and this must be recognised as a limitation to the logistic regression model.

5.7 RECOMMENDATIONS

- A larger community based study reviewing the potential drug-CM and disease-CM interactions that have been identified in the present study is required and should review which of the identified potential drug and/or disease interactions are of clinical importance. This could initially be done via the HMR program[200] and would involve reviewing full medication histories and following up patients to review actual and potential adverse drug reactions and actual and potential drug-CM and disease-CM interactions.
- The present study found that CMs were widely used in the Australian community. Patients regularly self-prescribed CMs and there was often no involvement of a HCP to review potential drug-CM or disease-CM interactions or to advise the patient of the evidence base for the use or otherwise of the CM. Pharmacists are in the ideal position to be to sole retailers of CMs and consideration should be give to restricting CMs to "pharmacist only" products. This would allow two important issues to be addressed;
    - The pharmacist could compile full medication histories to help identify potential and actual problems
    - An adverse drug reaction database that incorporates CMs could be established

  Funding would be required in this area to allow pharmacists the time to compile full medication histories and establish an adverse drug reactions database. This could be done initially as part of the HMR program and then be extended to the wider community.
- The number of randomised controlled trials involving CMs has increased in the last few years and this is an important trend. This trend must continue, especially where CMs are used for specific disease states. For example, 8% of the present sample were using chromium for diabetes, however there is no evidence base to support the use of this CM in diabetes. Funding should be sought to allow further well-designed trials to develop an evidence-based approach to the use of CMs.

CHAPTER 6

CONCLUSION

Diabetes mellitus is increasing in prevalence and is commonly associated with prolonged ill health and premature death.[9] It is clear that diabetes care needs to be improved in the Australian setting.[103, 214, 215] In addition to tertiary care for patients with diabetes, there is a need for simple programs to be implemented in the community that allow the benefits of improved metabolic and BP control to be realised more widely.[394, 324] As Australia is a multi-ethnic society, there is also a need to develop ethnic specific programs. A large Australian study concluded that diabetic complications were not well managed in the Australian population and that clinical care and education programs which recognised and targeted the different needs of specific ethnic groups may be the key to reducing diabetes complications.[324] PC is a process through which a pharmacist co-operates with a patient and other health professionals in designing, implementing and monitoring a therapeutic plan that can produce specific outcomes, such as improving glycaemic control in DM patients.[126] Ethnic considerations should also be incorporated into PC plans.

The initial retrospective investigation of data from a community-based cohort of patients with diabetes living in an urban Australian setting, found that SE patients were twice as likely to be on insulin compared with AC patients. It is presently unknown why more SEs progress to insulin than ACs. The reasons why more SE patients remain in the poorly controlled range (as measured by HbA_{1c}) despite the greater use of insulin still remains unanswered. There is a paucity of information in the literature addressing patient and physician specific factors that may have resulted in the difference in insulin use and glycaemic control between SEs and ACs. Patient factors may include preference for or fear of insulin therapy and physician factors may include pressures from patients either to initiate or not initiate insulin. This information needs to be researched to endeavour to improve the management of DM in specific ethnic groups in Australia and incorporate ethnic specific factors into PC programs.

The pilot PC program was carried out in "high-risk" DM patients attending a hospital outpatient clinic. In the PC arm of the study, a clinical pharmacist reviewed and monitored all aspects of the patients' drug therapy in collaboration with other HCPs at six weekly intervals

for six months. The control patients received usual outpatient care. The PC program provided patients with important medication information and resulted in changes to drug therapy. The medication review process highlighted a high level of complementary medicine use in this population. The pilot program also indicated the need to collect further demographic information including duration of diabetes, presence of complications and ethnicity. In addition all end points relevant to DM care including lipid levels, BP, microalbuminuria and BMI need to be reviewed. One diabetes specific HRQOL tool was used in the pilot program but multiple HRQOL tools should be used to more thoroughly address HRQOL in DM patients. These factors were subsequently incorporated into the larger community-based PC program.

The main findings of the community-based prospective PC program demonstrated that a PC program in type 2 DM patients was associated with beneficial reductions in modifiable vascular risk factors. There were improvements in glycaemic control and BP and these improvements persisted after adjustment for key demographic variables and intensification of pharmacotherapy. In addition the PC program was associated with a significant reduction in the 10-year risk of having a CHD event, for patients with no previous CHD events. The beneficial outcomes in the present study were due to the addition of a pharmacist to the care of community-based type 2 DM patients. The research sought to develop a simple but multifactorial PC program that would provide maximum benefit to the patient, with minimum impact on their daily lives. The PC program was also designed to facilitate communication between the patient, the general practitioner, the pharmacist and other relevant HCPs to raise awareness of the patients' medications, diabetes and associated co-morbidities. The beneficial changes seen may be due in part to this enhanced communication.

The simple PC program consisted of three major factors. One was the provision of a patient-specific medication profile, which was updated on a regular basis according to the needs of the patient. The medication profile was designed to give the patient clear instructions and guidelines on the use of their medications, with the goal of improving compliance and reducing confusion over medications. The relevant treatment goals were listed on the profile, with the aim of reminding patients to try and achieve their treatment goals. Importantly, the profile served as a communication tool between the pharmacist, patient, the general practitioner and other relevant HCPs. The second was using the telephone as a means of

communication, so that DM care issues could be addressed without undue disruption for the patient. This simple means of regular patient contact meant that the patients only had to attend the diabetes clinic for two visits in the 12-month intervention period. The third factor was the provision of individualised patient education, which was followed up with written education to reinforce the relevant messages. Easily accessible pamphlets from Diabetes Australia and the National Heart Foundation of Australia were used along with a regular newsletter written by the clinical pharmacist that targeted issues raised by many patients during individualised telephone education sessions.

This simple program could be easily used in the context of the current HMR program.[200] In Australia, this service exists to review all aspects of medication use in the patients' home environment and requires a referral to an accredited pharmacist from a general practitioner. The HMR program only allows one review per year, except where there are significant changes to the patients' drug therapy, a situation which may commonly apply to DM patients due to the chronic and progressive nature of the disease. However, the HMR process results in medication management plan and it is intended that this "plan" should be an active document which, is reviewed on an ongoing basis by both the community pharmacist and the general practitioner.

Based on the present study and other PC studies in patients with diabetes,[181, 209, 397] patients with diabetes do need frequent follow up to maintain improvements in metabolic parameters as the disease progresses. This study successfully used the telephone and newsletters as an additional means of communication and this could be incorporated into HMR programs. Using this methodology, this service could also then be offered to DM patients in rural and remote areas.

The PC program targeted two large ethnic groups in the Australian community, however patient numbers were too small to detect potential differences in outcomes between ethnic groups. While the Australian Aboriginal population has been widely studied with respect to complications and treatment of DM,[106, 109] there is a paucity of information on DM treatment in relation to other ethnic groups in Australia and there is a need to address this issue in ethnicity specific PC programs.

The pilot PC program found that patients with diabetes were consuming CMs. As the prevalence of CM consumption in patients with diabetes had not been reported in Australia, a sub-study determined both the range of CMs and their frequency of use in a community-based sample. Demographic and diabetes-specific factors associated with CM use were also assessed, together with their potential clinical impact. Approximately one quarter of the 351 patients with diabetes in the study were taking at least one CM and, of these, almost half were potentially at risk of a CM-related adverse effect. The sub-study found that patients regularly self-prescribe CMs and there is often no involvement of a HCP to review potential drug-CM or disease-CM interactions or to advise the patient of the evidence base for the use or otherwise of the CM. As such, it is recommended that pharmacists lobby the government to restrict CMs to "pharmacist only" products. Pharmacists are in an ideal position to be the sole retailers of CMs as they have the expertise to monitor these potential drug-related problems. Subsequently a larger community based study reviewing the potential drug-CM and disease-CM interactions that have been identified in the present study could be carried out with the purpose of identifying which of the potential drug and/or disease interactions are of clinical importance. This could initially be done as a study via the HMR program[200] and would need to involve reviewing full medication histories and following up patients to review adverse drug reactions and drug-CM and disease-CM interactions.

The number of randomised controlled trials involving CMs has increased in the last few years. This important trend must continue, especially where CMs are used for specific disease states. For example, 8% of the present sample were using chromium for diabetes, however there is no evidence base to support the use of this CM in diabetes. Funding should be sought to allow further well-designed trials to develop an evidence-based approach to the use of CMs.

The pharmaceutical care model was established to provide a framework by which drug use could be improved to enhance patients' clinical and health-related quality of life outcomes. For the present study, a straightforward pharmaceutical care program was adapted from a hospital setting to a community setting, where the principal requirement was a clinical pharmacist who had completed a self-directed diabetes-training program. In this context, clinically relevant parameters improved over the course of the study period. Pharmaceutical care programs such as this can begin the process of translating the findings of large and expensive clinical trials into standard clinical practice.

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APPENDIX 1

FDS INTERVIEW

D1. Have you changed your Blood Sugar Monitoring in the last 12 months in any way? 1=Y, 2=N

If Yes, How have your changed?

1. I have started my monitoring when before I didn't.
2. I have stopped my monitoring when before I did.
3. I have increased frequency of my monitoring.
4. I have decreased frequency of my monitoring.
5. Other (Please specify below)

If monitoring Blood Sugar:

Who does the blood tests? ☐

1. Self
2. Relative or friend
3. Medical Practitioner/Nurse
4. Other (Please specify below)

How often? ☐ times/week

If No, Why Not

1. Never been taught.
2. Fear of procedure
3. Physical disability
4. Lack of confidence
5. Lack of motivation
6. Prefer urine testing
7. Other (Please specify below)

D2. How many times are a week are you advised to measure your blood glucose levels?

[ ] Times/Week

D3. During the past week, what have your lowest and highest blood sugar level readings been?

1. As below
2. Don't know
3. Not applicable

	Before Meals	**After Meals**
Lowest	----------	----------
Highest	----------	----------

D4. Do you test your urine for glucose at home .
If yes, how often. [ ] 1=Y, 2=N

D5. How many times a week are you advised to measure your urine glucose level?
times/week [ ]

D6. Do you keep a diary of your diabetic monitoring? [ ]
1=Y, 2=N

D7 How are you currently advised to control your diabetes?

1. Diet only
2. Tablets
3. Insulin

[ ]

	Type	**Dose**	
Tab. 1	[ ]	[ ]	tab/day
Tab. 2			tab/day
Insulin 1	[ ]	[ ]	Units AM
			Units Lunch
			Units PM
Insulin 2			Units AM
			Units PM

How often do you currently take insulin or tablets? [ ]

1. As prescribed
2. Occasionally miss dose
3. Regularly miss dose
4. Not applicable

D9. Have you seen a dietitian for advice in relation to diabetes in the last 12 months? ☐ 1=Y, 2=N.

If yes. When was the last time you saw a dietitian?

D10 How well do you follow a recommended diet?

1. I only eat food which is recommended in my diet
2. I occasionally eat food not recommended in my diet
3. I regularly eat food not recommended in my diet.
4. I don't have any dietary advice to follow.

☐

D11. In the last 12 months how often have you been to your GP in relation to your diabetes? ☐ times

D12. In the last 12 months how often have you been to an outpatient clinic or medical specialist in relation to your diabetes. times ☐

D13. What examinations have you had specifically for your diabetes in the last 12 months.

1.	Ophthalmology	----------
2.	Blood Pressure	----------
3.	Examined feet for pulses	----------
4.	Sensory motor testing	----------
5.	Cardiac auscultation	----------
6.	Blood tests	----------
7.	Urine tests ...	----------
8.	Electrocardiogram	----------
9.	Other (Please specify below)	

☐

D15. Have you attended a Diabetic Outpatient Clinic in the last 12 months?

☐ 1=Y, 2=N

☐ Month/Year

D16. Have you attended a course or obtained advice from Diabetic Education Centre or Diabetes Association in the last 12 months? 1=Y, 2=N

☐ Month/Year

D17. Have you in the last 12 months received advice or treatment for foot care ?

☐ 1=Y, 2=N

If Yes, who gave you this advice or treatment?.

1. GP ☐
2. Hospital Doctor or Nurse ☐
3. Podiatrist ☐
4. Other Specialist ☐
5. Diabetes Education Centre ☐
6. Diabetes Association ☐
7. Other ☐

☐

D18. Have you been given an exercise programme for your diabetes in the last 12 months ?
1=Y, 2=N.

If yes. Who gave you this exercise programme?

1. GP ☐
2. Hospital Doctor or Nurse ☐
3. Physiotherapist ☐
4. Other Specialist ☐
5. Diabetes Education Centre ☐
6. Diabetes Association ☐
7. Other ☐

☐

D19. In the past 2 weeks, did you engage in vigorous exercise which made you breathe harder, puff or pant?

☐ 1=Y, 2=N.

If yes. Please estimate total time spent exercising during past 2 weeks. ☐ hrs.

D20. In the past 2 weeks, did you engage in less vigorous exercise which did not make you breathe harder puff or pant ☐ 1=Y, 2=N.

If Yes. Please estimate the total time spent. ☐ hrs.

D22. How often do you drink alcohol.

1. Daily
2. 5-6 days a week
3. 3-4 days a week
4. 1-2 days a week
5. Less than once a week
6. Never

[ ]

When you do drink, how many do you usually have?

1 >20
2. 13-20
3. 7-12
4 5-6
5. 3-4
6. 1-2

[ ]

D23. Have you changed your tobacco consumption in the last 12 months?

[ ] 1=Y, 2=N.

If yes. How have you changed?

1. Stopped smoking.

WHEN DID YOU STOP SMOKING IN 19 [ ]

2. Started smoking.

AT WHAT AGE DID YOU START SMOKING? [ ] Year Old

[ ] cigs per day
cigars per week
grams tobacco per week
grams pipe per week
Increased daily consumption

3.

[ ] cigs per day
cigars per week
grams tobacco per week
grams pipe per week

4.

[ ] Decreased daily consumption.
cigs per day
cigars per week
grams tobacco per week
grams pipe per week

D27. Has your Doctor or other medical professional informed you of the special risks of smoking with diabetes in the last 12 months? ☐ 1=Y, 2=N

D28. Have you attempted to stop smoking through a "Quit Smoking" programme, Hypnosis or acupuncture in the last 12 months ?

☐ 1=Y, 2=N.

D29. Do you consider yourself overweight . ☐ 1=Y, 2=N.

D30. Have you been informed in the last 12 months that you are overweight ?. 1=Y, 2=N.

If you have, who informed you?

1. GP ☐
2. Hospital Doctor or Nurse ☐
3. Dietitian ☐
4. Other Specialist ☐
5. Diabetes Education Centre ☐
6. Diabetes Association ☐
7. Other ☐

☐

D31. Do you weigh yourself regularly ? ☐ 1=Y, 2=N.
If you do, How many times per month ☐ times/month

Not only are we interested in the type of care you receive we would also like to determine how difficult it is for you to obtain medical care. The next few questions address this matter

E1. How long does it usually take you to get to your GP?
(HOURS/MINUTES) ☐

E2. How long does it take you to get to the hospital diabetes clinic?
(HOURS/MINUTES) ☐

E3. What means of transport do you generally use to get to a doctor's appointment?

1 I drive myself
2 I get a family member or friend to drive me.
3. I use public transport
4. I cycle or walk
5. Other

☐

E4. In the past 5 years have you ever postponed or cancelled a doctor's appointment because you found it too difficult to arrange for an interpreter to attend (or for an interpreter to make the appointment)? 'Interpreter' in this case could be anyone who can communicate in English on you behalf (e.g. relative, friend, professional)?

In annual review in past 1 year

1. Yes, frequently
2. Yes, on occasion
3. No, an interpreter was always available when required.
4. No, the doctor speaks my language..
5. No, as I have no need for an interpreter.

☐

E5. Do you require health care at home to help you with the management and treatment of you diabetes (e.g. insulin injection, glucose test, etc.,)?

1=Y, 2=N ☐

If yes. Is health care usually available when you need it?

1. Not usually
2. sometimes
3. Most of the time
4. Always

☐

E6. As a result of you diabetes, do you require any assistance at home to help you with meals, house chores and other activities (e.g. meals on wheels, silver chain etc.,)?

1=Y, 2=N

IF YES:

Is assistance usually available when you need it?:

1. Not usually
2. Sometimes
3. Most of the time
4. Always

☐

E7 Have financial constraints (i.e. high cost, lack of money) prevented you from obtaining any of the following? (Select as many as are applicable. Type Y or N

If annual review in the last year.

1 ☐ Medical appointment
2 ☐ Treatment (e.g. insulin, tablets)
3. ☐ Diabetes monitoring devise. (e.g. to check blood/urine glucose levels)

Diabetes can sometimes lead to other complications. We would therefore like to find out if you have suffered any complications related to you diabetes. We will also ask you a few other questions about your general medical history and condition.

F1. Since the onset of your diabetes are you aware of having developed ;any of the following complications? For each complication selected state the year in which the complication was first diagnosed.

CONDITION	Y/N	YEAR FIRST DIAGNOSED
1. Cataract		
2. Glaucoma		
3. Retinopathy		
4. Kidney Dysfunction		
5. Loss of sensation/pain in feet/hands		
6. Angina/Heart attack		
7. Stroke		
8 .Claudication/Foot ulcers		
9 .Slow healing wound/infection		
10. Autonomic Neuropathy/impotence		
11. Other (Please specify below)		

F2. Since the onset of Diabetes how many times have you been hospitalised?
If annual review, in the last 12 months ? ☐ times

F3. Have you ever had a Hypoglycaemic episode?
If annual review: In the last 12 months ? ☐ 1=Y, 2=N

If Yes: How many times have you had a Hypoglycaemic episode, in the past year? (Times) ☐

F4. Have any of your relatives had any serious diseases or illnesses, other than Diabetes? Please indicates the relative type (Parent, Brother, Sister, Child) and illness for each occurrence.

If annual review: In the last 12 months?

Relative Type	Illness	Code
		1. Mother/Father 2. Son/Daughter 5. Brother/Sister

F5. Have you had or do you currently have any of the diseases listed below? Also specify any other serious illness you have or have had.

Illness	**Status**	**Code**
1. Hypertension	-----	Blank = Never had
2. Chronic Respiratory Disease	-----	C= Current
3. Cancer	-----	P= Past i.e. now cured
4. Gout	-----	
5. Arthritis	-----	
6. Others 'Please specify'	-----	

	Status

F6. Are you currently taking any medication other than for your Diabetes? If so, please give details below.

Medication	**(Qty)**	**Dose (Units)**	**Frequency**

Are you allergic to any drugs? If so, please give details below.

DIABETES COMPLICATIONS AND RELATED CONDITIONS

All of these questions relate to the medical history of the patient including the time before diabetes was diagnosed.

Current Status of Complication
C: Currently suffering
D: Developed in last year
P: Past/Remissive
I: Intermittent
BLANK: Never suffered

	Status
Angina	---
Cataract	---
Glaucoma	---
Retinopathy	---
Visual Disturbance (Double/Blurred)	---
Kidney Failure	---
Dialysis	---
Kidney Infection	---
Kidney Transplant	---
Kidney Removed	---
Kidney Stones	---
Gangrene	---
Callus/Ulcers/Lesions/Blisters/Infections	---
Impotent	---
Numbness/Tingling in Feet/Hands	---
Thyroid (hypo/hyperthyroidism)	---
Gall Bladder	---

	No. of Occurrences this year
Heart Attack	---------
Stroke	---------
Heart By-Pass	---------
Heart Operation (other)	---------
Grafts Legs/Feet	---------
Amputation	---------
Laser Treatment	---------
Lens Implantation	---------

How many operations have you had in the last year? ☐

Operation Description

APPENDIX 2

DIABETES QUALITY OF LIFE SURVEY

This further assessment examines your quality of life as a diabetic

(PLEASE CIRCLE ONE NUMBER FOR EACHA ITEM LISTED, DEPENDING UPON THE DEGREE OF SATISFACTION, IMPACT OR FREQUENCY YOU ASSOCIATE WITH THE ITEM – AS APPLICABLE)

	Very satisfied				Very dissatisfied
How satisfied are you with:					
The amount of time it takes to manage your diabetes?	1	2	3	4	5
The amount of time you spend getting check-ups?	1	2	3	4	5
The time it takes to determine Your sugar level?	1	2	3	4	5
Your current treatment?	1	2	3	4	5
Your knowledge about your diabetes?	1	2	3	4	5
Your social relationships and friendships?	1	2	3	4	5
Your sex life?	1	2	3	4	5
Your work, school and household activities?	1	2	3	4	5
The time you spend exercising?	1	2	3	4	5
Life in general?	1	2	3	4	5
	Never				***Always***
How often:					
Do you feel physically ill?	1	2	3	4	5
Does your diabetes interfere with Your family life?	1	2	3	4	5
Do you feel good about yourself?	1	2	3	4	5
Do you feel restricted by your diet?	1	2	3	4	5

	Never				*Always*
How often:					
Does your diabetes keep you from driving a car or using a machine?	1	2	3	4	5
Do you miss work, school, or household duties because of your diabetes?	1	2	3	4	5
Do you find that your diabetes interrupts your leisure-time activities?	1	2	3	4	5
Do you tell others about your diabetes?	1	2	3	4	5
Do you feel that because of your diabetes you go to the toilet more often than others?	1	2	3	4	5
Do you find that you eat something you shouldn't rather than tell someone that you have diabetes?	1	2	3	4	5
	Never				*Always*
How often do you worry about:					
Whether you will not get a job you want?	1	2	3	4	5
Whether you will be denied insurance?	1	2	3	4	5
Whether you will miss work?	1	2	3	4	5
Whether you will be able to take a vacation or a trip?	1	2	3	4	5
Whether you will pass out?	1	2	3	4	5
Whether you will get complications from your diabetes?	1	2	3	4	5

APPENDIX 3

PATIENT SATISFACTION SURVEY

This survey is completely confidential and will be processed by a person who is not your doctor or your pharmacist – so please be honest – there is no way of identifying your response and your response will not affect the treatment you receive. Please colour in the correct response with the pen provided. Colour in the appropriate circle like this ●. Do not tick the circle. If you make a mistake, put a cross over the circle and mark the correct response.

This survey is asking you questions about your HOSPITAL DOCTOR (diabetes specialist) and your HOSPITAL PHARMACIST. Please indicate how often you have had contact with these HOSPITAL health professionals over the LAST YEAR:

How often have you seen the following people over the **past year**?

	First visit today	Once	Twice	Three times	Four times	Five or more times
Hospital doctor (diabetes specialist)	O	O	O	O	O	
Hospital Pharmacist	O	O	O	O	O	

If this is your first visit to the hospital doctor AND hospital pharmacist today, you do not need to answer any more questions.

With the following questions please mark the response that best describes your opinion. If you HAVEN'T seen a regular hospital doctor or hospital pharmacist – simply mark "not applicable". Please rate your experience by colouring in one circle per line.

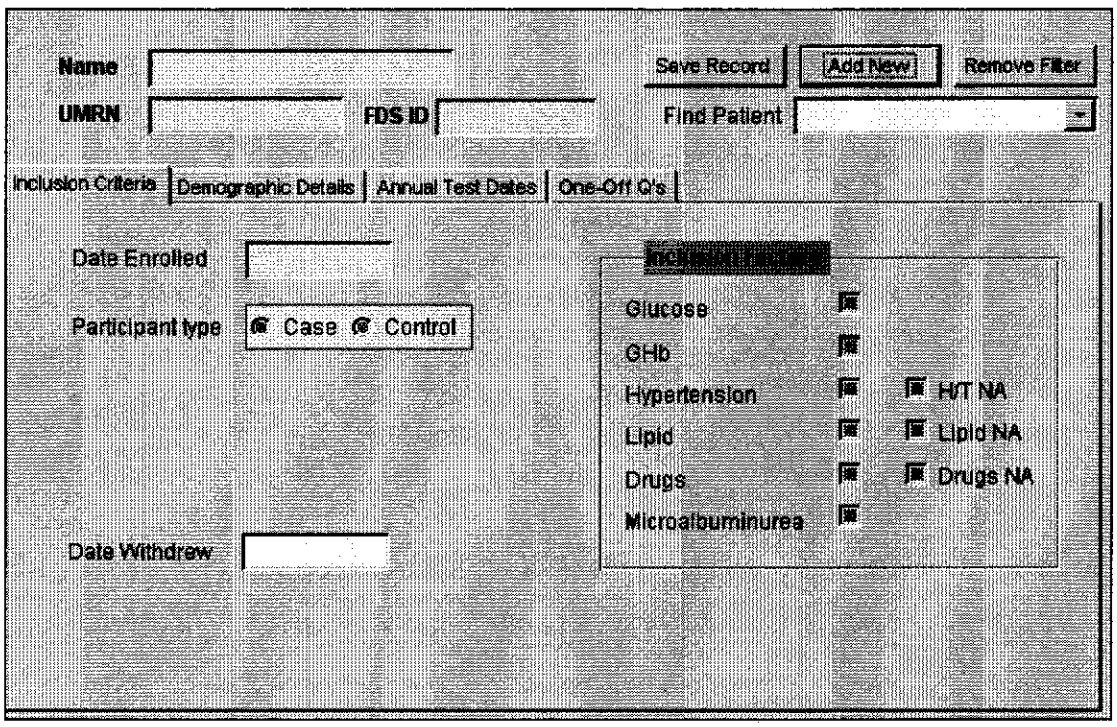
	Strongly disagree	Disagree	Agree	Strongly agree	Not Applicable
My hospital doctor explains my medicines to me carefully	O	O	O	O	O
My hospital pharmacist explains my medicines to me carefully	O	O	O	O	O
I feel comfortable enough to ask my hospital doctor questions about my medicines	O	O	O	O	O
I feel comfortable enough to ask my hospital pharmacist questions about my medicines	O	O	O	O	O
I feel confident in the ability and knowledge of the hospital doctor who looks after me	O	O	O	O	O
I feel confident in the ability and knowledge of the hospital pharmacist who looks after me	O	O	O	O	O
I find the printed information about my medicines confusing	O	O	O	O	O
I have never been given printed information about my medicines	O	O	O	O	O
I spend enough time with my hospital doctor to make sure I understand my medicines	O	O	O	O	O
I spend enough time with my hospital pharmacist to make sure I understand my medicines	O	O	O	O	O

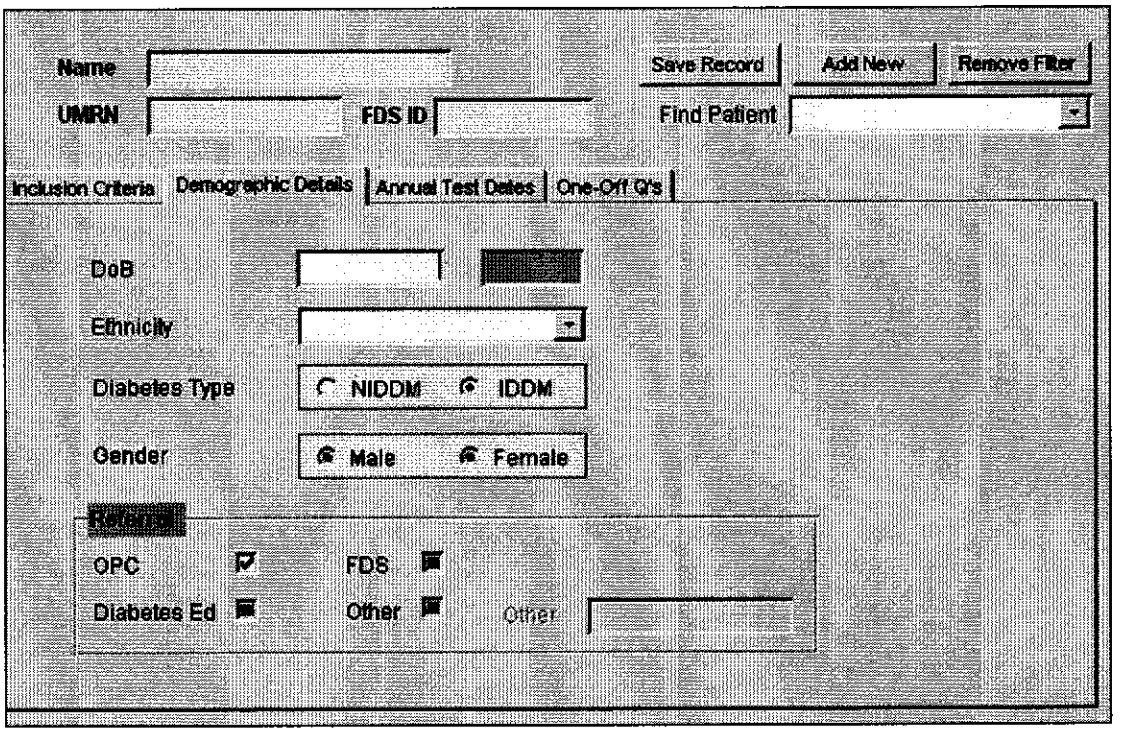
I understand how my medicines are to be used	O	O	O	O	O
I was given too much information on the medicines I take	O	O	O	O	O
I was not given enough information on the medicines I take	O	O	O	O	O
I find the printed information about my medicines useful	O	O	O	O	O
I do not understand how my medicines are to be used	O	O	O	O	O
I find to printed information about my medicine easy to understand	O	O	O	O	O

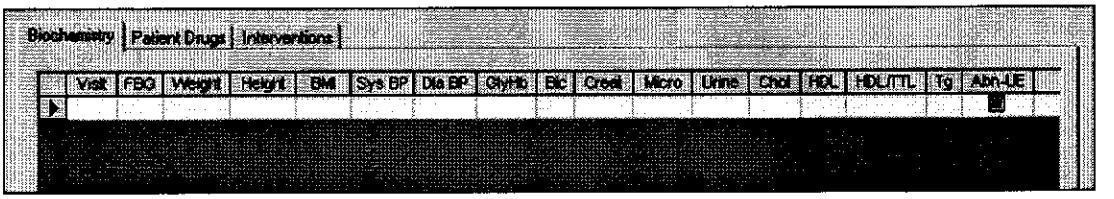
APPENDIX 4

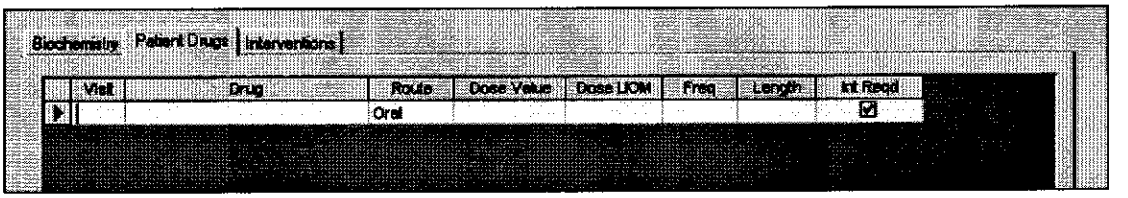
DATA COLLECTION FORMS FROM THE ACCESS® DATABASE

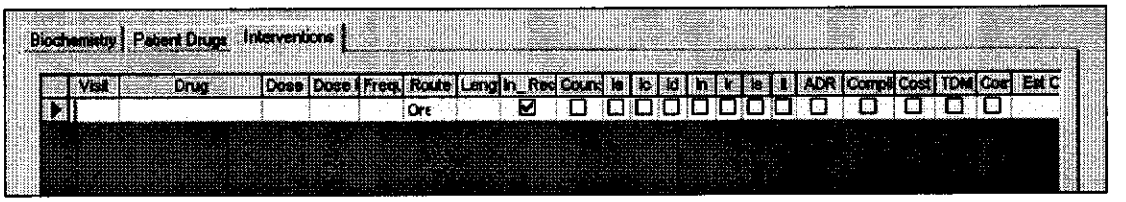
(USED TO COLLECT INFORMATION RELEVANT TO PHARMACOTHERAPY, BIOCHEMISTRY, DRUG THERAPY INTERVENTIONS AND COMPLEMENTARY MEDICINES, IN ADDITION TO THE FDS DATABASE INFORMATION WHERE APPLICABLE)




Name
Save Record
Add New
Remove Filter
UMRN
FDS ID
Find Patient
Inclusion Criteria
Demographic Details
Annual Test Dates
One-Off Q's
DoB
Ethnicity
Diabetes Type
NIDDM
IDDM
Gender
Male
Female
Referral
OPC
FDS
Diabetes Ed
Other
Other


Biochemistry
Patient Drugs
Interventions
Visit
FBG
Weight
Height
BMI
Sys BP
Dia BP
Glyhb
Bic
Creat
Micro
Urine
Chol
HDL
HDL/TL
Tg
Abn-LE


Biochemistry
Patient Drugs
Interventions
Visit
Drug
Route
Dose Value
Dose UOM
Freq
Length
Int Reqd
Oral


Biochemistry
Patient Drugs
Interventions
Visit
Drug
Dose
Dose
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Route
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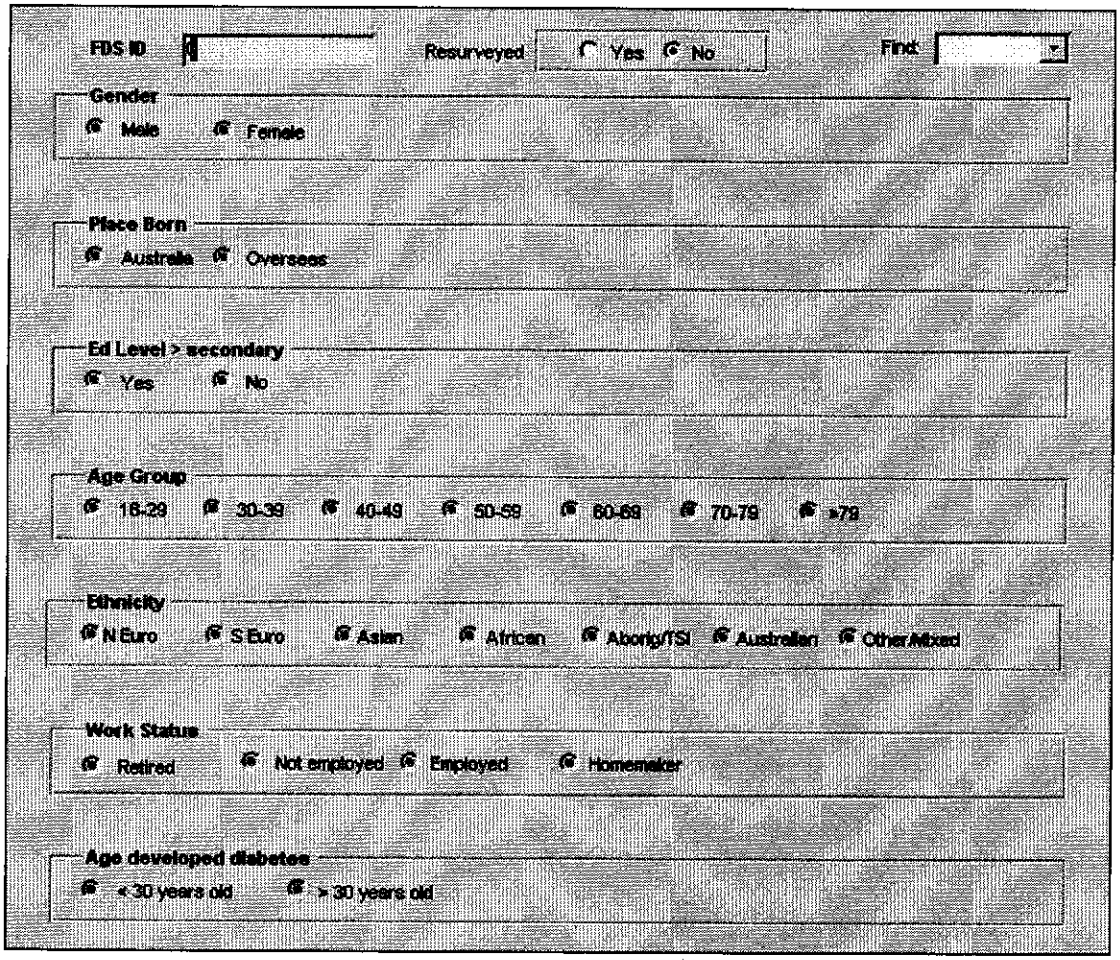
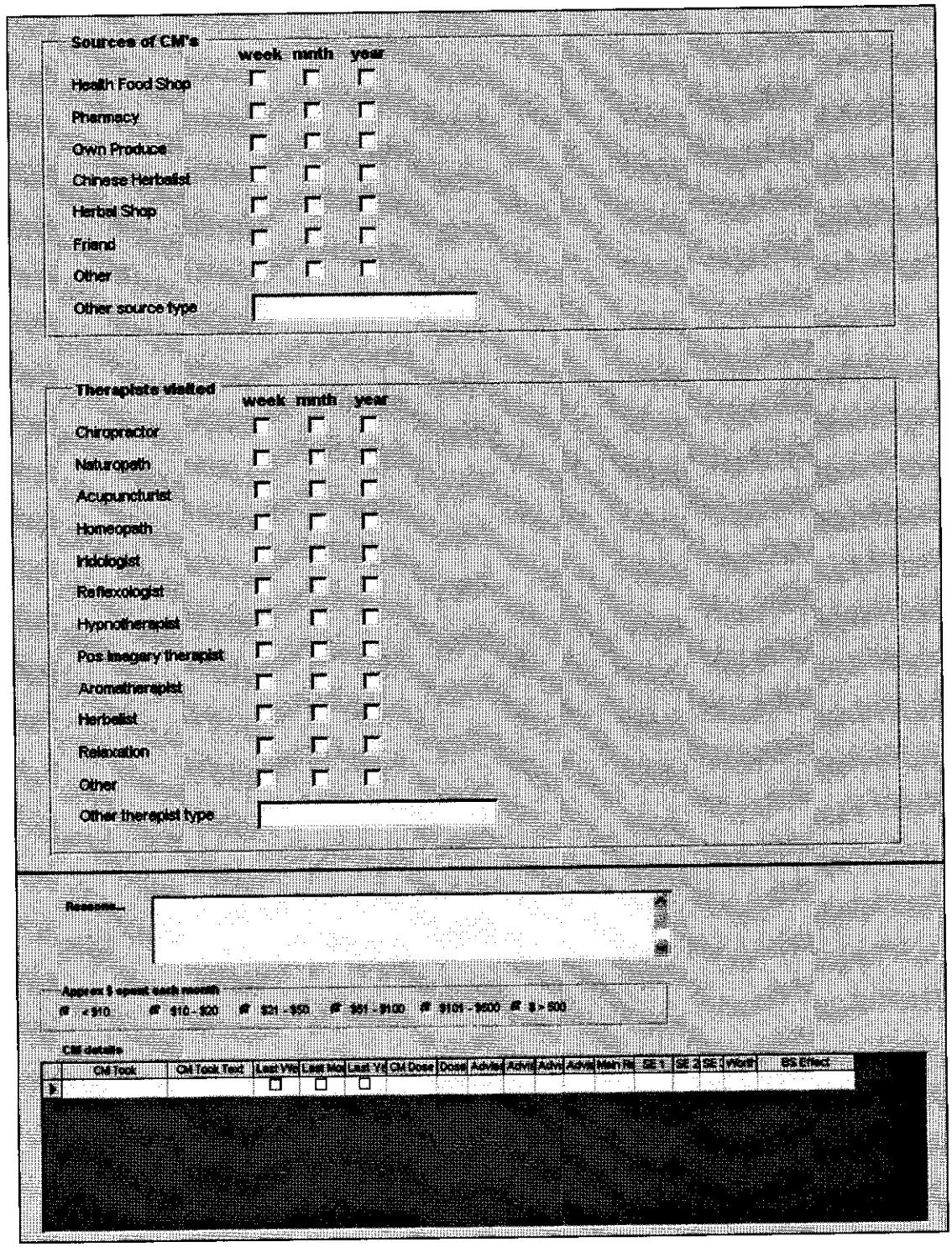

FDS ID
Resurveyed
Yes
No
Find
Gender
Male
Female
Place Born
Australia
Overseas
Ed Level > secondary
Yes
No
Age Group
16-29
30-39
40-49
50-59
60-69
70-79
>79
Ethnicity
N Euro
S Euro
Asian
African
Aborig/TSI
Australian
Other/Mixed
Work Status
Retired
Not employed
Employed
Homemaker
Age developed diabetes
< 30 years old
> 30 years old


Sources of CM's
week
month
year
Health Food Shop
Pharmacy
Own Produce
Chinese Herbalist
Herbal Shop
Friend
Other
Other source type
Therapists visited
week
month
year
Chiropractor
Naturopath
Acupuncturist
Homeopath
Iridologist
Reflexologist
Hypnotherapist
Pos Imagery therapist
Aromatherapist
Herbalist
Relaxation
Other
Other therapist type
Remarks...
Approx $ spent each month
< $10
$10 - $20
$21 - $50
$51 - $100
$101 - $500
$ > 500
CM details
CM Took
CM Took Text
Last Yr
Last Mo
Last Yr
CM Dose
Dose
Advise
Advise
Advise
Advise
Main Re
SE 1
SE 2
SE 3
Worst
BS Effect