High protein dietary patterns and Type 2 diabetes

A thesis submitted by

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Table of Contents

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes Trial
ADA	American Diabetes Association
AGE	glycation end product
AHA	American Heart Association
ATP III	Adult Treatment Panel III
ARIC	Coronary Heart Disease and Carotid Arterial Thickening in Patients with the Metabolic Syndrome Study
AUC	total area under the glucose curve
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
BCAA	branched chain amino acid
BM	basement membrane
BMI	body mass index
CARB-B	dietary carbohydrate loaded at breakfast
CARB-D	dietary carbohydrate loaded at dinner
CARB-E	dietary carbohydrate loaded evenly across the day
CARB-L	dietary carbohydrate loaded at lunch
CGMS	continuous glucose monitoring systems
CHD	coronary heart disease
CoDAM	Cohort Study of Diabetes and Atherosclerosis Maastricht
CRP	C-reactive protein
CVD	cardiovascular disease
DBW	Digits Backward Test
DCCT	Diabetes Control and Complications Trial

DECODE	Diabetes Epidemiology Collaborative Analysis of Diagnosis Criteria in Europe study
DFW	Digits Forward Test
DPS	Finnish Diabetes Prevention Study
DPP	Diabetes Prevention Program
DSST	Digit Symbol Substitution Test
EBAS DEP	Even Briefer Assessment Scale for Depression Test
EPIC	European Prospective Investigation into Cancer and Nutrition
ESRD	end stage renal disease
ESRF	end stage renal failure
FBG	fasting blood glucose
GFI	glomerular filtration rate
GI	glycemic index
GL	glycemic load
G_{max}	maximum postprandial peak glucose
Glut-1	insulin independent glucose transporter - 1
Glycemia	The use of the American spelling will be used in this thesis
HbA_1c	glycated haemoglobin: a measure of chronic glycemic control
HC	high carbohydrate
HDL-C	high density lipoprotein cholesterol
HGP	hepatic glucose production
HP	high protein
HPLC	high protein low carbohydrate
HPMC	high protein moderate carbohydrate
IDF	International Diabetes Federation

IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IL-6	interleukin-6
IRAS	Insulin Resistance and Atherosclerosis Study
IT	Inspection Time Test
KANWU	Kuopio Ischaemic Heart Disease Risk Factor Study
LDL-C	low density lipoprotein cholesterol
MMSE	Mini Mental State Examination
MODD	mean of the daily differences
MPHC	moderate protein high carbohydrate
MPHF	moderate protein high fat
NART	National Adult Reading Test
NCEP	National Cholesterol Education Program
NGSP	National Glycohemoglobin Standardization Program
NHANES	National Health and Nutrition Examination Survey Mortality Study
OGGT	Oral Glucose Tolerance Test
PKC	protein kinase C
PPG	postprandial blood glucose
SEM	standard error of the mean
SMBG	self monitoring of blood glucose
T>12	time spent with blood glucose levels above 12 mmol/L
TC	total cholesterol
TRIG	triglycerides
T_{fall}	study conducted in the fall

T_{spring}	study conducted in the spring
UKPDS	The United Kingdom Prospective Diabetes Study
VACSDM	Veterans Affairs Cooperative Study on Diabetes Mellitus Trial
VLDL-C	very low density lipoprotein cholesterol
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organisation
Wt	weight

DECLARATION OF ORIGINALITY

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Abstract

By the year 2025, it is anticipated that over 300 million individuals world wide will have type 2 diabetes, with a projected increase from 84 to 288 million (170%) in developing countries and from 51 to 72 million (42%) in developed countries. Diabetes leads to a markedly increased risk of heart disease and renal failure and to expensive and debilitating retinopathy and neuropathy. Cognitive decline is also increased.

As there is accumulating evidence of the beneficial effects of moderate carbohydrate, low fat dietary patterns compared to high carbohydrate diets, this thesis will focus on the effects of moderate carbohydrate high protein dietary patterns (total carbohydrate: protein: fat ratio of 40%:34%:26%) on glycemic control, risk factors for macrovascular disease and cognitive function. Information on two key areas in type 2 diabetes will be presented,

1. Acute effects of dietary patterns, moderately carbohydrate restricted and high in protein on glucose levels assessed using continuous glucose monitoring systems (CGMS) with verification of these results through a small repeat study.
2. Chronic effects of energy restricted dietary patterns, moderately carbohydrate restricted and high in protein on glucose levels, HbA_1c, cognitive function, cardiovascular disease (CVD) risk markers and renal function.

In the acute study, we recruited 23 subjects with type 2 diabetes. The participants were randomized to each of 4, 3-day interventions in a cross over design with a 4 day wash out period in which the carbohydrates were distributed differently at each meal;

carbohydrates evenly distributed across the day, or carbohydrates loaded at breakfast, lunch or dinner. Glucose levels were continuously measured using CGMS. Outcomes were assessed by postprandial peak glucose (G_{max}), time spent above 12 mmol/L (T>12) and total area under the glucose curve (AUC_{20}). The intervention showed that an even distribution of carbohydrates did not optimise blood glucose control, whereas carbohydrates loaded at the lunch time meal provided the most favourable postprandial profile.

To verify these results we conducted a repeat study. Six of the previous participants accepted the invitation to return and complete the even distribution arm of the study after a 20 week time lag. The intervention showed that although HbA_1c, fasting blood glucose (FBG), AUC, exercise and ambient temperature remained constant there was a significant effect of change in sunlight hours on G_{max}, suggesting an effect of sunlight.

To assess the chronic effects of energy restricted dietary patterns on the determinants of HbA_1c, cognitive function, CVD risk markers and renal function under conditions of weight loss, we recruited 82 participants with type 2 diabetes. These participants were randomised to one of two high protein energy restricted dietary patterns that differed in cholesterol content, for a 12 week period, in a parallel design. A sub group of these participants completed cognitive function testing with (n=34) or without (n=17) CGMS at baseline and at 8 weeks.

After 8 weeks of the intervention the determinants of HbA_1c under conditions of energy restriction were evaluated. The intervention showed the change in FBG accounted for most of the variance in change in HbA_1c, but % energy reduction also

contributed independently of FBG. Both energy restricted high protein diets equally improved glycemic control, particularly T>12, AUC, HbA$_1$c and FBG.

Fifty one participants completed cognitive testing to evaluate the effect of weight loss and blood glucose control on cognition. Cognitive function was not altered by time, diet, baseline lipid levels. Working memory was predicted by FBG. Short term memory was predicted by FBG, G$_{max}$ and AUC$_{24}$.

Sixty five participants completed 12 weeks of the intervention to assess CVD risk markers and renal function. Renal function was maintained and CV markers improved on both dietary patterns, with greatest improvement in HDL-C observed in the group consuming a high protein, energy restricted dietary pattern, high in dietary cholesterol.

In conclusion, in the context of a high protein, carbohydrate restricted dietary pattern, cognitive function and renal function did not change, while glycemia and CV risk profiles improved with weight loss over the short term. Under conditions of energy balance diurnal glucose profiles were optimal when the carbohydrates were loaded in the lunch meal.

Introduction

Type 2 diabetes mellitus and associated metabolic pathologies are becoming an epidemic in Australia and world wide. In 2000, 7.5% of the Australian population aged over 25 years reported that they had type 2 diabetes, with almost 25% of all Australians having diabetes or impaired glucose metabolism [1]. Over a similar time period, the world wide prevalence of diabetes, predominantly type 2, was 2.8% with an expected increase to 4.4% by the year 2030 [2].

Type 2 diabetes is a complex metabolic syndrome that culminates in hyperglycemia as a result of defects in either insulin secretion, insulin resistance or both [3]. As the disease progresses a number of comorbidities may eventuate such as cardiovascular disease (CVD) [4-6], nephropathy [7], neuropathy [8], retinopathy [9], cognitive dysfunction [10] and limb amputations [11].

The key issue in the management of type 2 diabetes is normalising glycemia to prevent or delay the development of complications. Dysglycemia has two components; fasting hyperglycemia and postprandial glucose fluctuations. The United Kingdom Prospective Diabetes Study (UKPDS), the largest landmark study conducted in individuals with type 2 diabetes clearly demonstrated that a 11% reduction in HbA_1c (a measure of chronic glycemic control) over 10 years reduced the risk of microvascular disease by 25%, and myocardial infarction by 16%, although the latter was not conventionally statistically significant [12]. This is supported by other studies [13, 14]. More recently, acute glucose fluctuations have been identified as a risk factor for diabetic complications, as these fluctuations, as well as chronic hyperglycemia are both responsible for activation of oxidative stress and excessive

protein glycation [14]. In free living situations, the measurement of acute fluctuations is best achieved through the use of continuous glucose monitoring systems (CGMS). CGMS provides 288 glucose measurements each day enabling a very detailed assessment of acute glucose control [15].

Dietary intervention can play a significant role in the management of type 2 diabetes. There is now substantial evidence that type 2 diabetes can be delayed or prevented altogether through lifestyle interventions. This was demonstrated by the Finnish Diabetes Prevention Study (DPS), where the risk of diabetes was reduced by 58% through intensive dietary modification group compared with a control group [16]. Similar risk reductions were observed using lifestyle interventions by the Diabetes Prevention Program (DPP). Of particular interest is the superior risk reduction achieved through lifestyle interventions (58%) compared to those achieved using a metformin treatment (31%) [17].

The key goals of dietary management are normalisation of glycemia and weight loss in those individuals who are overweight or obese. The majority of individuals with diabetes are obese [18], and obesity increases the abnormalities associated with diabetes such as hypertension and hyperlipidemia [19]. Numerous short term energy restricted studies have demonstrated that weight loss in non diabetic subjects was associated with improvements in glycemic and lipid profiles, and blood pressure [20, 21], with weight loss of 3-5kg reducing the incidence of type 2 diabetes by 40-60% [16, 22] in volunteers with impaired glucose tolerance. Individuals with type 2 diabetes are advised to reduced their weight to achieve a body mass index (BMI)< 25kg/m^2 [23-26]. The American Diabetes Association, the Canadian Diabetes Association and the Diabetes Nutrition Study Group of the European Association for

the Study of Diabetes advocate a weight loss of 5-7% of current weight [27-29], while dramatic improvements in glycemic and lipid profiles and blood pressure co-morbid risks have been observed in individuals with existing type 2 diabetes, with a weight loss of 10% of initial body weight [30].

Accumulating evidence supports a correlation between increasing total and saturated fat and diminished glucose tolerance and increased incidence of type 2 diabetes [31, 32]. Long term compliance (over a 5 year period) to an ad libitum low fat diet was shown to improve glucose tolerance [33]. A meta analysis of ad libitum diets suggest that high fat intakes contributed to an increase in body fat, which in turn could contribute to the incidence of type 2 diabetes [21]. Generally, human studies indicate that increased dietary fat intake over the longer term adversely affects lipoprotein metabolism [34], insulin sensitivity [35-37] and promotes insulin secretion [38, 39]. Saturated fat appears to more detrimentally affect insulin sensitivity relative to monounsaturated and polyunsaturated fat [37], while limited information suggests trans fatty acids tend to potentiate insulin secretion, more so than cis fatty acids, at least over the shorter term [38, 39].

Replacement of dietary fat with isocaloric amounts of carbohydrate was shown to increase postprandial glucose, insulin and triglyceride levels as well as decrease high density lipoprotein cholesterol (HDL-C) [40-42]. The type of carbohydrate as well as the amount also influences glycemic control. In addition, increased consumption of dietary fibre, particularly soluble fibre, reduced the risk of type 2 diabetes [43-45] and improved glycemic and lipid profiles [46, 47]. Increased intakes of refined carbohydrates in combination with decreased fibre intake was linked to increased risk of type 2 diabetes [48].

6

High protein diets are a form of moderately carbohydrate restricted diets and are increasingly gaining acceptance as an alternative to high-carbohydrate, low fat, high-fibre diets for weight loss and reduction of diabetes risk [49]. Studies show that HbA_1c was improved with a carbohydrate restricted, higher protein dietary pattern, both in energy balance [50-52] and energy restriction [53]. A recent meta analysis of 13 studies in type 2 diabetes demonstrated that moderately carbohydrate restricted, high protein diets, improved glycemic profiles and triglycerides [54]. Other benefits of high protein dietary patterns included increased satiety [55], which may be due the increased thermogenesis relative to carbohydrates [56]. Lean body mass was also spared [53].

In view of increasing evidence in support of the beneficial effects of moderate carbohydrate, low fat dietary patterns, compared to high carbohydrate diets, this thesis will focus on the effects of moderate carbohydrate, high protein dietary patterns (total carbohydrate: protein: fat ratio of 40%:34%:26%) on glycemic control, weight loss and the prevention of diabetic complications. Physical activity, although a key risk factor for type 2 diabetes disease progression, will not be the focus of this thesis and therefore only briefly discussed.

The most recent review of dietary advice for type 2 diabetes, a Cochrane review, highlighted the need for more research in the area of diet composition (both with and with out exercise) on weight loss, glycemic control and both macrovascular and microvascular diabetic complications [57]. This thesis will address these issues and present information on two key areas,

1. Acute effects of dietary patterns moderately carbohydrate restricted and high in protein on glucose levels assessed using continuous glucose monitoring

systems (CGMS) with verification of these results through a small repeat study. The aim of this study was to minimise acute postprandial excursions which activate oxidative stress and potentially impact on diabetic co-morbidities, particularly cardiovascular disease [58] using dietary manipulation. Trial registry number: ACTRN012606000432516.

2. Chronic effects of hypocaloric moderately carbohydrate restricted, and high protein dietary patterns on glucose levels, HbA_1c, cognitive function, cardiovascular disease (CVD) risk markers and renal function. Both fasting blood glucose levels and postprandial blood glucose levels contribute to chronic hyperglycemia, which in turn results in the production of oxidative stress and excessive protein glycation [58], the drivers of microvascular and macrovascular complications. The aims of these studies were to evaluate the use of these dietary patterns to improve glycemic and lipid profiles, which may impact on diabetic related complications. Trial registry number ACTRN: ACTRN012606000475549.

Key words: type 2 diabetes, high protein moderately carbohydrate restricted dietary pattern, carbohydrate distribution, glycemic control, cardiovascular risk markers, cognitive function, renal function, energy balance, energy restriction.

Chapter 1: Literature Review

1.1 Diabetes Mellitus

1.1.1 The Diabetes "Epidemic" and impact on society

Diabetes Mellitus is recognised as one of the most common non communicable diseases and challenging health problems facing the world in the 21st century [59]. It also results in extensive morbidity and mortality, principally from macrovascular [60] and microvascular disease [61, 62].

Over 1 million Australians and 170 million people world wide were affected by Diabetes Mellitus in 2000 and the World Health Organisation predicts that figure to rise to over 360 million, predominantly type 2 diabetes [63], by the year 2030 [64]. The Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the biggest population-based, longitudinal study conducted in Australia, demonstrated a two fold increase in diabetes prevalence since the Bussleton study in 1981. In 2000, the prevalence of diabetes in the Australian population aged over 25 years was 7.5%; 8.0% for males and 7.0% for females. Furthermore, for every reported case of diabetes there was one undiagnosed case. In addition, almost 25% of all Australians had diabetes or impaired glucose metabolism [1]. The follow up study in 2005 revealed individuals with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) were 15 times more likely to develop diabetes compared to individuals with normoglycemia with about 100,000 Australians progressing to frank diabetes annually (which equates to 275 individuals per day) [65].

Direct annual health care costs of diabetes for people aged 20–79 years world wide were estimated by the International Diabetes Federation (IDF) to range from US$153 billion to US$286 billion in 2003. By 2025 the IDF estimated that this figure will

have risen to US$396 billion [66]. In Australia, diabetes related health system expenditure in 2000-2001 was estimated at approximately AUS$789 million [66]. The Fremantle Diabetes Study reported that over the same time period the government spent AUS$204 million subsidising hypoglycemic medication and monitoring equipment, while the average diabetic spent around AUS$1,500 in managing their condition [67]. This large cost can be partly reduced through dietary and lifestyle management given that 85-90% have type 2 diabetes [68].

The Australian Institute of Health and Welfare (1996) reported that diabetes represented 5% of the total burden of disease. Given that by 1996 Australia had already witnessed a two fold increase in the prevalence of diabetes over the previous 15 years [69, 70], the management of type 2 diabetes already presents as a major health priority for individuals, governments, the broader health system and society at large in the 21st century. Further, individuals with diabetes and additional comorbidities considerably increase the demand on health care services and related medical costs [71-75]. This has the potential to place an ever increasing economic burden on the Australian society. Federal, state and territory governments in Australia have identified Diabetes Mellitus as one of the 6 national health priority areas along with cancer, asthma, cardiovascular disease, mental health and trauma [67].

1.1.2   Defining type 2 diabetes

Prediabetes, hyperglycaemia, increased insulin secretion, metabolic syndrome [76], (also described as syndrome X [77], the Insulin Resistance Syndrome [78-80], or the "Deadly Quartet'[81]) and type 2 diabetes can all be viewed as different facets of the

same disease having the same dietary, genetic and lifestyle causes [82, 83]. Body fat distribution, and in particular visceral fat, physical inactivity and high fat diets are also thought to be contributing factors [82]. Molecular mechanisms and the genetic basis for decreases in β-cell function are not fully elucidated. Individuals with IFG were more insulin resistant that those with IGT, whereas impaired secretion of first and second phase insulin predominates in individuals with IGT [83]. The UKPDS found that at the point of type 2 diabetes diagnosis, individuals with poor glycemic control presented with a 50% reduction in β-cell function [84].

1.1.2.1   Risk factors for the development of Diabetes Mellitus

Modifiable risk factors for type 2 diabetes include poor dietary choices (dietary patterns high in total energy intake, total fat or high saturated and trans fatty acids intake and low in fibre and polyunsaturated fatty acids), obesity, particularly central obesity, lack of physical activity and smoking. Moderate alcohol consumption [85, 86] and high coffee consumption were associated with reduced risk of type 2 diabetes [87, 88]. The Nurses Health Study determined that obesity was the single most important predictor of diabetes; Women with a BMI>35kg/m^2 had a 40 fold increased risk of developing diabetes compared to individuals who were not overweight. Regular exercise of >7hr/week decreased the risk of type 2 diabetes by 39% compared with women who exercised less than 0.5hrs/week. Alcohol intake >10g/day decreased the risk by 41%, while smoking >14 cigarettes/day increased the risk of developing Type 2 diabetes by 39% [89]. The importance of BMI and central adiposity as major risk factors are supported through other studies [90, 91].

A sedentary lifestyle is also a major risk factor for type 2 diabetes [92]. The National Health Interview Survey [93], the Whitehall Study [94], the Nurses study [95], the Health Professionals' Follow-Up Study [96] and the Aerobics Centre Longitudinal Study [97] all report that regular physical activity increased insulin sensitivity, glycemic control and weight loss in type 2 diabetes [16, 98-100]. Physical activity reduces total and visceral fat mass [101].

Several non modifiable factors influence the incidence of diabetes. They include ethnicity, genetic predisposition, age and sex (higher in men than women[1]). Evidence from epidemiological studies corroborate that this syndrome occurs widely across many different ethnic groups including Australian Aborigines and Torres Strait Islanders [102], Europeans [103], Indians [104], Micronesian and Polynesian Pacific Islanders [105], Caucasians, Mexican-Americans [106], Afro-Americans [106] and Chinese [102]. The severity of insulin resistance in these groups is the strongest predictor of development of type 2 diabetes [107]. Also the offspring of these individuals, particularly if both parents have type 2 diabetes, are almost certain to develop diabetes in the longer term [108].

The aging process is also associated with decreases in muscle mass and increases in body fat, both of which contribute to an insulin resistant state [109, 110] and a significant risk factor for disease progression [69], although type 2 diabetes is now increasingly being identified in younger age groups [1].

1.1.3 Diagnostic criteria for diabetes

Glucose intolerance and diabetes diagnosis are based on blood glucose levels in both the fasting state and after an oral glucose load. The 2-hour oral glucose tolerance test (OGTT) measures the postprandial glucose response to a 75g oral glucose load 2 hrs after consumption [111].

The current World Health Organisation (WHO) criteria recommend that individual diagnosis should be based on both the fasting blood glucose and 2 hour post glucose load values [64]. Diagnosis by these two measures is supported by the Australian criteria [112], but differs from the American criteria (ADA Expert Committee) which gives priority to the fasting plasma glucose values [113].

The basis of the diagnostic threshold values is the increased risk of microvascular and macrovascular complications beyond these points. The current threshold for fasting blood glucose (FBG) concentrations detects those at risk of microvascular diseases when HbA_1c exceeds 6.5%[114, 115], while the 2 hour post glucose load concentration predicts cardiovascular morbidity and mortality more than fasting [116, 117].

NOTE:
This table is included on page 14 of the print copy of
the thesis held in the University of Adelaide Library.

Table 1.1. Plasma venous diagnostic criterion for diabetes [118].

14

1.1.4   Measurement of blood glucose

HbA$_1$c is the gold standard in assessing chronic glycemic control [119]. It reflects the average amount of glycosylated haemoglobin over a 2-3 month period. The concentration of HbA$_1$c in the blood is proportional to the average concentration of glucose in the blood over a 2-3 month period. All individuals have glycosylated haemoglobin in their blood with levels 3-5% considered normal. Individuals with poorly controlled blood sugar levels have elevated HbA$_1$c [90].

It is now acknowledged that HbA$_1$c is a poor predictor of acute glycemic control as it does not reflect any information on the frequency and extent of glucose excursion, providing an overall mean value only [120]. Individuals with similar HbA$_1$c levels may have vastly different levels of glycemic variability [121]. Figure 1.1. There is now a growing body of evidence that suggests that hyperglycemic excursions and glycemic variability may be independent risk factors for diabetes related complications [122].
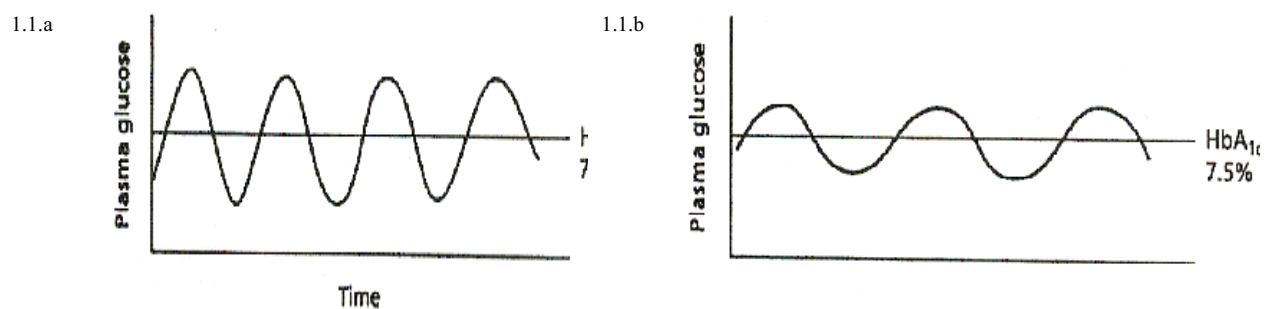
Figure 1.1 Individuals with similar HbA$_1$c may exhibit different glucose variability throughout the day.
Figure 1.1. a. Glucose fluctuations increased in number and magnitude throughout the day. Figure 1.1.b. Decreased magnitude and number of fluctuations within the day [123].

As absorption of food continues 5-6 hours after a meal, the optimum time to measure postprandial glucose is variable and is influenced by the macronutrient composition, volume and timing of the meal, and the resulting insulin secretion and inhibition of glucagon secretion [14]. However, it is generally accepted that peak postprandial glucose occurs about 2 hours after a meal [124]. Post challenge hyperglycemia refers to the glucose levels attained 2 hours after ingestion of 75g of glucose in solution [125]. A strong correlation exists between the postprandial response to a standardised meal and the 75g glucose solution [126, 127].

CGMS is a tool used to gain a more comprehensive picture of an individual's glycemic status [128]. CGMS glucose sensors are able to collect an interstitial blood glucose reading every 10 seconds and store an average of those readings in a monitor every 5 minutes, yielding 288 readings each day; this technique is able to identify dynamic changes in blood glucose concentrations which could not be detected with intermittent self monitoring of blood glucose (SMBG), particularly in a free living situation [128]. The kinetics of dermal interstitial fluid glucose and plasma glucose are similar [129] and interstitial glucose has been shown to consistently predict plasma glucose independent of increases in either exogenous or endogenous insulin [130] with small discrepancies in the hypoglycemic range [131, 132].

The initial work with CGMS was performed with type 1 diabetes primarily to identify the timing and causes of hypoglycemia and hyperglycemic spikes [133-136]. However, it also showed that despite FBG and HbA_1c levels being within target ranges, postprandial glucose levels often varied extensively [137]. More recently,

CGMS has been used in type 2 diabetes to obtain a complete picture of diurnal glucose profiles [138, 139].

1.1.4.1 Management of diabetes – normalising glycemia

The key issue in the management of type 2 diabetes is normalising glycemia to prevent or delay the progression of complications. Diabetes related complications include coronary heart disease [60, 140-145], prothrombotic state [146-148], stroke [117, 149-152], nephropathy[7], neuropathy [153], retinopathy [9, 154, 155], diabetic foot [153], limb amputations [156], and cognitive decline [157, 158]. Individuals with diabetes have a two fold incidence of depression compared to individuals without diabetes [10, 159] which may impact on their ability to manage their blood glucose levels.

1.1.4.1.1 The impact of hyperglycemia on macrovascular complications

CVD is the leading cause of death in type 2 diabetes, accounting for 40-50% of total deaths [22, 60]. Normalisation of blood glucose levels appear to significantly decrease the risk of CVD and atherosclerosis [120, 160, 161]. Individuals with type 2 diabetes account for 20-30% of acute coronary syndrome admissions [22] and have a 2-3 fold increased rate of death after myocardial infarction, compared to individuals without diabetes [162]. The increased rate of CVD in men (2-3 fold increase) [163-165] was lower than in women (3-4 fold increase) [166, 167].

Numerous large epidemiological studies have been extensively reviewed [168-171] and have repeatedly demonstrated that in individuals with type 2 diabetes, the higher the blood glucose concentration (either plasma or HbA_1c), the higher the incidence of CVD [149, 172-179]. The UKPDS study was the largest observational study to assess the relationship between microvascular and macrovascular complications and blood glucose control in type 2 diabetes. Three thousand, six hundred and forty two UKPDS patients, newly diagnosed individuals with type 2 diabetes, were assigned to either a control group treated by dietary restriction alone or an intensively treated group (treated with hperglycemic medication). After 10 years, observational data suggest the risk of any complication related to diabetes, death related to diabetes, fatal and non fatal myocardial infarction, and microvascular disease fell by 21%, 21%, 14%, 37% (p<0.0001 for all) respectively with every 1% reduction in HbA_1c [172].

Many large studies have also demonstrated that individuals with IGT have an increased risk of developing macrovascular disease [180-185]. For example, the Diabetes Epidemiology Collaborative Analysis of Diagnosis Criteria in Europe Study (DECODE) demonstrated an increase risk for death of 32%, coronary heart disease of 27%, stroke of 21% [180] for people with IGT, compared to those with NGT. The Cardiovascular Health Study [183] and the National Health and Nutrition Examination Survey Mortality Study (NHANES II) [184] found that individuals with IGT had an increased risk of CVD of 20-22%. Furthermore, several studies have demonstrated a relationship between raised postprandial or 2 hour post challenge glucose levels and increased risk of macrovascular complications and mortality [186-192], whereas the relationship between FBG and macrovascular complications was inconclusive (reviewed in Ceriello et al. [14]).

The key clinical studies outlined in Table 1.2 collectively suggest that the relative risk of cardiovascular events could potentially be reduced by 39-46%, as a result of improving glycemic control, although comparison is confounded as the studies vary in design and the final outcomes reported [193, 194]. The findings also suggested that when HbA_1c was reduced below the therapeutic goal of 7% to 6%, the incidence of myocardial infarction was reduced from 25/1000 to 15/1000 person years. In contrast to these results, the Veterans Affairs Cooperative study on Diabetes Mellitus Trial (VACSDM)[195] and the UKPDS [12] reported that individuals with intensively controlled glucose had a non significant change in the risk of cardiovascular events. The Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD) was suspended on June 6, 2008. It was specifically designed to assess the relationship between intensive lowering of blood sugar levels, intensive lowering of blood pressure, or treatment of blood lipids and cardiovascular risk in individuals with type 2 diabetes. The trial found that the use of intensive therapy to target normal glycated haemoglobin levels for 3.5 years compared with standard therapy, increased mortality and did not significantly reduce major cardiovascular events. Uniquely, this study identified the harm of intensive glucose lowering in individuals with poorly controlled type 2 diabetes [196].

Besides glycemic control, duration of diabetes, hypertension, obesity, abnormal lipid metabolism aging and smoking are also risk factors for macrovascular disease [192]. The Kumamoto [193] and UKPDS studies [12, 194] all showed no significant effects on CV outcome. However, despite these encouraging results, the VACSDM study suggested that the use of intensive insulin therapy in type 2 diabetes resulted in increased CV events [195].

19

Table 1.2: Glycemic control in type 2 diabetes and CV risk.
[1]not powered to detect CV outcomes. ns=non significant. Adapted from Goldstein and
Muller-Wieland [197].

1.1.4.1.2   The impact of hyperglycemia on microvascular complications.

Elevated blood glucose levels are a risk factor for microvascular disease [198]. Other
factors that influence the rate of progression include duration of diabetes, age of onset
and hypertension [199]. Microvascular disease includes diabetic retinopathy which is
responsible for the majority of adult cases of blindness [156], nephropathy [156] and
neuropathy [200], which develops in 10-40% and 20-30% of type 2 diabetes cases
respectively.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) determined a
prevalence of retinopathy in type 2 diabetes 10 years after diagnosis of 60% [201].
Individuals with type 2 diabetes managing their glycemic control with insulin had
almost twice the prevalence of retinopathy (70%), compared to those not requiring
insulin (39%) [202]. Although glucose levels alone are not wholly responsible for the
development and progression of retinopathy, epidemiologic studies have not been

able to conclusively link hypertension, race and gender to the progression of retinopathy [203-206].

Diabetic nephropathy is characterised by albuminuria, hypertension and progressive decline glomerular filtration rate and is the principal cause of end stage renal disease (ESRD) [206]. Between a quarter (UK and Canada) to half (USA) of all individuals with long term type 2 diabetes have clinically detectable nephropathy [207-209]. Furthermore, a 6-10 fold increase in the incidence of end stage renal failure (ESRF) has been observed from 30-50 years to 70-90 years of age [210, 211]. Annually, 2-3% of individuals with type 2 diabetes will advance to overt proteinuria [212].

The prevalence of diabetic nephropathy is dependant on ethnicity and gender; Asians [213], Pima Indians [214, 215], African Americans [216, 217], Pacific Islanders [218] and Israeli Jews of non Ashkenazi origin [219] appear more vulnerable compared to Europeans. Black individuals with type 2 diabetes were up to 4 times more likely than white individuals to develop ESRD [216, 217]. Furthermore, gender becomes more important as the disease progressed with the prevalence of microalbuminuria similar between males and females, and the incidence of microalbuminuria progressing to macroalbuminuria three fold higher in males than females [176]. As many individuals with type 2 diabetes do not develop nephropathy, it is likely that other factors such as age [220], blood pressure [183, 221-223], ethnicity [224], genetic predisposition and familial clustering [214, 216, 225-228], diabetes duration [229], socioeconomic factors [217], smoking [230, 231], physical inactivity and obesity are involved [232]. Protein intake has also been implicated in

disease initiation and progression, particularly in individuals with impaired renal function [233].

Diabetic neuropathy represents a collective group of nerve disorders classified as peripheral, autonomic, proximal, and focal. The Rochester Diabetic Neuropathy Study showed that 56% of individuals with type 2 diabetes displayed some form of neuropathy; 29% asymptomatic polyneuropathy, 16% symptomatic polyneuropathy, 5% visceral autonomic neuropathy, other varieties 6% and 1% completely unable to walk on their heels [234]. Elevated blood glucose levels, age and duration of diabetes [235-238] are the main risk factors, although some have identified additional factors such as increasing blood pressure, cigarette smoking, increased levels of triglycerides, and the presence of background or proliferative diabetic retinopathy [239].

Controlled clinical trials such as the UKPDS [12], the Kumamoto Study [193] and the Steno type 2 study [240] have convincingly shown that strategies aimed at normalising glycemia successfully reduced the development of microvascular complications.

The UKPDS study demonstrated that an 11% improvement in HbA_1c corresponded to a 25% reduction in all microvascular endpoints. The risk reduction for cataracts, retinopathy progression and microalbuminuria was 24%, 21% and 33% respectively at 12 years. No threshold was found for any microvascular endpoint [12].

A much smaller study, involving 110 Japanese subjects with type 2 diabetes, individuals were randomised to an intensively treated group (treatment with multiple

insulin injections), or a control group (treated with conventional insulin therapy). Half the participants had presented with urinary albumin excretion <30 mg/24hr and no retinopathy and at baseline, were appraised as a primary-prevention cohort. The other 55 participants presented with urinary albumin excretions <300 mg/24hr and simple retinopathy, and were appraised as the secondary-intervention cohort. After 6 years, the HbA$_1$c in the control group was 9.4% compared to 7.1% in the intensively treated group. In the primary prevention cohort, 7.7% of the intensively treated individuals progressed to retinopathy compared to 32% in the control group. In the secondary prevention cohort, 19.2% of the intensively treated individuals developed retinopathy compared to 44% in the control group. Similar reductions were observed with nephropathy and neuropathy; in the primary and secondary prevention group development of nephropathy was 7.7% and 11.5% respectively, for the intensively controlled group and 28.0% and 32.0% respectively, for the control group. Neurological assessments after 6 years revealed improvements in nerve conduction velocities, in contrast to the control group, that showed deterioration in vibration threshold and nerve conduction velocities [193].

Other clinical studies in individuals with type 2 have reported similar relationships with postprandial glucose levels, retinopathy [241] nephropathy [7, 241, 242] and neuropathy [153]. These results are also supported by the very large Diabetes Control and Complications Trial (DCCT) in Type 1 diabetes [243].

Epidemiological analysis from the UKPDS demonstrated that the macrovascular risk was greater than three times that of a microvascular event at HbA$_1$c levels below 6%. However, when HbA$_1$c levels exceeded 10%, the relative risks were reversed,

suggesting that the susceptibility to specific diabetes comorbidities is altered relative to glycemic control [172]. Figure 1.2.

Although not routinely studied, the link between diabetes and cerebral function was first postulated in the year 1684 [244] in [245]. This research area was largely neglected until 1973 when Bale [246] performed the first modern study on cognition; It was only recently that diabetes was acknowledged as a risk factor for cognitive decline [247-249] and dementia [250, 251].

NOTE:
This figure is included on page 24 of the print copy of the thesis held in the University of Adelaide Library.

Figure 1.2. Relationship between HbA$_1$c and microvascular or macrovascular disease-

95% confidence intervals and incidence rate for microvascular and macrovascular complications for mean HbA$_1$c adjusted for possible confounders at diagnosis of diabetes [172]. Red line; macrovascular end points, blue line; microvascular end points.

There are several comprehensive reviews of longitudinal studies examining the impact of hyperglycemia and diabetes on cognitive functions [247, 248, 250, 252, 253], and they generally concluded that type 2 diabetes is an independent risk factor for cognitive decline [247, 248, 250, 252, 253]. Cukierman et al. quantified the risk; diabetes increased the risk of cognitive decline by 1.2 fold, as assessed by the mini

mental state examination (MMSE), with the risk of future dementia increased by 1.7 fold [253].

There are a limited number of intervention studies that have examined whether improvements in glycemic control (achieved through medication) lead to improvements in cognitive function. The largest study involving 145 individuals with type 2 diabetes found improvements in working memory with improved glycemic control [254]. Cognitive deficits also appeared to increase with an increase in age, particularly in those above 70 years old [254]. Other smaller studies indicated that improvements in glycemic control were associated with improvements in verbal learning [255], concentration tasks [256], measures of processing speed (Trail-Making part A), modified cued recall, mental dexterity and nonverbal reasoning [257] (although this study has been criticized because it did not control for practice effects or use alternative tests across the testing period, and possibly did not have enough power to draw conclusions) [258]. Collectively, memory and mental processing speed are the cognitive realms most often compromised, whereas attention, problem-solving, and general intelligence tend to be unaffected.

While poorer performance on cognitive tasks is also observed in individuals with IGT or IFG compared to individuals without diabetes, researchers generally believe these changes in brain function are reversible [259-263], suggesting a "cause and effect" relationship [264]. Early cognitive deficits may result from the synergistic effect of hyperglycemia and the presence of microvascular and macrovascular disease. In older individuals (>70 years), the combination of vascular disease, Alzheimer's disease and diabetes, accelerate the rate of cognitive decline. This certainly becomes important in

self management, as poor cognitive function may cause difficulties in adherence to medical protocols [265-268].

1.1.4.1.3 Biochemical consequences of hyperglycemia

There is now evidence from observational studies that chronic hyperglycemia increases the risk of microvascular disease (and to a lesser degree macrovascular disease) and that reduction in blood glucose levels would reduce the risk [12, 172, 243, 269]. Vascular endothelial cells are unable to regulate glucose uptake, therefore with hyperglycemia the insulin independent glucose transporters GLUT-1 are able to facilitate the transfer of glucose across the endothelial membrane and into the endothelial cells. Cellular hyperglycemia leads to vascular damage through formation of advanced glycation end products (AGE's), activation of the protein kinase C (PKC) and increased flux through both the polyol and hexosamine pathways ultimately resulting in vascular complications. Overproduction of mitochondrial superoxide appears to be the single hyperglycemia driven process that initiates all 4 pathways [270]; elevated absolute glucose concentration appears to activate AGE production and increase the glucose flux through both the polyol and hexosamine pathways [270], whereas uncontrolled glycemic peaks or 'spikes' stimulate the PKC pathway. PKC alters the contraction of pericytes and smooth muscle cells, augments the production of basement membrane (BM) material and enhances capillary permeability and cell proliferation [271]. As it is the postprandial 'spikes' rather than the absolute levels of glucose that activate this pathway, there is evidence that these complications may be developing prior to diabetes diagnosis.

The current postprandial glucose limits to reduce arterial risk, as outlined by the European Diabetes Policy group, are 7.5mmol/L to reduce arterial risk and 9mmol/L

to reduce microvascular risk [170]. The American Diabetes Association has set no such limits preferring to advise individuals with diabetes to maintain their 'glucose levels in the normal range or as close to normal as is safely possible' [272].

1.2 Weight loss

1.2.1 BMI and the risk of type 2 diabetes

Obesity is a powerful risk factor for type 2 diabetes [89, 273-277]. Over 20 years ago the World Health Organisation (WHO) declared obesity the single most modifiable factor in reducing type 2 diabetes risk [278]. Increasing central adiposity, rather than weight gain per se, is associated with insulin resistance - the main culprit in diabetes and diabetes associated complications such as hypertension, dyslipidemia and increased risk of CVD [279-285]. Although obesity implies excess body fat, instrumentation to measure body composition is not routinely used in a clinical setting [286]. The body mass index (BMI; body mass(kg)/ height^2(m^2)) originating from Quetelet's 'average man'[287] in [288], provides a measure of the body mass corrected for height and serves as a surrogate measure of the overall fat content of the body [289]. Standard ranges of BMI are used to classify overweight and obesity despite potential differences due to age, gender and ethnicity [290]. The current diagnostic criteria for overweight and obese individuals are 25–29.9kg/m^2 and >30kg/m2 respectively [290, 291]. Individuals classified as 'normal weight' have a BMI of 18.5-24.9kg/m^2. Obesity increases both the risk of diabetes and the comorbidities associated with diabetes incrementally above a BMI of 20-22kg/m^2 [19, 286, 292, 293]. Individuals with type 2 diabetes are advised to reduce their weight to achieve a BMI<25kg/m^2 [23-26]. Some studies have used waist circumference or waist to hip ratio as a valid predictor of central obesity, although the lack of consensus

between different cut off points for different nationalities [276, 294], age groups [294] and gender [273, 274, 295] hinders comparisons between studies. Other organisations advocate a weight loss of 5-7% of current weight [27, 28, 296].

The minimum mortality and morbidity risk occurs at a BMI of $20–25kg/m^2$ [290, 291]. Although increasing mortality and morbidity risk is generally associated with increasing BMI [297, 298], factors such as the distribution of the fat [101, 285, 299, 300], level of physical fitness [301], age [302] and gender (greater risk in men than women [303]) may alter the risk of diabetes. Genetics may also be important, with some individuals more susceptible to insulin resistance when exposed to environmental factors that promote obesity, while others are more resistant [304].

Weight gain in obesity arises because of disproportionate fat accumulation in the adipose tissue as a result of discrepancies in long term energy balance; energy intake exceeding energy expenditure over a prolonged period of time [305, 306]. Negative energy balance achieved through energy restriction has the greatest impact on the rate and amount of weight loss, while the impact of macronutrient composition is comparatively much smaller over the longer term [306-308]. The contribution of over nutrition, obesity and diabetes is perhaps best illustrated by examining the prevalence data in the Asia Pacific region during and post World War I and II; the abundance of food post war increased in parallel with the food consumption per capita which also mirrored the increased prevalence of type 2 diabetes [309]. In addition, Eaton and Kronner reported over 20 years ago that the prevalence of diabetes in hunter-gatherer societies was 1-2% compared to 10% in industrialised nations [310]. Furthermore,

small babies with large placenta have a sixfold increase in the risk of diabetes or impaired glucose metabolism [311].

1.2.2 Prevalence, obesity and type 2 diabetes

World wide, 60-90% of individuals with type 2 diabetes are either overweight with excessive abdominal fat distribution [312] or obese [16, 18, 106, 313]. In Australia, the obesity rates are rapidly rising, increasing from 7.2% to 17.1% for men and 7% to 18.9% in women from 1980 to 2000 [305] with 66% of type 2 diabetes currently attributed to obesity [1]. Furthermore, the average waist circumference increased 2.1cm between 2000 – 2005 [65].

Almost 50% of the population of developed countries is overweight or obese [314]. In developing countries, obesity often coexists with malnutrition, with 79% of the adult population in Nauru reported as obese[315]. Parallel with obesity, the number of individuals with type 2 diabetes in developing countries is expected to climb from 84 million in the year 2000 to 228 million by 2030, representing a 170% increase [316].

1.2.3 Epidemiology, weight gain and risk of type 2 diabetes

Prospective and cross sectional studies in a number of countries such as Norway [317], Sweden [318], Israel [319] and the United States [320] have demonstrated that increasing weight elevates the risk of type 2 diabetes. More recent studies have shown that obesity can increase the risk of developing type 2 diabetes by greater than 90 fold[299, 313] and CHD by six fold [30], particularly when the fat is distributed intra-

abdominally[101, 299, 300]. The Nurses Health Study followed 114,824 women over 14 years and reported an age adjusted risk of developing diabetes, which increased from 1.0 at 18 years for a BMI of <22kg/m^2, to a relative risk of 93.2, at age 35-55 years for a BMI>35kg/m^2 [313]. In a different population, Knowler et al. reported similar risks in Pima Indians, with one or both parents with type 2 diabetes; the age adjusted risk of developing diabetes was 90.3 with a BMI>40kg/m^2, compared to a BMI of <20 kg/m^2[106]. The data from these diverse populations suggest the impact of obesity on the risk of developing type 2 diabetes is universally applicable [30].

A weight gain of 5-10kg in adults correlated with a two fold increase in type 2 diabetes risk. This risk was increased in individuals with a greater baseline weight [313, 321] or in individuals who gained more weight over the measurement period [313, 321]. A weight loss of 15-20% in the year following the diagnosis of diabetes has been shown to reverse the additional morbidity of being overweight [322] and reverse type 2 diabetes [323].

1.2.4   Intervention studies, IGT and progression to type 2 diabetes

Weight reducing dietary patterns have demonstrated the importance of lifestyle interventions in preventing the progression of IGT to type 2 diabetes [16, 17, 324, 325]. Two key studies, the Finnish Diabetes Study [16] and the Diabetes Prevention Study (DPS) [17], both conducted on overweight individuals with IGT, reported a reduction of 58% in the risk of attaining diabetes achieved through lifestyle interventions, compared to a control group. This corresponded to a sustained weight loss of 5% of initial body weight and moderate increases in exercise. Interestingly,

the DPP study showed that lifestyle changes were more effective than metformin in reducing the incidence of diabetes (58% compared to 31% respectively) [17].

Other studies support these results. The Da Qing study conducted over six years among Chinese individuals with IFG reported that lifestyle interventions decreased the incidence of type 2 diabetes by 30-40% [325]. The Japanese lifestyle intervention study compared 458 men with IGT to a control group and demonstrated a 67% relative risk reduction over a four year time frame [326]. A further six year study in Asian Indians (Indian Diabetes Prevention Programme) demonstrated a 28% decrease in the development of type 2 diabetes could be achieved through lifestyle intervention, compared to a control group [327].

New data from the DPS follow up study strengthens the case for lifestyle intervention in preventing the progression of IGT to type 2 diabetes. Participants in the active lifestyle arm of the study, who were free of diabetes at the completion of the initial study (approximately four years), were followed for a further three years over which time the was no dietetic counselling. The type 2 diabetes incidence rates over the follow up period were further reduced by 36%, suggesting that the changes achieved during the initial intervention were maintained three years post intervention [328].

In the DPP study, 38% of individuals with metabolic syndrome at baseline were free of the syndrome after the lifestyle intervention. Furthermore, the intervention prevented the development of metabolic syndrome in participants who did not have metabolic syndrome at baseline [329]. This suggests that lifestyle interventions were

also associated with improvements in other CV risk factors including blood pressure, LDL-C, triglycerides and HDL-C [329].

1.2.5 Intervention studies and type 2 diabetes

Over the last 30 years very low energy diets (1700-3400 kj/day) have been used to manage weight loss in individuals with type 2 diabetes, however such approaches are labour intensive, expensive and require medical supervision (reviewed by Henry and Gumbiner [330]). A number of studies have shown that just 7 days of very low caloric restriction can reduce weight and significantly improve glycemic control [331], although neither intensive nor intermittent use of very low calorie diets have been successful in maintaining these benefits long term [331]. More recently, moderate energy reduced diets (3500-6000kj/day) have demonstrated greater weight loss over the longer term than very low energy diets, possibly due to greater compliance, and have since gained widespread acceptance [332]. A meta analysis of 13 clinical trials using either very low or moderate energy restricted diets to treat type 2 diabetes was performed over two time periods. After 12 weeks of energy restriction, decreases in body weight, FBG, triglycerides, total cholesterol, SBP and DBP of 9.6%, 27.5%, 26.7%, 9.2%, 8.1% 8.6% were observed respectively. Over 16 weeks a steady weight loss of 14.7% was observed, followed by a regain of weight over the next 32 weeks to achieve an overall weight loss of 11.1% after two years. FBG levels decreased by 30.2% from baseline over the first 16 weeks, and remained steady for the following eight weeks and then increased proportionally to the weight regained, with a correlation established between weight loss and FBG [30]. When commencing a low

or very low diet in a patient with diabetes, care must be taken to avoid hypoglycaemia by adjusting medication if needed.

Although the benefits of weight loss in obese individuals have been clearly demonstrated, long term weight loss is elusive for many individuals. The UKPDS, in which weight loss was used to manage glycemic control, showed that after three years only 20% of individuals receiving regular dietary counselling in the 'diet alone' subgroup (and not receiving medication) maintained their blood glucose levels within the target range of <7.8mmol/L. After nine years this figure was reduced to just 9% [333].

A combined analysis of two long term studies in individuals with type 2 diabetes showed an intentional weight loss of 0.5-13kg reduced the risk of mortality by 25-28%, although those individuals who lost weight generally had a higher BMI [334, 335]. As CHD is responsible for 60-70% deaths in individuals with diabetes, reducing the increased risk due to excess weight is critical [336, 337].

In the majority of individuals, weight loss is associated with improvements in glycemic control [338-340], although individuals with severely impaired β-cell function may not be as responsive [340]. Improvements in glycemic control are achieved through decreased insulin resistance in peripheral tissues [330, 341-343] and increased insulin secretion [343-345]. The impact of reduced food intake on improved glycemic control can be observed within the first two weeks of energy restriction and is independent of body weight reduction [330, 341, 346]. Fat accumulation contributes to increased insulin resistance and has been associated with

a reduced sensitivity of glucose uptake to insulin stimulation [347], decreased rate of free fatty acid re-esterification [348] and an enhanced resistance of lipolytic enzymes to the inhibitory effect of insulin in peripheral and visceral adipocytes [349, 350].

1.2.6   Physical activity

1.2.6.1   Observational and prospective studies

A number of prospective studies have demonstrated the benefits of physical activity in obese individuals with elevated glucose levels on reducing the progression to type 2 diabetes [98, 351-355]. The risk reduction is due to the ability of increased physical activity to improved insulin sensitivity [356-358]. The Insulin Resistance Atherosclerosis Study, an observational study in middle aged individuals with normal glucose tolerance, IGT or type 2 diabetes clearly demonstrated that both habitual vigorous and non vigorous exercise were associated with insulin sensitivity [359]. In addition, the effect of physical activity on insulin sensitivity is independent of weight loss [356], age, gender and initial BMI [358].

1.2.6.2   Intervention studies, IGT and progression to type 2 diabetes

Physical activity forms an important part of any weight management program as regular physical activity aids in the maintenance of weight loss and prevention of weight regain [360]. For example, the Swedish Malmö feasibility study combined diet and exercise to control weight in men with IGT to prevent or delay the development of type 2 diabetes. Participants reduced their risk of developing diabetes by 50% over six years compared to controls [324].

The associations of physical activity, physical fitness, and changes in the lifestyle with the risk of type 2 diabetes have been assessed by a number of prospective studies and clinical trials in the past decade [351-353, 361, 362]. Review of the scientific evidence confirms that 30 minutes/day of moderate or high-level physical activity is an effective and safe way to prevent type 2 diabetes in all populations [57].

1.2.6.3   Intervention studies and type 2 diabetes

Individuals with type 2 diabetes are generally very sedentary. In inactive individuals, an initial physical activity program of low intensity and limited duration (10 minutes/day) is advocated [363]. Recent studies reviewed by Nield et al. in individuals with type 2 diabetes comparing the effect of diet alone and diet combined with exercise have shown enhanced improvements in glycemic control at both six months and 12 months when dietary treatment was combined with exercise [57]. The benefits of improved aerobic fitness and regular physical activity in type 2 diabetes include increased glucose uptake and enhanced insulin sensitivity (reviewed in [364]) [100, 365], improved blood lipid profiles [332, 366, 367], a decreased risk of diabetes [361, 368] and a reduction in mortality [369]. The reason that many individuals do not lose weight with increased levels of physical activity alone is that they usually increase their energy intake simultaneously; therefore increased physical activity combined with energy restriction should result in increased energy expenditure.

1.2.6.4   Surgery, IGT and type 2 diabetes

Surgical weight loss in individuals with morbid obesity and IGT prevents the development of diabetes by greater than 30 fold, compared with a control diet [370]. Similarly, extreme weight loss, achieved through surgery in clinically obese

individuals with type 2 diabetes, showed that 80-93% of individuals went into remission or improved with respect to glucose metabolism within five to six years [371, 372].

1.3 Diet and Type 2 diabetes

1.3.1 Overview

Diet composition can influence energy intake and has a role to play in the treatment of obesity and type 2 diabetes, although the greatest effects are observed during maintenance of decreased body weight [307]. A lifestyle that favours a traditional high fat diet combined with low physical activity results in weight gain through increased palatability [373], loss of portion control [374] and over consumption of energy, as fat has more than twice the energy density of carbohydrates or protein (reviewed in Bray et al. [306], Astrup et al. [21], Westerterp [373] and Pirozzo et al. [375]). Hence, lowering fat intake is one strategy to maintain weight loss.

The traditional dietary pattern of a low fat (~30% fat of energy) and high carbohydrate (~55% carbohydrate of energy) intake formed the cornerstone of dietary treatment for type 2 diabetes [376]. These recommendations were also endorsed by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [377] and the American Heart Association [378] for the treatment of diabetes associated complications. An analysis aimed at evaluating the effectiveness of weight reducing low fat diets in attaining sustained weight loss in obese individuals compared to other dietary patterns demonstrated that low fat diets were equally as effective (but not more so) in achieving weight loss [375], suggesting

that other factors such as dietary fibre, dietary protein and physical activity may also play a role [379, 380].

The most recent American Diabetes Association nutritional recommendations for type 2 diabetes have been somewhat relaxed suggesting that the optimum mix of macronutrients is yet to be determined, and may vary according to 'individual circumstances' [381]. They do however suggest that dietary intake guidelines should be used as a reference point for the basis of diet formulation. These guidelines recommend a carbohydrate intake of 45-65% of total energy, protein intake of 10-35% and fat intake of 20-35% [382]. Furthermore, saturated fat intake should be maintained below 7% total energy intake/day [376, 383] with a variety of high fibre foods included in the diet [376]. Energy intake should meet weight management goals [382] and physical activity should include 150 minutes of exercise per week [381]. The Australian Guidelines are equally non prescriptive, advising a minimum intake of 130g of carbohydrate daily, inclusion of high fibre food and a reduction in foods containing large amounts of saturated fat [384].

1.3.2 Diet composition

Discussion of individual macronutrients is fraught with uncertainties because each of the individual macronutrients contributes potentially non calorific vitamins, minerals and fibre. Furthermore, changing the quantity of one macronutrient is compensated by a change in either of the two remaining macronutrients. In addition, if the fat is either increased, or decreased and not replaced, the change in energy balance will result in a change in the metabolic milieu, so that a change in weight may overshadow any

metabolic changes. Similarly, changes in the source of macronutrient may alter the metabolic outcomes. These caveats need to be taken into consideration in the following discussion.

1.3.3 Dietary Protein

1.3.3.1 Definition of a high protein diet

There is no standard definition for a high protein diet. Dietary patterns with protein contents >20% of total energy are considered high in protein (HP) and may contain either low or moderate levels of carbohydrates. Higher protein, low carbohydrate diets (HPLC; eg 15-20% total energy from protein, 5% carbohydrate, 70 - 80% fat) are often termed ketogenic diets[385]. It has been proposed that these diets typically divert fat from storage to oxidation and produce measurable levels of ketones in response to carbohydrate restriction and altered insulin and glucagon levels. High protein diets (100-150g/day) with moderate carbohydrate intakes (50-200g/day) contain sufficient carbohydrates to prevent the generation of urinary ketones in most individuals [386] and are gaining popularity for use in individuals with insulin resistance or type 2 diabetes. However, high protein diets may be either high or low in saturated fat depending on the protein source and energy restricted patterns don't always give a clear indication of the absolute amount of protein [387]. The use of high protein, moderate carbohydrate dietary patterns (HPMC; protein content of 20-30%, carbohydrate content 20-45%, total fat content <30% and saturated fat <7% of overall energy intake) in individuals with type 2 diabetes is the main focus of this thesis.

1.3.3.2   Satiety

Satiety is subjectively defined as satisfaction or a feeling of fullness [388]. Protein provides a greater satiety sensation than carbohydrate, followed by lipids [389-393], but is also influenced by palatability, food density and volume, fibre content and GI. Halton and Hu [394] comprehensively reviewed the effects of high protein preload meals on satiety in healthy or obese subjects. These studies, typically constructed using a cross over design, presented subjects with a series of preloads of differing protein concentrations on a number of separate occasions. In some studies, participants were presented with a buffet meal three hours after the preload meal and instructed to eat until full. Food consumption at the buffet was measured. They concluded that 80% of the preload studies reviewed indicated that high protein meals were more satisfying than either high carbohydrate or high fat meals, although several of these studies have been criticized for not controlling for confounding variables, and some of the test meals differed in sensory and physical properties. When these sensory properties were controlled for, high protein preloads resulted in lower energy consumption at a subsequent meal in both lean [392] and obese individuals [393]. Bowen et al. designed a study to compare isocaloric, isovolumetric and palatably matched whey protein with glucose in liquid form in obese individuals. They found the protein to be more satiating than the glucose drink. Whey, soy and gluten were all shown to decrease energy intake at a buffet three hours after preload consumption. Importantly, the different protein sources behaved in a similar manner with results independent of BMI [393]. A possible explanation for the increased satiety of protein may relate to its increased thermic effect compared to the other macronutrients (protein > carbohydrates > lipids [56]).

There are several potential mechanisms by which an HPMC dietary pattern may lead to weight loss, compared to lower protein diets over the shorter term (6 months); increased satiety, decreased subsequent energy and increased thermogenesis [394, 395]. The increased thermogenesis for protein is thought to be due to the fact that the body can not store protein and needs to metabolise it immediately, although there is some evidence that in clinically obese individuals the thermic effect of protein (and fat) is somewhat blunted compared to normal individuals [396]. The higher energy requirement for peptide bond synthesis, urea production and gluconeogenesis are also a probable explanation for the increased thermogenesis of proteins [397, 398]. Figure 1.3.

NOTE:
This figure is included on page 40 of the print copy of the thesis held in the University of Adelaide Library.

Figure 1.3. Mechanisms for weight loss after consumption of a high protein diet. (Adapted from [396]).

1.3.3.3   Epidemiological studies and the risk of diabetes

Epidemiological data suggests that there is no association between protein intake and risk of diabetes in women [399, 400], although vegetable protein has been shown to reduce the risk of diabetes [400]. Studies suggest that HP diets, high in saturated fats

and to a lesser extent dietary cholesterol may increase the risk of CHD [394]. This occurs through consumption of animal protein, which is a primary source of saturated fat and cholesterol. American studies suggest the source of the animal protein may alter the level of saturated fat and dietary cholesterol with red meat higher than white meat, although, in the case of fish, other nutrients such as ω-3 fatty acids may also be involved. Epidemiological studies provide limited evidence that poultry, fish and low fat dairy foods [401, 402] may be more cardio protective than diets high in meat [401, 403], particularly processed meats [404, 405]. In a large 10 year study assessed through a diet history interviews, dairy consumption was inversely associated with all components of insulin resistance syndrome in individuals with BMI > 25kg/m^2 at baseline. Hence, dairy consumption may reduce the risk of diabetes and CVD in overweight individuals [406], with enhanced benefits achieved through replacing high fat with low fat dairy products [401]. No relationships were evident in individuals with BMI < 25kg/m^2 [406]. Similarly, consumption of nuts [407] has been associated with a reduced risk of type 2 diabetes. This having been said, the epidemiological data implies that the effects of protein rich foods low in saturated fats may offer health benefits [396].

1.3.3.4 Energy balance and type 2 diabetes

Nuttal and Gannon have comprehensively reviewed the role of protein in the diet [408]. They reported, as others have, that proteins and amino acids as part of single meal studies consisting of beef, turkey, cottage cheese, fish and soy marginally decreased plasma glucose concentrations but increased insulin production in individuals with untreated type 2 diabetes, suggesting that protein was a potential insulin secretagogue. The only exception was egg white which is slowly digested [409,

410]. Furthermore, the addition of dietary protein to a glucose load synergistically increased insulin release and diminished the postprandial glucose response [410, 411].

An energy balanced HPMC diet, conducted over a five week period, showed that the substitution of carbohydrate to 40% of total energy with protein in individuals with type 2 diabetes improved blood glucose profiles (HbA$_1$c and incremental 24-hour glucose area under the curve) and plasma triglyceride levels [50]. Further reduction of carbohydrate from 40% to 20% of total energy intake and replacing it with fat further improved FBG, HbA$_1$c, incremental 24-hour glucose area under the curve and triglyceride levels [51]. These results are in contrast to the study by Sargrad et al. which showed dietary patterns consisting of 55% and 40% carbohydrate showed minimal improvements in blood lipids, with the 55% carbohydrate pattern significantly improving HbA$_1$c [52]. Table 1.3.

1.3.3.5   Weight loss
1.3.3.5.1   Ad libitum studies in obese and insulin resistant individuals.

The limited number of ad libitum studies comparing HP dietary weight loss regimes in obese and hyperinsulinemic individuals to other dietary patterns have found mixed results; some have observed enhanced weight loss on HP patterns [412, 413], while others found similar weight loss between the diets [414, 415].

Skov el al., comparing two ad libitum fat reduced diets (HP vs. HC; high carbohydrate diet) in overweight individuals, found that substituting protein for carbohydrate enhanced weight loss. After six months, 35% of the individuals

consuming the HP diet achieved a weight loss >10kg compared to 9% in the HC group. Similarly, after 12 months, 17% of participants in the HP group maintained a weight loss >10kg compared to 0% in the HC group [395]. At a two year follow up weight loss was unchanged in both groups from the previous one year weigh in [413]. A more recent ad libitum study, comparing the effects of two HP and two HC diets of varying GI in obese individuals, showed similar overall weight loss, however the proportion of individuals who lost more than 5% weight varied significantly across the dietary pattern suggesting that macronutrients other than protein may also effect satiety in ad libitum settings [416].

Table 1.3: Studies evaluating the role of high protein diets under conditions of energy balance in type 2 diabetes.

Reference	Design	Population	Diet (HPMC) %P:C:F	Control %P:C:F	Duration	Compliance	Results							
								Baseline data	HP diet	Control diet		Baseline data	HP diet	Control diet
Gannon et al. 2003[50]	R, C	12 (10=m, 2=w) T2D	30:40:30	15:55:30	5 weeks	Urea: creatinine ratio	HbA1c	8.1±0.2	-9.9%		+TC	4.4±0.5	-5.5%	
								8.0±0.4		3.9%	+HDL-C	1.0±0.1	2.6%	
							FBG	6.3±0.3	0.0%	0.0%	+LDL-C	2.6±0.4	1.0%	
							+AUC24	21.0±4.2	-43%		++TRIG	1.8±2.6	-17.6%	
Gannon et al. 2004[51]	R, C	8 T2D	30:20:50	15:55:30	5 weeks	Urea: creatinine ratio	HbA1c	9.8±0.4	-22.4%		TC	4.9±0.5	-5.9%	
								9.8±0.9		0.0%		5.0±0.6		-5.6%
							FBG	9.3±0.6	-28.7%		LDL-C	2.7±0.3	4.8%	-2.9%
								10.0±2.5		-11.7%	HDL-C	1.0±0.1	-2.7%	-2.6%
							+AUC24	41.0±8.8	-77%		TRIG	2.8±0.5	-39.4%	
								38.0±9.7		8.9%		3.0±0.8		-14.4%
Sargrad, 2005[52]	R, P	12 (3=m, 9=w) T2D	30:40:30	15:55:30	8 weeks	24 Food recall questionnaire counselling	HbA1c	7.6±1.0	-13.2%	-15.9%	TC	4.7±0.6	-17.1%	-15.8%
								8.2±0.6				5.1±0.6		
							FBG	8.3±1.2	0.0%	-17.6%	LDL-C	2.3±0.3	-14.3%	-12.8%
								8.8±1.3				2.8±0.5		
											HDL-C	0.13±0.3	-5.9%	-5.0%
												1.0±0.1		
											TRIG	5.4±2.9	-36.8%	-31.0%
												6.4±1.7		

HPMC=high protein, moderate carbohydrate dietary patterns, R=Randomised, C=crossover study, P=parallel study, T2D= type 2 diabetes, m=men, w=women, Results stated at mean +SEM (%change relative to baseline), + baseline results for control group not provided; results stated for HPMC diet only, FBG= fasting blood glucose mmol/L, AUC_{24} = mean 24 hr integrated glucose area under the curve with fasting glucose concentration as a baseline; mmol x h/L, HbA_1c =% Glycosylated hemoglobin, Wt= weight in kg, TC= total cholesterol; mmol/L, LDL-C= low density lipoprotein; mmol/L   HDL-C= high density lipoprotein; mmol/L,   TRIG=triglycerides; mmol/L,   Conversion of cholesterol (LDL-C, HDL-C or total cholesterol) mmol/L to mg/dL, multiply mmol/L by 38.7 [cholesterol of 193mg/dL=5.00mmol/L], Conversion of triglycerides mmol/L to mg/dL, multiply by 88.5 [Triglycerides of 159mg/dL=1.8mmol/L], conversion of glucose from mmol/L to mg/dL multiply by 18. Adapted from Kirk et al [54] and Halton et al [394].

Keogh et al. followed up insulin resistant individuals consuming either a HP or high monounsaturated fat eating plan without intensive dietary counselling for four months. Dietary compliance was poor and similar weight losses of around 6.2kg were observed in both diet groups [415]. A one year follow up study showed similar results, although over 50% of the participants dropped out and compliance was again poor [414]. In another four month study, 25-36% of insulin resistant obese women randomised to one of three dietary patterns (two HP patterns (Atkins or zone diet) or a HC diet) lost more than 10% of their baseline weight consuming either of the HP diets compared to only 4% on the HC diet. In all cases no guidance was provided in relation to energy intake [417].

1.3.3.5.2 Energy restriction

Five weight loss studies involving HPMC dietary patterns have been conducted in hyperinsulinemic or type 2 diabetes and are outlined in Table 1.4 [53, 387, 414, 418, 419]. Comparison of these studies is made difficult because of the varying macronutrient composition, study designs and durations. However, the majority of studies demonstrated that equivalent weight loss could be achieved using a variety of dietary approaches [53, 385, 387, 414, 418-421].

1.3.3.5.3 Body composition

What may be of greater importance, particularly in the prevention of insulin resistance, is the location of weight loss. Comparison of isocaloric HP with HC diets has found positive changes in body composition in favour of the HP protocols. Hyperinsulinemic and overweight obese women [419, 422, 423], rather than men, lost

more abdominal fat and total fat consuming a HPMC, compared to a HC dietary pattern [53], despite similar weight losses. Similar results were also observed in women with type 2 diabetes [53], where the metabolic effects were directly attributed to carbohydrate restriction [412]. Gougeon et al. has found that dietary protein requirements may be greater in type 2 diabetes, with the greater flux associated with increased visceral adiposity as well as insulin resistance of glucose and resting energy expenditure particularly in men [424]. Furthermore, a meta regression analysis determined that HP diets with protein intakes > 1.05g/kg, compared to dietary patterns containing protein intakes < 1.05g/kg improve body mass and composition irrespective of energy intake [425].

1.3.3.5.4   Glycemic control in insulin resistance or type 2 diabetes

HPMC and HPLC weight loss dietary patterns in individuals with insulin resistance or type 2 diabetes exhibited reductions in glucose levels, with most [387, 414, 418], but not all [53, 419] significantly more effective than the HC dietary patterns. Table 1.4. A meta analysis of high protein diets in individuals with type 2 diabetes suggested that a 10% increase in carbohydrate intake (energy) was associated with a 3.2+1.2% increase in FBG [54].

The mechanisms for enhanced glycemic control due to the HPMC patterns have only in part been elucidated and reviewed by Layman and Baum [426]. The postprandial response to protein and amino acids is much slower than carbohydrates. Amino acids are delayed in leaving the gut [427]; less than 20% of the amino acids are degraded in the same time frame as carbohydrates [428]. Both the total protein intake providing precursors for gluconeogenesis and total BCAA (branched chain amino acid) intake

influencing glucose-alanine cycling (glucose recycling) [429, 430] impact on overall glycemic control. Jangas et al. have quantitated the role of dietary amino acids in glucose homeostasis whereby they provide a primary carbon source for gluconeogenesis and fuel for the liver [431]. Gluconeogenesis was later found to be responsible for over 70% of the hepatic FBG release, with amino acids responsible for the major carbon source [432]. Other investigators found that every 1g of protein contributes to 0.6-0.7g of glucose through de novo glucose synthesis with carbon sources from amino acids [409, 433]. Furthermore, BCAA from visceral tissue is continually fed to skeletal muscle and blood where transamination provides an amino acid functional group capable of combining with pyuvate to form alanine. Alanine is then transported to the liver to facilitate hepatic gluconeogenesis; it is thought that alanine may contribute as much as 40% of endogenous glucose production under conditions of extensive exercise and 25% under normal conditions [434]. Collectively, these studies corroborate the involvement of dietary protein in glucose homeostasis.

Leucine also appears to have a key role in glycemic control via skeletal muscle. During periods of energy restriction, leucine modulates the insulin signalling pathway, specifically the downstream signal for regulating protein synthesis, the insulin/P13-k signal pathway, in the maintenance of muscle protein.

Elevated leucine concentrations trigger mTOR kinase activity. This mechanism permits mTOR to react in response to leucine concentrations, which in turn permits skeletal muscle to detect the quality and quantity of dietary protein and regulate the rate of muscle protein synthesis relative to the amount of substrate.

Table 1.4: Studies evaluating the role of dietary protein under conditions of energy restriction in individuals with insulin resistance and type 2 diabetes.

Reference	Design	Population	Diet (HPMC) %P:C:F	Control (MPHC) %P:C:F	Duration	Compliance	Results	Baseline data	HP diet	Control diet		Baseline data	HP diet	Control diet
Baba 1999 [418]	R, P	13 obese hyperinsulinemic	40:25:30	12:58:30	4 weeks	Food provided. Diet records, counselling	FBG	5.4±0.1 / 5.2±0.1	-8.2%	-0.1%	TC	5.3±1.3 / 4.4±0.8	-53.4%	-44.2%
							Wt loss	113.2±6.8 / 105.5±4.7	-7.3%	-5.6%	LDL-C	2.6±0.2 / 2.4±0.02	-26.7%	-22.7%
							Fat loss		-7.1 overall	-6.3 overall	HDL-C	1.0±0.1	-12.5%	-8.2%
											TRIG	2.3±0.6 / 1.9±0.3	-53.2%	-44.3%
Brinkworth 2004[414]	R, C	38 obese T2D	30:40:30	15:55:30	64weeks	Urea: creatinine ratio	HbA$_1$c	6.5±0.2 / 6.2±0.2	0.0%	0.1%	TC	5.17±0.2	0.0%	1.2%
							FBG	8.6±0.5 / 7.5±0.3	0.0%	14.6%	HDL-C	0.93±0.05 / 0.95±0.06	2.3%	2.1%
							Wt loss	96.2±4.0 / 91.2±4.3	-3.9%	-2.5%	LDL-C	3.3±0.2	-1.4%	1.3%
							Fat loss	39.2±2.7 / 38.2±2.6	-3.5%	0.0%	TRIG	2.1±0.2 / 2.0±0.2	2.9%	6.6%
Farnsworth 2003[419]	R, P	57 obese hyperinsulinemic; 14=m, 43=f	27:44:29	16:57:27	16weeks	Supplied 60% energy, food records, counselling	FBG	5.4±0.1 / 5..3±0.1	3%	-2%	TC	m=6.1±04 / m=5.2±0.3 / w=5.4±0.2 / w=5.7±0.2	-15% / -4%	-8% / -3%
							Wt loss	m=107±5.8 / m=109±5.2 / w=89.5±2.1 / w=88.1±2.3	-10% / -7%	-9% / -8%	LDL-C	m=4.1±0.3 / m=3.5±0.3 / w=3.7±0.2 / w=3.8±0.2	-17% / 4%	-10.8% / -4%
							Fat loss	m=38.2±3.7 / m=38.2±3.3 / w=43.7±2.0 / w=42.7±2.0	-30% / -19%	-20% / -16%	HDL-C	m=0.9±0.1 / w=1.0±0.1	14% / 3%	9% / 4%
											TRIG	m=2.4±0.3 / m=1.8±0.3 / w=1.7±0.1 / w=1.9±0.1	-28% / -22%	-14% / -8%
Parker 2002[53]	R	36 T2D 19=m, 35=f	28:42:28	16:55:26	8weeks	Supplied 60% energy, food records, counselling	FBG	8.4±0.4 / 7.8±0.2	-14%	-10%	TC	5.16±0.2	-10%	-6.6%
							Wt loss	97.7±17.4 / 91.4±17.4	-4.6%	-4.9%	LDL-C	3.3±0.2 / 3.2±0.2	-9.0%	-3.4%
											HDL-C	0.93±0.03 / 0.95±0.05	-1.0%	-4.2%
											TRIG	2.0±0.2 / 2.2±0.2	-22.7%	-18.9%

Reference	Design	Population	Diet (HPMC) %P:C:F	Control (MPHC) %P:C:F	Duration	Compliance	Results		
								Baseline data	HP diet	Control diet
Gutierrez 1998[387]	C	28 T2D	45:25:30	20:55:25	8 weeks	Food records, counselling	HbA$_1$c	Med=9.9+1.9	-18.2%	9.8%
								Med=8.1+1.0	-15.2%	14.1%
								D= 9.2+1.6		
								D= 7.8+1.9		
							FBG	Med=14.3+2.8	-25%	-4.6%
								Med=10.7+2.1	-34.4%	35%
								D= 14.5+2.9		
								D= 9.5+3.4		
							Wt loss	Med=76.0+15.1	-2%	3%
								Med=74.6+16.8	-1%	1%
								D= 81.7+2.9		
								D= 95.5+3.4		

HPMC=high protein, moderate carbohydrate dietary patterns, MPHC= moderate protein high carbohydrate dietary patterns, R=Randomised, C=crossover study, P=parallel study, T2D= type 2 diabetes, m=men, w=women, Med= individuals taking medication, D= individuals consuming diet alone and no medication, Results stated at mean +SEM (%change relative to baseline), [+] baseline results for control group not provided; results stated are those for the HPMC diet, FBG= fasting blood glucose mmol/L, HbA$_1$c=% Glycosylated hemoglobin, Wt= weight in kg, TC= total cholesterol; mmol/L, LDL-C= low density lipoprotein; mmol/L, HDL-C= high density lipoprotein; mmol/L, TRIG=triglycerides; mmol/L, Conversion of cholesterol (LDL-C, HDL-C or total cholesterol) mmol/L to mg/dL, multiply mmol/L by 38.7 [cholesterol of 193mg/dL=5.00mmol/L], Conversion of triglycerides mmol/L to mg/dL, multiply by 88.5 [Triglycerides of 159mg/dL=1.8mmol/L], conversion of glucose from mmol/L to mg/dL multiply by 18. Adapted from Kirk et al [54] and Halton et al. [394]

In tandem with this cascade of reactions, mTOR has also been shown to trigger upstream phosphorylation of IRS-1, potentially modifying the insulin receptor signal [435-437]. Importantly, these processes do not alter the rate of glucose uptake into the muscles [437]. Figure 1.4.

NOTE:
This figure is included on page 50 of the print copy of the thesis held in the University of Adelaide Library.

Figure 1.4. Insulin signalling cascade regulated by dietary protein [426].

Under conditions of energy restriction or prolonged exercise and a HPMC diet, BCAA are more readily available in the muscle and insulin levels are reduced, leucine regulates fuel choices sparing blood glucose. Parallel to these series of reactions leucine also hampers pyruvate dehydrogenase, reducing the rate of oxidation and regulating glucose degradation by skeletal muscle [428, 438]. Therefore, in the presence of high intracellular levels of leucine, the muscle is able to source glucose from either the blood or muscle glycogen and then capture pyruvate carbon as alanine [426].

1.3.3.5.5   Blood lipids in insulin resistance or type 2 diabetes

In ad libitum studies it has been demonstrated that HPLC and HPMC diets in obese [395, 439] and normal individual [440, 441] significantly lowered plasma triglyceride levels [395]. Similar changes seen in triglyceride levels in energy balanced and weight reducing studies when carbohydrates are exchanged for fat, suggest that carbohydrate reduction is important.

Energy balanced studies showed that replacement of carbohydrate with protein reduced triglyceride in mildly hyperlipidemic individuals by 23% [442] and in individuals with type 2 diabetes by 17 - 39% [51, 52] over periods of four to eight weeks. In the same studies, LDL-C was lowered by 6.4% and HDL-C increased by up to 12% in mildly hyperlipidemic individuals. In those with type 2 diabetes, LDL-C ranged from a decrease of 14% to an increase of 5% and HDL-C decreased by 3 – 6%. Calculation of the cardiovascular risk marker non HDL-C (as total cholesterol minus HDL-C from the data provided) revealed a change in non HDL-C ranging from an increase of 1% to a decrease of 40%.

Under conditions of weight loss, reduction of triglyceride levels was more pronounced in the HP patterns in individuals with insulin resistance or type 2 diabetes [53, 418, 419]. HP dietary treatments have also more effectively lowered plasma total cholesterol in some [53, 419], but not all studies [414]. Table 1.4. Kirk et al. demonstrated that a 10% increase in carbohydrate intake was significantly correlated with a 7.6±0.6% rise in triglycerides in type 2 diabetes [54]. They also suggested a reduction in carbohydrate intake from 65% to 35% may be followed by a decrease of 23% in triglyceride levels although, one would expect individuals with higher baseline triglycerides to be even more responsive to this change [419, 423].

1.3.3.5.6   Limitations to study comparisons

Limitations to the comparisons made between the studies in Tables 1.3 and 1.4 included the lack of differentiation between the protein sources and differences in study designs and timeframes.

1.3.3.6   Hypertension

A limited number of studies have shown that HP diets more effectively lower blood pressure than HC diets [443, 444] in the normal population, however in a diabetic population, most studies have shown this not to be the case [414, 445]. This could be due to the fact that many individuals with type 2 diabetes are sensitive to salt, fortunately with concomitant greater responsiveness to sodium reductions [446]. Moderate reductions in dietary sodium intake (2400 mg/day) decreased blood pressure by 5mm Hg systolic and 2mm Hg diastolic in hypertensive patients and by 3mm Hg systolic and 1mm Hg diastolic in normotensive patients [447]. Although there are wide variations in blood pressure responses, the lower the sodium intake, the greater the lowering of blood pressure [448].

1.3.3.7   Potential adverse effects of protein diets

1.3.3.7.1   Diabetic nephropathy

1.3.3.7.1.1   Defining diabetic nephropathy

Diabetic nephropathy is the decline in kidney function as a consequence of diabetes [229]. It is usually first clinically detected by the presence of small amounts of

albumin in the urine. Increasing inflammation and damage to the glomeruli results in increased levels of albumin in the urine to the point where full-fledged proteinuria develops [229].

Several large scale, well controlled, intervention trials provide convincing evidence of the role of hyperglycemia the development of nephropathy [224, 269, 449, 450]. As many individuals with type 2 diabetes do not develop nephropathy, it is likely that other factors such as age [220], blood pressure [183, 221-223], ethnicity [224], genetic predisposition and familial clustering [214, 216, 225-228], diabetes duration [229], socioeconomic factors [217], smoking [230, 231], physical activity and obesity are involved [232]. Protein intake has also been implication in disease initiation and progression, particularly in individuals with impaired renal function, although this point remains controversial [233].

Epidemiological data suggests that a high protein intake was not related to a decline in renal function in individuals with normal renal function. In mild renal insufficiency defined as a glomerular filtration rate (GFR) > 55 but < 80 mL/min per $1.73m^2$, high protein intake was associated with a decrease in GFR, however a causal relationship has not been demonstrated [451]. There is a suggestion that substitution of red with white meat, fish or chicken may be beneficial [452]. Compelling evidence for restricting dietary protein in the early stages of disease progression in individuals with type 2 diabetes is not yet available.

1.3.3.7.1.2   Prevalence

Diabetic nephropathy is the principal cause of end stage renal disease (ESRD). A two fold increase in the incidence of ESRD has been observed in the US [453], Europe [454] and Australia [455] over the last 10 years-almost certainly related to diabetes. Consistent with this trend, the incidence of ESRD is likely to increase as the increasing prevalence of diabetes in an aging population [456]. The AusDiab Kidney study was the first population based Australian nationwide diabetes prevalence wide study; it showed that approximately 16% of the Australian adult population have proteinuria, hematuria, or reduced GFR. In individuals with diabetes compared to individuals without diabetes the prevalence of proteinuria was four times higher (10.7% *versus* 1.9%), the prevalence of a GFR < 60 ml/min per 1.73 m^2 was three times higher in those with diabetes mellitus (33.1% *versus* 9.8%) [455]. Between a quarter (UK and Canada) to half (US) of all individuals with long term type 2 diabetes have clinically detectable nephropathy [207-209]. Furthermore, a 6-10 fold increase in the incidence of ESRF has been observed from 30-50 years to 70-90 years of age in the UK [210, 211].

Cross sectional studies in individuals with diabetes suggest that 20% of individuals have microalbuminuria, the majority present at the time of diagnosis; this is usually indicative of irreversible renal damage in approximately 10-30% of these individuals [457]. In individuals with advanced retinopathy, this prevalence rises to almost 50% [458]. In addition, annually, 2-3% of individuals with microalbuminuria will advance to overt proteinuria [212].

The prevalence of diabetic nephropathy is dependant on ethnicity and gender; Asians [213], Pima Indians [214, 215], African Americans [216, 217], Pacific Islanders [218], Israeli Jews of non Ashkenazi origin [219] appear more vulnerable compared to Europeans. Within these populations black individuals with type 2 diabetes were up to four times more likely than white individuals to develop end stage renal disease (ESRD) [216, 217]. Furthermore, gender becomes more important as the disease progresses. A European study demonstrated that while the prevalence of microalbuminuria was similar between males and females, the incidence of microalbuminuria progressing to macroalbuminuria was three fold higher in males than females [176].

1.3.3.7.1.3   Optimum Targets for diabetic nephropathy

At the point of diabetes diagnosis, clinical strategies should be put in place to prevent the development of renal disease [459, 460] and minimize CVD [461].

Microalbuminuria is the best index of renal damage [209, 462]. Microalbuminuria is defined as the urinary albumin excretion rate (UAE) of 20-200 μg/min or 30-300mg/24hr or 30-300mg/g in a spot urine sample [463-466]. Macroalbuminuria or overt proteinuria is defined as UAE >300 mg/24 hr in at least three consecutive urine samples [208, 463-467].

The largest study in type 2 diabetes with nephropathy, the Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study (RENAAL), examined the effects of baseline level albuminuria, the response to

intensive albuminurea lowering therapy and the effect of residual albuminuria on kidney function. This study found that in individuals with nephropathy and type 2 diabetes, the chief risk factor for elevated creatinine was albuminuria. It also suggested that albuminuria should be deemed a key targeted for therapy with the "lowest achievable reduction in residual albuminuria the goal" [462].

The GFR is also used to evaluate kidney function and is the best approximation of number of functioning nephrons. GFR is a measure of the rate at which the glomeruli produce ultrafiltrate per unit of time. Serum creatinine, blood urea nitrogen (BUN) or creatinine clearance are used to estimate the GFR.

The normal creatinine clearance (Crcl) after adjustment for body is 70 ± 14 mL/min/m^2 for males and 60 ± 10 mL/min/m^2 for females. The typical range for plasma creatinine is 70-114 mmol/L (0.8-1.3 mg/dL) for men and 53-88 mmol/L (0.6-1.0 mg/dL) for women [468]. Normal creatinine clearance rates in healthy lean individuals are 20-25 mg/kg/24hr in men and 15-20 mg/kg/24hr in women [469-471].

Importantly, plasma creatinine is inversely related to GFR in a non linear relationship [472]; in the early stages of renal dysfunction, slight changes in creatinine are indicative of large changes in GFR. Conversely, large changes in creatinine reflect smaller changes in GFR during advanced kidney failure [468]. Chronic kidney disease is defined as a GFR < 60ml/min per 1.73 m^2 for 3 months.

Tight glycemic control has been shown to have a beneficial effect on the initial rate of decline in renal function [460]. The majority of researchers agree that poor

glycemia is one of the key risk factors for the progression of normoalbuminuria to microalbuminuria [231, 473-476], although normalization of GFR at this stage of renal decline is variable [477]. The DCCT demonstrated that the prevalence of proteinuria could be lowered by 40% under conditions of good glycemic control [243]. A goal of HbA$_1$c below 7% is optimum [478].

Hypertension is the second cause of chronic kidney disease and associated with the presence of microalbuminuria, declining GFR and the onset of overt proteinuria [460, 479]. Early intervention with antihypertensive treatment has been shown to lower proteinuria levels and preserve GFR [480-484], while untreated patients experience a decline in GFR of approximately 10 ml/min/year [460]. Both the British hypertension society guidelines for blood pressure control [485] and the UK renal association standards for blood pressure control in renal failure [486] recommend for individuals with diabetes, optimum control is achieved at levels below 130/80 mm Hg or below 125/75mmHg in the presence of overt proteinuria (>1.0 g/24hr). In the early years after diabetes diagnosis, both tight control of blood pressure and glycemic control dramatically reduce the progression of kidney disease. In long term duration of diabetes, blood pressure control has the greater influence on microvascular disease progression [487].

Dyslipidemia is a risk factor for nephropathy and also contributes to macrovascular changes [231, 467]. Aggressive correction of dyslipidemia through medication has shown to delay the progression of chronic kidney disease [488, 489]. A meta analysis of 13 prospective studies in individuals with nephropathy demonstrated that lipid reduction may reduce proteinuria and preserve GFR function [490]. The American

Diabetes Association suggests the goal for LDL cholesterol is < 100 mg/dl for diabetic patients [478] or < 70 mg/dl if cardiovascular disease is also present [491]. Other abnormalities such as retinopathy[492], reduced renal perfusion (due to fluid imbalance) [461] and generalized vascular disease have also be associated with microalbuminuria [493-497].

1.3.3.7.2   Calcium loss

There is some concern that high dietary protein intakes promote urinary calcium excretion. However, most researchers agree that HP diets (1.0–1.5 g protein/kg) have little effect on skeletal metabolism and are associated with normal calcium metabolism [498-502] and are beneficial in reducing fracture rates [503]. Approximately 40% of all adults in the US consume protein intakes in this range and have normal calcium homeostasis [502].

1.3.4   Dietary Fat

1.3.4.1   Total dietary fat intake

1.3.4.1.1   Epidemiological studies, IGT and progression to type 2 diabetes

While large cross sectional epidemiological studies suggest that high total fat intakes may be associated with development of impaired glucose metabolism and type 2 diabetes [37, 504], the data for prospective studies are less consistent. The San Luis Valley Diabetes Study suggested that a higher fat intake predicted the progression from IGT to type 2 diabetes [32] and hyperinsulinemia [505]. The Zutphen study, a 20 year follow up study, suggested positive associations between total fat, especially saturated fat, and glucose intolerance and hyperglycemia [31].   In the Finish and

Dutch cohorts of the Seven Countries Study, the dietary intake of total fat at baseline was associated with an increase in men with newly diagnosed type 2 diabetes, compared to individuals with IGT or normal glucose tolerance [31]. In contrast, the Insulin Resistance and Atherosclerosis Study (IRAS) was unable to establish a significant relationship between fat intake and insulin sensitivity in a total population of 1173 individuals [506]. However, when the data was split according to BMI, obese individuals demonstrated a relationship between higher fat intake and decreased insulin sensitivity [506]. In addition, the relationship between fat intake and diabetes risk was attenuated after adjustment for BMI in the Health Professionals 10 year follow up study [507].

1.3.4.1.2   Intervention studies, obese individuals and total fat intake.

In short term studies (<1 year), a 10% reduction of dietary fat expressed as total energy corresponded to a weight loss of 4-5kg in obese individuals (reviewed by Astrup et al. [508]). Similarly, a fat intake of 25-30% under ad libitum conditions produced weight losses between 2-4kg [509]. A meta analysis of ad libitum diets in normal and obese individuals suggested that high fat intakes contributed to increased body fat, which in turn could contribute to the incidence of type 2 diabetes [21, 510].

Two 12 month studies with a total fat reduction of 10% of total energy demonstrated only modest weight loss in overweight or obese individuals [511, 512]. This is supported by the analysis from a meta study comparing a range of hypocaloric dietary patterns in attaining sustained weight loss in obese individuals [375].

Perhaps the impact of fat reduction on lipid profiles when replaced by carbohydrate is more significant, resulting in increased levels of triglycerides, VLDL-C and decreased levels of HDL-C in the normal population [513], hypercholesterolemic populations [514] and in individuals with type 2 diabetes [41, 515, 516]. Table 1.5. A less favourable total cholesterol: HDL-C ratio was also observed by others in the general populations [517]. Increases in plasma glucose and insulin were also observed when carbohydrate isocalorically replaced fat in type 2 diabetes in some [41, 515] but not all studies [516, 518]. Table 1.5.

1.3.4.2   Type of fat

1.3.4.2.1   Epidemiological studies, IGT and progression to type 2 diabetes

Dietary fatty acids are classified on the basis of their chemical structure and include saturated, monounsaturated and polyunsaturated (ω-3 and ω-6) fatty acids [519, 520]. Hu et al.[521], Lichtenstein et al. [37] and Vessby [522] reviewed the effect of fat type on glycemic control to discover mixed results; some studies in individuals with normal glucose metabolism [505] and IGT [31], but not all [523, 524], reported an increased risk of diabetes associated with an increased intake of saturated fat.

Table 1.5. The effect of high fat (moderate protein) compared to high carbohydrate (moderate protein) dietary patterns on weight loss, glycemic and lipid profiles in type 2 diabetes.

Reference	Design	Population	Diet (MPHF) %P:C:F	Control (MPHC) %P:C:F	Duration	Compliance	Results							
								Baseline data	HP diet	Control diet		Baseline data	HP diet	Control diet
Garg 1988[515]	R, C	10 T2D	15:35:50	15:60:25	4 weeks	All foods provided, in patient setting	HbA1c	11.3±0.6	-31%	-28%	TC	5.8±0.3	-13%	-9%
							FBG	6.5±0.4	-13.7%		LDL-C	3.5±0.3	-1%	-3%
								5.6±0.2		-21.6	HDL-C	0.8±0.1	1%	-6%
							Wt	88.5±3.8	-1.8%	1.9%	TRIG	3.2±0.7	-42%	-23%
Garg 1992[516]	R, C	8 (8=m) T2D	15:35:50	15:60:25	3 weeks	All foods provided, in patient setting	HbA1c	8.7±1.1	-18.4%	-10.3%	TC	6.1±0.6	-21.3%	-16.2%
											LDL-C	3.7±0.6	-18.2%	-18.2%
											HDL-C	0.7±0.06	1.2%	-9.3%
											TRIG	4.0±0.6	-36.2%	-18.0%
Garg 1994[41]	R, C	42 T2D	15:40:45	15:55:30	6 weeks	All foods provided, in and out patient setting	+HbA1c	8.2±0.4	-3.7%		+TC	5.1±0.2	-2.0%	
							+FBG	8.3±0.4	-3.3%		+LDL-C	2.9±0.2	0%	
											+HDL-C	0.9±0.1	4.5%	
											+TRIG	2.19±0.17	-20.1%	
McCargar 1998[518]	R, P	32 T2D	17:33:50	15:55:30	4 weeks	Food records, counselling	FBG	9.2±0.7	-17.6%	-8.9%)	TC	5.3±0.3	-3.9%	-9.7%
								8.7±0.7				5.1±0.3		
											HDL-C	1.5±0.2	-20.0%	-20.8%
												1.4±0.2		

MPHF=moderate protein, high fat dietary patterns, MPHC= moderate protein high carbohydrate dietary patterns, R=Randomised, C=crossover study, P=parallel study, T2D= type 2 diabetes, Results stated at mean +SEM (%change relative to baseline), + baseline results not provided for the control diet; results stated are those for the MPHF diet, FBG= fasting blood glucose mmol/L, HbA1c =% Glycosylated hemoglobin, Wt= weight in kg, TC= total cholesterol; mmol/L, LDL-C= low density lipoprotein; mmol/L HDL-C= high density lipoprotein; mmol/L, TRIG=triglycerides; mmol/L, Conversion of cholesterol (LDL-C, HDL-C or total cholesterol) mmol/L to mg/dL, multiply mmol/L by 38.7 [cholesterol of 193mg/dL=5.00mmol/L], Conversion of triglycerides mmol/L to mg/dL, multiply by 88.5 [Triglycerides of 159mg/dL=1.8mmol/L], multiply mmol/L by 38.5 [cholesterol of 193mg/dL=5.00mmol/L], Conversion of triglycerides mmol/L to mg/dL, multiply by 18. Adapted from Kirk et al [54] and Halton et al. [394].

- 61 -

There is a suggestion that ω-3 polyunsaturated fatty acids may reduce the risk of progression to type 2 diabetes in some [31, 43, 524-526], but not all studies [525, 527]. The most convincing results were observed through the regular consumption of fish containing ω-3 polyunsaturated fatty acids in which the risk of developing diabetes was halved, compared to individuals who did not regularly consume fish [31].

A prospective study involving 84204 middle aged women suggested that saturated or monounsaturated fatty acids, when compared with an isocaloric amount of carbohydrate, was not associated with risk of type 2 diabetes, but that trans fatty acids increase and polyunsaturated fatty acids decrease the risk. They also concluded that replacing 2% of energy from trans fatty acids with an isocaloric amount polyunsaturated fat would lead to a 40% lower risk of diabetes [524]. A subgroup analysis from the same study showed trans fat was directly, and ω-3 polyunsaturated fat was inversely related to C-reactive protein and interleukin-6, both markers of inflammation [528]. The EPIC-Elderly study showed that overall mortality was reduced by 7% in elderly Europeans when polyunsaturated fatty acids were substituted for monounsaturated fatty acids [529].

Vegetable fat, compared to animal fat, was associated with a decreased risk of diabetes in some [89] but not all studies [31, 530].

1.3.4.2.2   Intervention studies, IGT and type 2 diabetes.

The Finnish Diabetes Prevention Program (FDPP) [16], the DPP [531], and the Da Qing Impaired glucose tolerance and Diabetes Study [325] all included dietary advice

to reduce total and saturated fat intake. Collectively, these studies demonstrated a 50% decreased risk for progression from IGT to type 2 diabetes when saturated fat was reduced to less than 10%. Previous studies had set no such limits on either total or saturated fat. Arguably, the most convincing evidence comes from the KANWU study, in which improvements in insulin sensitivity were observed when a proportion of saturated fat was replaced with monounsaturated fat in individuals with type 2 diabetes [532]. Importantly, these benefits were only observed when the total fat intake was below 37% of the total energy intake, which may in part explain the mixed results from the earlier epidemiology studies. The KANWU study also showed that varying the type of fat had no effect on insulin secretion [532].

When compared with high monounsaturated fat diets, high carbohydrate diets (~55% of total energy from carbohydrate) elevated triglycerides and postprandial plasma glucose and insulin, although the monounsaturated diets did not facilitate improvements in FBG or HbA_1c. Under conditions of energy restriction, the effects of the high carbohydrate diets were ameliorated in individuals with type 2 diabetes [53, 533]. Further studies have demonstrated that plasma lipid profiles appear to be similarly affected by polyunsaturated and monounsaturated fatty acids in obese individuals with or without type 2 diabetes [534, 535].

Several studies have shown that trans fatty acids compared to cis unsaturated fatty acids elevate LDL-C and decrease HDL-C [34, 536, 537]. Limited studies have examined the effects of trans fatty acids on glucose metabolism. A 6 week intervention study, in 16 obese individuals with type 2 diabetes resulted in an elevated postprandial insulin response compared to a diet high in cis monounsaturated fat [39] after consumption of a diet in which 20% of the energy was provided as trans-

monounsaturated fatty acids. This suggested trans fatty acids may potentiate insulin secretion, more so than cis fatty acids, at least over the shorter term [39].

Studies in which individuals with type 2 diabetes and hypertriglyceridemia were provided with a dietary pattern supplemented with ω-3 polyunsaturated fatty acids (either from supplements [529] or fish [520, 538]) increased their HDL-C levels and decreased their plasma triglyceride levels [529, 538]. The small increase in LDL-C was off set by the increase in HDL-C [538].

The current recommendation to limit dietary cholesterol to < 200mg daily is based on data gained from the normal population [197]. Weggemans et al (2001) conducted a meta-analysis of 17 studies involving 556 normoglycemic participants. They showed that the addition of 100 mg dietary cholesterol/day increased the ratio of total to HDL-C by 0.020 units (95% CI: 0.010, 0.030), total cholesterol concentrations by 0.056 mmol/L (95% CI: 0.046, 0.065 mmol/L), and HDL-C concentrations by 0.008 mmol/L (95% CI: 0.005, 0.010 mmol/L) [539].

Three clinical trials investigating the role of dietary cholesterol (from eggs) have been carried out with varying results. In the context of a 12 week, low fat, carbohydrate restricted diet, consumption of three eggs (640 mg/day additional dietary cholesterol) by overweight men resulted in improved HDL-C and triglycerides, while the LDL-C and LDL-C: HDL-C ratio remained unaffected. In addition, there was an 83% reduction in the number of individuals classified as having metabolic syndrome 12 weeks from baseline [540]. A second study, conducted with insulin sensitive and insulin resistant postmenopausal women, demonstrated that total and LDL-C concentrations changed very little in all participants when cholesterol intake from

eggs ranged from 113-941mg/day for a period of 4 weeks as part of the US National Cholesterol Education Program (NCEP) Step 1 diet [541]. A further clinical trial investigating whether insulin resistance in overweight participants influenced LDL-C response to dietary cholesterol (up to 800 mg/day) and saturated fat (from eggs) found total cholesterol levels increased, LDL-C did not change and HDL-C levels only increased when four or more eggs per day were consumed [542].

Fernandez and Heron have evaluated the response of plasma cholesterol to dietary cholesterol [543]. Although the within individuals response to dietary cholesterol appears to be reproducible, there is a vast variability between individuals [544-546]. It is thought that approximately 30% of the population are sensitive to dietary cholesterol. These individuals usually have an elevated LDL-C and HDL-C levels which permit the maintenance of the LDL-C: HDL-C ratio, also a marker of cardiovascular risk [547]. McNamara et al. identified that a 100mg/day increase in dietary cholesterol intake may produce a three fold greater increase in plasma cholesterol in sensitive individuals, compared to those that are non responsive [547]. Genetic variation is thought to play a role in responsiveness, and lipid profiles and BMI have been suggested as potential contributors, however the full mechanism is yet to be eluded [543]. The relationship of these finding to type 2 diabetes is unknown.

Collectively, these studies suggest that in type 2 diabetes, increased intakes of polyunsaturated fat and ω-3 polyunsaturated fatty acids may be beneficial, whereas increased dietary intakes of saturated fat and trans fatty acids may adversely impact on insulin resistance and lipid metabolism. The dietary intake of cholesterol in type 2 diabetes requires further investigation.

1.3.5   Dietary Fibre

1.3.5.1   Epidemiological studies and progression to type 2 diabetes

There is a suggestion that food rich in fibre or containing high levels of slowly digested starch may be protect against type 2 diabetes, however the results from the case control and prospective studies have been mixed [31, 43-45, 524, 548-551]. Low levels of diabetes are associated with countries that consume high levels of these foods. In the Nurse's Health study [45], the Health Professionals follow up study [44], the Nurse's Health study II [549], the ARIC study [550] and the Finnish Mobile Clinic Health Examination Survey [551] dietary patterns with high glycemic loads and low in cereal fibre were associated with an elevated risk for diabetes after adjustment for other risk factors. The risk of self reported diabetes in the Iowa Woman's Health study was lowest in the group with the highest whole grain intake. The lowest consumption of refined grain was also associated with a lower risk of diabetes after adjustment for total energy intake and age. A higher ratio of whole grain to refined grains was also significantly related to a reduced risk of diabetes, suggesting a benefit from limiting the intake of refined grains and replacing them with whole grains [43]. In contrast, no association was found between impaired glucose tolerance or diagnosed diabetes and total dietary fibre intake in the 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study [31]. Similarly, no relationship was observed between diabetes risk and total dietary fibre intake in a study of male health professionals [44] or a Nurses Health Study [524].

Several papers have been published using different baseline and follow up data from the Nurse's Health study. These studies examined the role of cereal grains and whole fibre on the incidence of type 2 diabetes with mixed results [45, 399, 552, 553].

Colditz et al. did not find a relationship between dietary fibre and risk of diabetes after the 6 year follow up [399], however subsequent follow up studies did detect a inverse relationship with increased whole grain and cereal fibre intake and reduced risk of diabetes [45, 553].

Low rates of type 2 diabetes have been observed in countries where the intakes of foods rich in fibre or slowly digested starch are high, suggesting these foods may be protective for type 2 diabetes [31]. Others have reported that insoluble fibre has been associated with a reduced diabetes risk [43-45, 549-551].

1.3.5.2   Intervention studies and type 2 diabetes

Thirteen individuals with type 2 diabetes randomized in a cross over design to energy equivalent dietary patterns with either 50g of fibre or 24g fibre (as part of the American Diabetes Association diet; 55% carbohydrate, 15% protein and 30% fat). The high fibre diet reduced pre meal glucose levels by 8.9% (0.7mmol/L) and glucose and insulin AUC by 10% and 12% respectively, more so than the lower fibre dietary pattern [554]. A further study evaluated the benefits of replacing white rice with 70g of whole grain and legume powder on glycemic and CV risk factors in 67 individuals with coronary artery disease (CAD). FBG levels in individuals with (n=21) and without (n=55) diabetes were reduced significantly by 27% and 22% respectively. Similarly, the 2 hour postprandial glucose and insulin levels and β-Cell function estimates were improved in individuals with type 2 diabetes, compared to the control group [555]. Others have demonstrated the benefits of 40g fibre in improving lipid profiles and decreasing blood pressure in those with hypertension and in reducing body weight, although palatability, gastrointestinal side effects and limited food choices are potential barriers to consuming such intakes [381, 556, 557].

Improvements in insulin sensitivity, triglyceride levels and blood pressure were observed in individuals with type 2 diabetes receiving a supplement of 4g of soluble fibre twice a day [558]. A meta analysis of 67 controlled clinical trials demonstrated that dietary patterns high in soluble or viscous fibre decreased both total and LDL-C, although studies involving individuals with type 2 diabetes were not separated from the general population [559].

These improvements are most likely to be caused by the ability of fibre to reduce the rate of digestion and adsorption of carbohydrates and in regulating several metabolic hormones (including glucagon-like peptide-1 and gastric inhibitory peptide [560, 561]) and by slowing of rate of gastric emptying and absorption of food [556, 557]. These hormones are secreted in response to the ingestion of lipids, glucose or non digestible carbohydrate and are responsible for the enhanced insulin secretion following a meal [561].

1.3.6   Carbohydrates

Both the quantity [562] and source of dietary carbohydrates [563], the nature of the starch [564], food structure and method of food processing [565] as well as other food components including proteins and fats and the composition of the previous meal (reviewed in [566]) all impact on the postprandial glucose response to food intake. The glycemic index (GI) of a food provides a measure of the carbohydrate's ability in the food to elevate postprandial glucose levels when compared to an equivalent amount of carbohydrate (50g) provided as either glucose or white bread. Glycemic

load (GL) is estimated from the GI by multiplying it by the amount of carbohydrate [562, 567].

1.3.6.1   Epidemiological studies and progression to type 2 diabetes

Several epidemiological and cross sectional studies report a relationship between increased total dietary carbohydrate intake and a reduced prevalence of type 2 diabetes [504, 568, 569]. In contrast, the findings from cohort studies do not support a relationship between high intakes of carbohydrate and type 2 diabetes [44, 45, 399, 570].

Mayer-Davis et al [562] report inconsistent relationships between type 2 diabetes incidence and GI and GL; one study reports a positive relationship between carbohydrate amount and GI and GL [45], other studies report a negative protective relationship [43, 550], while other studies report a positive relationship between carbohydrate and GI and a negative relationship for GL [44, 549], with the last study positive for GI [571]. A possible explanation for these inconsistencies includes the physiological effect of other macronutrients in mixed meals on the postprandial glucose and insulin response. These effects may extend beyond the 2 hour limit for measuring GI [572-574]. Furthermore, the response to repeated exposure to the same meal at different times of the day can vary [572, 573, 575].

Cross sectional analysis from both the Cohort study Diabetes and Atherosclerosis Maastricht (CoDAM) Study and the Hoorn Study examined the relationship of GI and GL with blood glucose, insulin and lipid profiles and CRP. Cereal and dairy products, tuber vegetables, and fruit were the main predictors of GI and GL. GI was positively

associated with fasting insulin, insulin resistance, total:HDL-C and CRP and inversely associated with HDL-C after adjustment for confounders. No significant relationships were observed with GL [576]. In contrast, Mosdol et al. could not confirm the protective effects of low GI and GL dietary patterns on the risk of type 2 diabetes [577].

1.3.6.2   Intervention studies type 2 diabetes

A very recent 12 month randomised study in type 2 diabetes evaluated the effects of a low GI diet compared to the American Diabetes Association dietary pattern [27] on HbA$_1$c. Similar reductions in HbA$_1$c were observed with both dietary patterns [578]. A larger study, also conducted in type 2 diabetes confirmed that body weight and HbA$_1$c were not affected by altering the amount of carbohydrate or GI of the diet, however over the longer term (12 months) postprandial glucose levels were reduced [579].

1.3.6.3   Simple sugars and type 2 diabetes

In the Australian diet, sucrose is the main sugar sweetener. Clinical studies suggest that dietary sucrose does not play a role in the aetiology of type 2 diabetes [571, 580] and there is no need to restrict sucrose any more than starch [571, 581]. Fructose stimulates insulin secretion less than either glucose or glucose-containing carbohydrates [582]. In the American diet, high-fructose corn syrup is the major sweetening agent. Fructose has been shown to reduce postprandial glucose levels when replaced for sucrose or starch [581, 583-585], although these benefits are

negated by the adverse effects on fasting total and LDL-C in individuals with type 2 diabetes [585], and fasting total and LDL-C and triglycerides in individuals without diabetes [586-589].

1.3.6.4   Other Dietary Factors

1.3.6.4.1   Dietary Alcohol

A minimum of 13 studies demonstrated that a moderate consumption of alcohol is associated with a protective effect on type 2 diabetes, whereas a high consumption was associated with increased risk of diabetes (reviewed in Hodge et al [85]). In a 20 year follow up Finnish study, compared to a control group consuming 5g alcohol/day, men consuming between 5-29.9g alcohol/day and women consuming 5-19.9g alcohol/day correlated with a decreased incidence of diabetes [86]. Data from a prospective study including almost 90,000 individuals suggested that low to moderate alcohol consumption was associated with a reduced risk of coronary vascular disease risk in men with type 2 diabetes compared to men without diabetes [590].

1.3.6.4.2   Coffee consumption

Even though coffee is the most consumed beverage in the world, only a few studies have been conducted to evaluate the relationship between coffee consumption and type 2 diabetes. Limited research suggests that high coffee consumption ($\geq$ 6 cups per day) is associated with reduced IGT [87] and type 2 diabetes risk [591-594] independent of BMI, the levels of physical activity and alcohol consumption, yet the reason for the reduction remains unclear. In the general population, the relationship between CVD and coffee consumption remains controversial, however a recent large

prospective study has shown that habitual coffee intake was associated with reduced total, CVD and CHD mortality in individuals with type 2 diabetes [595]. Green tea, containing caffeine has also been associated with a protective effect for type 2 diabetes in a Japanese population [596].

1.3.6.4.3   Micronutrients, vitamins and the risk of diabetes

Vitamins and minerals have also been implicated in the development of type 2 diabetes. Increased dietary intakes of vitamin C [31], vitamin D [597-600], vitamin E [601-603] and several tocopherols [601], carotenoids [604], chromium [605-607], calcium [597] and magnesium [608-610] have been associated with a reduced risk of development of type 2 diabetes.

1.3.6.4.3.1   Magnesium, grain and type 2 diabetes

Epidemiological data suggest that the intake of magnesium from whole grains (and green leafy vegetables and nuts) was inversely associated to the incidence of type 2 diabetes [399]. A 16 week randomised clinical trial determined that magnesium supplementation in individuals with low serum magnesium levels (serum magnesium levels $\leq$ 0.74mmol/l) and type 2 diabetes improved insulin sensitivity, FBG and HbA$_1$c levels, compared to a control group consuming a placebo [611]. Others have observed improvements in systolic blood pressure with magnesium supplementation [612]. A meta analysis of 9 studies conducted over 4–16 weeks in individuals with type 2 diabetes support these results, with the additional finding that dietary magnesium improves HDL-C [610]. Similar improvements in glycemic control were observed in individuals with insulin resistance [613].

1.3.6.4.3.2   Chromium and type 2 diabetes

The metabolism of both carbohydrates and lipids requires chromium [614-616]. Cr deficiency has been linked to raised blood glucose, insulin, triglycerides and cholesterol levels and decreased HDC-C in the general population consuming a normal diet [617]. Individuals with glucose intolerance require about 200 μg Cr /day of supplemental Cr to improve glucose metabolism. Individuals with diabetes have a much higher requirement for chromium and usually require more than 200 μg Cr /day, such that the response to Cr is related to the degree of glucose intolerance [617].

The form of chromium supplementation in diabetes is also important. Chromium as Cr chloride (200 μg/day) did not elicit a positive response in individuals with type 2 diabetes [618, 619]. However, levels of supplementation > 400 μg/day or more yield positive effects; sixteen to 32 weeks of daily supplementation with 600 μg of Cr as Cr chloride produced a decrease in FBG from 14.4 mmol/L to 6.6 mmol/L [620]. Positive effects were also reported with supplementation of 500 μg/day [621] and up to 1000 μg/day of Cr as Cr chloride [622]. Furthermore, Glinsmann and Mertz reported 250μg Cr /day produced favourable effects on blood lipids, although it took 28 – 64 weeks for the effects to become noticeable. Cr picolinate has been found to be more effective than Cr chloride in both animal [623] and human studies [622]. Two hundred micrograms of Cr consumed daily as Cr picolinate resulted in improved glucose and lipid parameters in individuals with Type 2 diabetes [624, 625] with a enhanced response at 1000 μg Cr /day [626].

Chromium acts through increasing increased insulin receptor number, increased insulin receptor phosphorylation and increased insulin binding [617].

1.4 Summary

Diabetes or 'diabesity' is one of the fastest growing non communicable diseases in the world and is largely preventable through diet and exercise. The evidence from epidemiological and clinical studies suggests that diet can profoundly affect the development and progression of type 2 diabetes. Diets high in fats potentially lead to over consumption of energy and subsequently obesity. In particular, dietary patterns high in saturated fats and trans fatty acids increase insulin resistance and are detrimental to lipid metabolism elevating LDL-C, whereas monounsaturated and polyunsaturated fat improve LDL-C. The high carbohydrate dietary approach, promoted for numerous years through many diabetes associations around the world has clearly done little to halt or overcome the burgeoning problem of type 2 diabetes, although diets high in fibre or slowly digested starch may be protective of type 2 diabetes. In contrast, a dietary pattern higher in protein offers an alternative promising approach to diabetes management.

Currently, there are still only a limited number of studies that have investigated the effects of HP dietary patterns in individuals with type 2 diabetes. Based on these studies, short term use of HP reduced carbohydrate diets primarily resulted in significant improvements weight loss, body composition, glycemic control (HbA$_1$c and FBG) and lipid profiles (lower triglycerides and total cholesterol) and hypertension in individuals with type 2 diabetes. Improved glycemic control over the longer term will result in reduced resistance to insulin in peripheral tissues (and possibly increased secretion of insulin). This will more efficiently facilitate the disposal of glucose in the adipose tissue and skeletal muscle. Improved glycemic

control will reduce the influx of glucose through the polyol and hexosamine pathways, and decrease both the activation of protein kinase C and the formation of AGE's, with a net result of a reduction in the production of ROS superoxide and consequent endothelial damage. This could potentially reduce microvascular damage and to a lesser extent macrovascular damage and requires investigation through well controlled clinical trials.

Benefits of HP diets also include increased satiety, thermogenesis and sparing of lean body mass. It appears the relationship between glucose and leucine is pivotal in understanding the relationship between dietary protein and carbohydrates. Leucine is known to alter the insulin signalling pathway responsible for the down stream control of protein synthesis; this is particularly important in maintaining muscle mass under conditions of energy restriction. Although total dietary protein is important for providing precursors for gluconeogenesis, leucine concentrations appear to dictate glucose recycling through the glucose-alanine cycle, and ultimately the use of glucose by skeletal muscle. Hence, dietary patterns higher in protein and in particular leucine have the potential to offer advantages in diabetes management.

While long term research in this area is still in its infancy, it appears that in general HP dietary patterns are not harmful and may be beneficial in improving body composition, blood glucose and lipid profiles, and reducing the risk of diabetes associated complications. However, there is a need for a greater number of well designed and supported clinical studies to investigate the role of dietary protein in the management of type 2 diabetes. Following this, there is also a need for mechanistic studies to determine all metabolic pathways so that diets may be adequately tailored to

optimise glycemic control and minimise microvascular and macrovascular complications.

1.5 Research arising from this review

1.5.1   Thesis aims and hypothesis

Chapter 2: To comprehensively assess diurnal glucose profiles in free living individuals with type 2 diabetes using continuous blood glucose monitoring (CGMS), when consuming a high protein moderate carbohydrate diet in energy balance, when carbohydrate distribution at meals is variably distributed, but total carbohydrate remains the same. We hypothesised that an even distribution of carbohydrates across the day may be an optimum pattern compared to carbohydrate loaded at breakfast, lunch or dinner for attenuating PPG excursions to reduce vascular complications.

Chapter 3: To confirm in the same subjects, the acute measures of glycemic control over time using a CGMS, when consuming a controlled high protein, moderate carbohydrate diet, in which the carbohydrates were evenly distributed across the day, in free living subjects with type 2 diabetes. We examined HbA_1c, FBG and assessed diurnal blood glucose profiles as G_{max}, T>12 and AUC_{20}. We hypothesised that all measures of acute blood glucose control would remain constant over time.

Chapter 4: To determine the contribution of the postprandial glucose response as assessed by G_{max}, T>12 and AUC to HbA_1c, the most common measure of glycemic control in type 2 diabetes. As it is generally accepted that weight management is one of most important factors in achieving glycemic control in individuals with type 2

diabetes, we examined diurnal glucose profiles on a high protein moderate carbohydrate diet during weight reduction in free living individuals with type 2 diabetes. We hypothesised that postprandial measures of glycemia in addition to fasting glucose would correlate with HbA$_1$c.

Chapter 5: To explore the relationship between modest weight loss induced by 8 weeks of an energy restricted high protein, moderate carbohydrate regime, in obese individuals with type 2 diabetes, and its consequential effects on cognition, and to investigate whether these changes could be related to changes in blood glucose levels. The effect of eggs as a dietary source of cholesterol on cognitive function was also evaluated. We hypothesized that daily consumption of an additional 400mg of dietary cholesterol (2eggs/day), compared to an equivalent animal protein low in both saturated fat and dietary cholesterol would result in similar weight loss and similar improvements in cognitive function compared to baseline values (ie dietary cholesterol would have no adverse effects). Cognitive functioning was assessed using short term memory, working memory, speed of processing, psychomotor speed and executive function. Simultaneous glucose levels were attained using CGMS. Glycemic control was measured by FBG, HbA$_1$c, G$_{max}$, T>12, and AUC$_{24}$.

Chapter 6: To investigate the effect of a hypocaloric high protein, moderate carbohydrate diet, either high or low in dietary cholesterol, on blood glucose and lipids profiles and cardiovascular risk markers, in individuals with type 2 diabetes. We hypothesized both HP dietary patterns would similarly improve glycemic control, lipid profiles and cardiovascular risk markers.

Chapter 7: To investigate the effect of a weight loss high protein moderate carbohydrate diet on renal function in individuals with type 2 diabetes. We hypothesized that a hypocaloric HPMC diet would not alter renal function in individuals with normal renal function.

Chapter 2: Effect of carbohydrate distribution on post prandial glucose peaks using continuous glucose monitoring in type 2 diabetes.

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Developed protocol, prepared ethics applications (CSIRO and University of Adelaide),

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wrote manuscript and acted as corresponding author.

Signed…………………………..   Date…………………………

Jennifer Keogh

My contribution to this paper involved:

Contribution to the diet design.

I give consent for Karma Pearce to present this paper for examination towards the

Doctor of Philosophy.

Signed…………………………..   Date…………………………

Manny Noakes

My contribution to this paper involved:

Contribution to the study design, assistance with data interpretation and manuscript

evaluation.

I give consent for Karma Pearce to present this paper for examination towards the

Doctor of Philosophy.

Signed…………………………..   Date…………………………

Peter Clifton

My contribution to this paper involved:

Contribution to the study design, assistance with data interpretation and manuscript evaluation.

I give consent for Karma Pearce to present this paper for examination towards the Doctor of Philosophy.

Signed………………………..   Date…………………………

2.1 Abstract

Background: Large postprandial glucose peaks are associated with increased risk of diabetic complications and cardiovascular disease.

Objective: To investigate the effect of carbohydrate distribution on postprandial glucose peaks using continuous blood glucose monitoring (CGMS), when consuming a moderate carbohydrate diet in energy balance in subjects with type 2 diabetes.

Design: Twenty three subjects with type 2 diabetes were randomized to each of 4, 3-day interventions in a cross over design with a 4 day wash out period. Identical foods were provided for each treatment with a total carbohydrate: protein: fat ratio of 40%:34%:26%, but differing in carbohydrate content at each meal: even distribution (CARB-E ~70g carbohydrate), breakfast (CARB-B), lunch (CARB-L) and dinner (CARB-D) each containing ~125g carbohydrate in the loaded meal in a 9MJ diet . Glucose levels were continuously measured using CGMS. Outcomes were assessed by postprandial peak glucose (G_{max}), time spent above 12 mmol/L (T>12) and total area under the glucose curve (AUC_{20}).

Results. Daily G_{max} differed between treatments (p=0.003) with CARB-L(14.2 $\pm$ 1.0mmol/L) = CARB-E(14.5$\pm$0.9mmol/L) = CARB-D(14.6$\pm$0.8mmol/L) < CARB-B(16.5$\pm$ 0.8mmol/L). Meal G_{max} was weakly related to carbohydrate amount and glycemic load (r=0.40-0.44)

T>12 differed between treatments (p=0.014) and there was a treatment x fasting blood glucose (FBG) interaction (p=0.003) with CARB-L (184$\pm$74min) <CARB-B (190$\pm$49min) <CARB-D (234$\pm$87min) <CARB-E (262$\pm$91min).

Total AUC_{20} was not significantly different between treatments. After adjustment for FBG treatment became significant ($p=0.006$), AUC_{20} CARB-L (10049 ± 718) <CARB-E (10493 ± 706) <CARB-B (10603 ± 603) < CARB-D (10717 ± 638) [mmol/Lx20hr].

Conclusion: CARB-E did not optimise blood glucose control as assessed by postprandial peaks whereas CARB-L provided the most favourable postprandial profile.

Key words: type 2 diabetes, carbohydrate distribution, moderate carbohydrate diet, continuous glucose monitoring, energy balance, postprandial blood glucose.

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Chapter 3: Consistency of diurnal glucose control over time in individuals with type 2 diabetes.

3.1 Abstract

Background: Elevated postprandial glucose levels are associated with increased risk of diabetic complications and cardiovascular disease.

Objective: To investigate the reproducibility of 24 hour glucose monitoring (CGMS) when consuming a controlled diet, in free living subjects, with type 2 diabetes.

Design: Six subjects with type 2 diabetes were provided with identical daily meals to be consumed for 3 consecutive mid week days in both the fall(T_{fall}) and spring T_{Spring}. The dietary pattern consisted of a total carbohydrate: protein: fat ratio of 40%:34%:26% in which the carbohydrates were evenly distributed across the day in 9MJ diet. Glucose levels were continuously measured using CGMS. Outcomes were assessed by HbA_1c, fasting blood glucose (FBG), postprandial peak glucose (G_{max}), time spent above 12 mmol/L (T>12) and total area under the glucose curve (AUC_{20}).

Results. G_{max} differed between treatments ($p=0.017$) with T_{fall} (13.6$\pm$1.4mmol/L) significantly higher than T_{Spring} (10.4$\pm$0.82mmol/L).

T>12 approached significance ($p=0.\ 0.084$) with T_{fall} (436.7$\pm$211.4mins) higher than T_{Spring}(26.6$\pm$26.7mins).

Total AUC_{20} ((T_{fall} 160.2$\pm$17.4 > T_{spring} 138.9$\pm$1.0[mmol/L/hr over 20 hr] ($p=0.133$)), HbA_1c ((T_{fall} 8.2$\pm$0.68% > T_{spring} 8.0$\pm$0.63%); $p=0.699$) and $FBG_{5.30am}$ ((T_{fall} 6.0$\pm$0.

< T_{spring} 6.6 $\pm$0.41)mmol/L; p=0.211) were not significantly different between T_{fall} and $T_{spring.}$

Differences in daily sunlight hours approached significance (p=0.097) with T_{fall} (10:42$\pm$0:33 hrs) lower than T_{Spring} (11:51$\pm$0:09hrs).

Conclusion: With the exception of G_{max}, and a trend toward change in T>12, HbA_1c, $FBG_{5.30am}$, AUC_{20} and T>12 remained constant over time when exercise levels and ambient temperature remained constant.

3.2 Introduction

HbA_1c is the most common marker of glucose control in type 2 diabetes, although individuals with the same HbA_1c levels may have different glucose variability, both within the day and from day to day [123]. The majority [634-636] but not all [637] studies evaluating the consistency of HbA_1c over time have shown an effect of seasonality; HbA_1c values were higher in winter and lower in summer; this may adversely affect cardiovascular risk and increase mortality [635] with the incidence of cardiovascular related deaths reported to be higher in winter than summer [638-640]. The explanation given for higher HbA_1c winter values include increased dietary intake and higher fat mass [641, 642], reduced exercise [641, 642], northern hemisphere holiday period [137] and lower ambient temperatures [634, 635, 643, 644]. We aimed to explore the reproducibility of glycemic control over time by repeating one intervention arm of a previously conducted study (chapter 2), using a continuous glucose monitoring system (CGMS), in free living subjects with type 2 diabetes. We examined HbA_1c, fasting blood glucose (FBG) and assessed diurnal blood glucose

profiles as glucose peak amplitude (G_{max}), time>12mmol/L (T>12) and glucose area under the curve over 20 hours (AUC_{20}).

3.3 Subjects and Methods

Of the 24 subjects with type 2 diabetes who completed a prior study (chapter 2), six subjects (men=2 and women=4) with a mean age of 57$\pm$2.3years, BMI 30.3$\pm$6.4kg/m^2, HbA$_1$c 8.2$\pm$0.7% and FBG$_{5.30am}$ 6.1$\pm$0.7mmol/L, a stable dose of hypoglycemic medication (3 managed their diabetes by diet alone, 3 by diet and medication) and stable exercise levels accepted the invitation to return 16 – 24 weeks later. All food was provided. The initial study T_{fall} was conducted toward the end of autumn or early winter with an identical repeat treatment T_{Spring} in spring. Medication dose and timing were logged and kept constant over T_{fall} and through to T_{Spring}.

A validated Medtronic MiniMed CGMS (Northridge, CA) [15, 645-647] was used to obtain comprehensive blood glucose data by continuously measuring glucose concentrations in subcutaneous tissue. A venous blood sample was collected in an EDTA tube for the measurement of HbA$_1$c. Methodology reported in Chapter 2. Methodology to measure the MODD is reported in Chapter 2 [27].

Methodology to measure resting blood pressure, body weight, body height and activity levels (pedometer) is reported in Chapter 2.

In both T_{fall} and T_{Spring} subjects were provided with identical daily meals to be consumed for 3 consecutive mid week days. Subjects were free to consume breakfast

at anytime they wished, with subsequent meals consumed 6 hours apart. Fasting blood glucose levels were obtained from the CGMS data at 5.30am prior to breakfast consumption. Each person's meals were individualised to achieve energy balance on a moderate carbohydrate diet (carbohydrate: protein : fat ratio of 40% : 34% : 26%), in which the carbohydrates were equally distributed across the day as described in chapter 2.

Even though subjects were instructed to consume their meals 6 hours apart, the minimum length of time between meals was 5 hours. In an effort to initialise the effect of each meal from the point of meal consumption, the 24-hour CGMS trace was divided into 5-hour intervals from the time of meal initiation for breakfast, lunch and evening meals with a 5-hour overnight slice beginning 5 hours after consuming the evening meal (fasting block), representing a total of 20 hours of blood glucose data over a 24-hour period of monitoring. The three days of monitoring produced 3 x 20 hours of blood glucose data used in the analysis

The number of sunlight hours on the testing days were calculated from tables provided by the Weather Centre [648].

All data are presented as means $\pm$ SEM. Statistical analysis was performed using SPSS for Windows 14.0 (SPSS, Inc., Chicago, IL). AUC_{20} responses were calculated using zero as a baseline, with the trapezoidal rule [649]. Correlation analyses for blood glucose parameters (G_{max}, AUC_{24}, and T_{12}) were used to determine relationships between T_{fall} and $T_{Spring.}$ (2 tailed; $p=0.05$). The differences between treatments were

analysed using a repeated measures Analysis of Variance (ANOVA) test. Statistical significance was set at $P<0.05$.

3.4 Results

The average time between T_{fall} and T_{Spring} was 20.0±4.5weeks. AUC_{20}, (160.2±17.4mmol/L x hr vs. 138.9±1mmol/L x hr; $p=0.133$), HbA_1c (8.2±0.68 vs 8.0±0.63; $p=0.699$), $FBG_{5.30am}$ (6.0±0.73mmol/L vs 6.6 ±0.41mmol/L; $p=0.211$), BMI (30.4±2.6kg/m^2 vs 30.4±2.6kg/m$^{2;}$ $p=0.854$), diastolic blood pressure (74.7±5.1 vs. 73.8±2.8; $p=0.852$) , daily temperatures (20.6±1.3^{0}C vs 20.0±3.4^{0}C; $p=0.788$), physical activity (6719±1249 vs. 5429.9±1670steps; p=0.192) and meal timing (0.7±0.3hrs; $p=0.102$) were not significantly different between T_{fall} and T_{Spring} respectively. G_{max} differed between treatments ($p=0.017$) with T_{fall} (13.6±1.4mmol/L) significantly higher than T_{Spring} (10.4±0.82mmol/L). T>12 approached significance($p=0.084$) with T_{fall} (436.7±211.4mins) higher than T_{Spring}(26.6±26.7mins). Differences in daily sunlight hours approached significance ($p=0.097$) with T_{fall} (10:42±0:33 hrs) lower than T_{Spring} (11:51±0:09hrs)[648].

Correlation coefficients for the blood glucose parameters G_{max}, AUC_{24}, and T_{12} between T_{fall} and $T_{Spring.}$ were r=0.792, r=0.727 and r=0.826 respectively.

A initial larger study involving these same participants (described in chapter 2) showed no significant differences on the same parameters for individuals managing their diabetes by diet and medication, compared to those using diet alone [650].

Dietary compliance ranged from 98-99%. The average daily blood glucose comparative data obtained through CGMS are displayed in Figure 3.1.

The average MODD for T_{fall} and T_{Spring} were 1.5mmol/L and 1.1mmol/L respectively. The MODD obtained after comparing the average blood glucose levels for both T_{fall} with T_{Spring} was 2.1mmol/L.
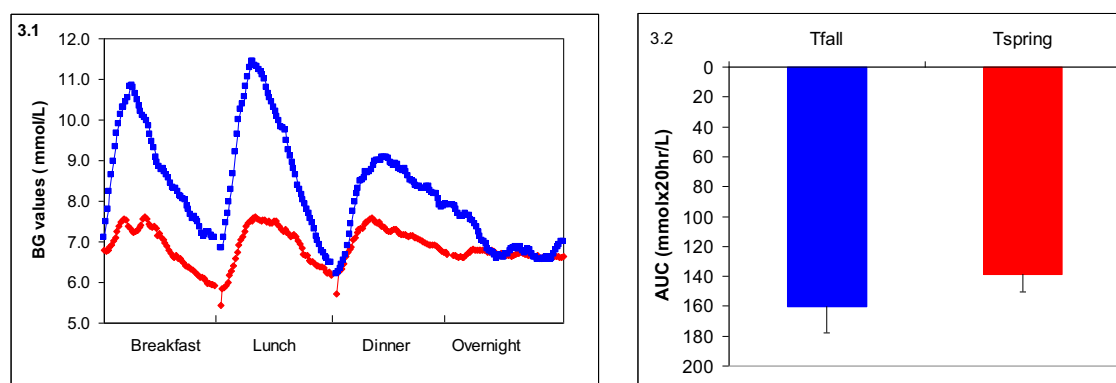
Figure 3.1-2 Blood glucose data.
3.1.Diurnal glucose values. Blue line; T_{fall}, Red line; T_{spring} (n=6). Note: Each graph represents 420 individual blood glucose measurements; the data has been initialized from the point of meal consumption for a 5 hour block and then averaged. FBG data collected at 5.30am each day are not displayed.
3.2 Blue line; T_{fall}, Red line; T_{spring} (n=6). AUC_{20} represents average daily (20hour) total area under the curve. For conversion from mmol/L to mg/dL for blood glucose levels, multiply by 17.86. Values are mean±SEM.

3.5 Discussion

The main findings of the study were; there were no significant differences observed in BMI, blood pressure, HbA_1c, $FBG_{5.30am}$ between T_{fall} and T_{spring}. Acute absolute postprandial "spikes", as determined by the G_{max} levels, were significantly more pronounced in T_{fall}; a mean difference of >3mmol/L was observed between the two identical dietary patterns. Differences in T>12 were greater (although not significant) in T_{fall}.

As the diet was identical and exercise, daily temperatures and lifestyle activities were not significantly different between treatments, a possible explanation for the differences in G_{max} may be differences in sunlight hours, which may have impacted on circadian rhythm; the sunlight hours in T_{Spring} were approximately 70 minutes greater per day than T_{fall}. Circadian rhythm is the diurnal "clock" responsible for the release of cortisol [651], insulin [652] and melatonin. These physiological rhythms are predominantly regulated through the sleep/wake cycles of the individual and endogenous factors within the nervous system [653], which are sequentially synchronized with external rhythms, most importantly the light/dark cycle [654]. These processes vary seasonally in healthy individuals [655] and those with diabetes [635, 636].

Most studies confirm that the total carbohydrate intake from either a snack or a meal is a consistent predictor of PPG levels [10]. This has been observed in both single meal [11] and mixed meal studies [10]. Participants were observed to space their meals 5-6 hours apart. According the G_{max} values occurred during the day.

Several studies have reported increased plasma cortisol concentrations in winter in healthy adults [656, 657]. Although we did not measure cortisol, we can only speculate that the reduced sunlight hours in T_{fall} may have subtly increased plasma cortisol levels, hence increasing the rate of gluconeogenesis [658] and enhancing postprandial hepatic glucose release [659], while decreasing the rate of glucose oxidation [658] and postprandial muscle glucose uptake, in part by antagonizing insulin action [659] or stimulating lipid oxidation [660]. This could partially explain the greater G_{max} values for T_{Fall}.

The level of hyperglycemia [661] and acute glucose fluctuations or 'spikes' [662] after a meal is important because of their potential contribution to the generation of oxidative stress [663]. Oxidative stress induces detrimental changes in the endothelium, the release of cytokines [662, 664] and in turn activation of transcription factor NF- κB, which plays a major role in inflammation and endothelial function[665] and could possibly impact on the seasonal variation of cardiovascular disease.

Limitations to the study include a lack of control for sunlight hours, "sleep time" and stress levels, while the lack of randomization of treatment order (T_{Fall}) may have introduced an order effect. Twenty four participants completed the fall treatment [650]. The low number of participants in the Spring treatment was due to a change in medication (n=9), personal reasons (n=4), poor health (n=1), work commitments (n=1), extended holidays (n=3).

The strengths of this study include the timing of the study between Spring and Fall to avoid peak holiday periods; it is customary for many Australians to celebrate the festive summer season with a 4 week holiday period which potentially may have produced atypical food consumption and lifestyle patterns. Similarly, many retired individuals from South Australia holiday in the warmer states or overseas during Winter.

The use of CGMS enabled very detailed dynamic changes in the blood glucose profiles to be detected relatively non invasively in free living individuals. The dietary pattern of the study main meals was similar to that of a higher carbohydrate diet which in addition to three main meals incorporated higher carbohydrate snacks. Meal

frequency and energy distribution were chosen to mirror what had been reported elsewhere[666]. Exceptional compliance we believe was due to the choice of commonly consumed foods and the provision of all foods. Larger studies incorporating measures of cortisol and insulin would be required to confirm these results and to understand potential mechanisms. These results would have implications for chronic clinical trials, treatment evaluations or epidemiological studies.

In conclusion, HbA_1c may only be part of the answer in assessing glycemic control. HbA_1c, $FBG_{5.30am}$, and AUC remained constant over time. Differences in G_{max} and a trend toward change in T>12 control independent of the change in HbA_1c, $FBG_{5.30am}$, AUC, exercise and ambient temperature suggest an effect of the change in sunlight levels on circadian rhythm.

Chapter 4: Determinants of the change in HbA$_1$c under conditions of energy restriction

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4.1. Abstract

Background and aims: Elevated postprandial glucose peaks are correlated with greater risk of diabetic complications. We aimed to understand the components of glucose control that contribute most to the change in HbA1c and investigate the effect of an eight week energy restricted diet on glucose metabolism in Type 2 diabetes using continuous glucose monitoring (CGMS).

Methods and results: 34 subjects with Type 2 diabetes ($32.8 \pm 4.2 kg/m^2$, $59.0 \pm 6.2yrs$, HbA_1c $6.9 \pm 1.0\%$) undertook a high protein, energy restricted diet (40% carbohydrates, 34% protein, 26% fat, 6MJ) for 8 weeks. Glucose levels were continuously measured using CGMS for 24hrs at baseline and week 8. Outcomes measures were daily postprandial peak glucose(G_{max}), time spent above 12mmol/L(T>12), area under the glucose curve(AUC), HbA_1c and fasting blood glucose(FBG).

Reductions in FBG ($0.8 \pm 0.3mmol/L$; $p=0.02$), HbA_1c ($0.7 \pm 0.8\%$; $p<0.000$), G_{max} ($1.3 \pm 0.6mmol/L$; $p=0.034$) and T>12 ($2.0 \pm 0.9hr$; $p=0.037$) were observed over time. Reductions in AUC trended toward significance ($47.6 \pm 26.2mmol/Lxhr$; $p=0.071$).

Subjects with FBG>7 (n=18): Reductions were observed in AUC ($27.6 \pm 12.6mmol/Lxhr$;p=0.043), T>12 ($2.5 \pm 0.3hr$; $p=0.043$), HbA_1c ($1.1 \pm 0.2\%$; $p<0.001$) and FBG ($1.5 \pm 0.4mmol/L$; $p=0.017$) but not G_{max}.

Subjects treated by medication (n=17): Reductions were observed in AUC ($30.9 \pm 11.5mmol/Lxhr$; $p=0.019$), T>12 ($7.3 \pm 2.7hr$; $p=0.021$), HbA_1c (0.9 ± 0.2); $p=0.001$) and FBG ($0.9 \pm 0.5mmol/L$; $p=0.015$).

Changes in FBG (p<0.000), % energy reduction (p=0.030) and changes in T>12 (p=0.040) predicted 60% of the variance in reduction in HbA$_1$c.

Conclusions: The change in FBG accounted for most of the variance in change in HbA$_1$c but %energy reduction also contributed independently of FBG. Hypocaloric high protein diets significantly improved glycemic control, particularly T>12, AUC, HbA$_1$c and FBG in poorly controlled individuals.

Pearce, K.L., Noakes, M. & Clifton, P.M. (2008) Determinants of the change in HbA$_1$c under conditions of energy restriction.
Nutrition, Metabolism and Cardiovascular Disease, submitted.

NOTE:
This publication is included on pages 114-130 in the print copy
of the thesis held in the University of Adelaide Library.

Chapter 5: Weight loss and reduction in FBG on a carbohydrate restricted high protein dietary pattern does not improve cognitive performance in type 2 diabetes.

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5.1 Abstract

Background and aims: Energy restricted diets are often used to improve glucose profiles in type 2 diabetes but the effect on cognition is largely unknown. We aimed to evaluate the affect of a high protein, energy restricted, treatment diet through weight loss and a reduction in fasting blood glucose (FBG) on cognitive function.

Methods and results: 57 Caucasian subjects with type 2 diabetes (59.0 ± 6.2years; BMI 32.8 ± 4.2kg/m^2; HbA$_1$c 6.9 ± 1.0%) were assigned to an 8 week, isocaloric treatment diet (40% carbohydrates, 34%protein, 26% fat, 8.5% saturated fat, 400mg dietary cholesterol, ~6-7MJ, 30% deficit). Cognitive functioning (short term memory, working memory, speed of processing, psychomotor speed and executive function) were assessed during 2 practice sessions, and tests at baseline and week 8. Simultaneous glucose levels were attained using continuous glucose monitoring systems (CGMS). Glycemic control was measured by FBG, postprandial peak glucose (G_{max}), time spent>12mmol/L (T>12) and area under the glucose curve (AUC$_{24}$). We found cognitive function was not altered by time, gender, baseline lipid levels or National Adult Reading Test (NART). At week 0 Digits Backward (DBW) correlated with FBG (r=-0.43;p<0.01). Digits forward (DFW) correlated with FBG (r=-0.39;p<0.01), Gmax (r=-0.46;p<0.05) and AUC24 (r=-0.50;p<0.01). At week 8, 72% of the variance in DFW was due to baseline scores, depression scores and % weight loss.

Conclusion: An 8 week, high protein, isocaloric dietary pattern did not improve cognitive function. Short term memory was predicted by FBG, G_{max} and AUC_{24}. Working memory was predicted by FBG.

Pearce, K.L., Noakes, M., Clifton, P.M. & Wilson, C. (2008) Weight loss and reduction in FBG on a carbohydrate restricted high protein dietary pattern does not improve cognitive performance in type 2 diabetes.
Nutrition, Metabolism and Cardiovascular Disease, submitted.

NOTE:
This publication is included on pages 134-152 in the print copy of the thesis held in the University of Adelaide Library.

Chapter 6: The effect of egg consumption as part of a moderate carbohydrate dietary pattern on blood lipid profiles in individuals with type 2 diabetes.

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Doctor of Philosophy.

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6.1. Abstract

The role of dietary cholesterol in people with diabetes has been poorly studied. We aimed to investigate the effect of a hypocaloric diet, high in protein and cholesterol from eggs (Hchol) compared to a similar amount of animal protein (high protein low cholesterol; Lchol) on plasma lipids, glycemic control and cardiovascular risk markers in Type 2 diabetes. Sixty five participants with type 2 diabetes (age; 54.4 ± 8.2, BMI; 34.1 ± 4.8 kg/m^2, low density lipoprotein cholesterol (LDL-C; 2.67 ± 0.10mmol/L)) were randomised to either Hchol or Lchol. Both hypocaloric dietary interventions (6-7MJ) contained a total carbohydrate : protein : fat ratio of 40%:30%:30%, but differed in cholesterol content; (Hchol; 590mg cholesterol, Lchol; 213mg cholesterol). After 12 weeks, all subjects reduced weight (6.0 ± 0.4kg; $p<0.001$). LDL-C while homocysteine remained unchanged ($p=0.9$, $p=0.37$ respectively). There was a significant effect of time on total cholesterol (-0.3 ± 0.1mmol/L; $p<0.001$), triacylglycerol (-0.4 ± 0.1mmol/L; $p<0.001$), non high density lipoprotein cholesterol (-0.4 ± 0.1mmol/L; $p<0.001$), apolipoprotein-B (-0.04 ± 0.02mmol/L; $p=0.003$), HbA1c (-0.6 ± 0.1%; $p<0.001$), fasting blood glucose (-0.5 ± 0.2mmol/L; $p=0.005$), fasting insulin (-1.7 ± 0.7mU/L; $p=0.003$), systolic blood pressure (-7.6 ± 1.7; $p<0.001$) and diastolic blood pressure (-4.6 ± 1.0mmHg; $p<0.001$). Significance was not altered by diet, gender, medication or amount of weight loss. Over time high density lipoprotein cholesterol (HDL-C) increased on Hchol ($+0.02\pm0.02$mmol/L) and decreased on Lchol (-0.07 ± 0.03mmol/L; $p=0.01$). The results suggest that a high protein energy restricted diet high in cholesterol from eggs improved glycemic and lipid profiles, blood pressure and apolipoprotein-B in individuals with type 2 diabetes, similarly to Lchol. The HDL-C response to Hchol was greater than Lchol.

Pearce, K.L., Noakes, M. & Clifton, P.M. (2008) The effect of egg consumption as part of a moderate carbohydrate dietary pattern on blood lipid profiles in individuals with type 2 diabetes.
The American Journal of Clinical Nutrition, submitted

NOTE:
This publication is included on pages 155-174 in the print copy of the thesis held in the University of Adelaide Library.

Chapter 7: The effect of a high protein energy restricted diet on renal function in individuals with type 2 diabetes

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I give consent for Karma Pearce to present this paper for examination towards the

Doctor of Philosophy.

Signed………………………..   Date…………………………

7.1. Abstract

Abstract

Compelling evidence for restricting dietary protein to prevent kidney disease progression in type 2 diabetes is not yet available. We investigated the effect of a high protein (102g/day) dietary intervention on renal function in subjects with type 2 diabetes withoutkidney dysfunction. Outcomes were assessed using Creatinine clearance (Crcl) and estimated glomerular filtration rate (eGFR). 65 participants with type 2 diabetes (age; 54.4 ± 8.2years, BMI; 34.1 ± 4.8kg/m^2, microalbuminuria; 9.6 ± 3.9mg/24hr) consumed a 6MJ carbohydrate: protein: fat: saturated fat diet of 40%:30%:30%:8.6% for 12 weeks.

We observed a weight loss of 6.0 ± 0.4kg (p<0.001). Overall, there was no change in microalbuminuria over the intervention ($p=0.5$) and changes in microalbuminuria were unrelated to weight loss, gender, medications, or changes in systolic blood pressure (SBP) or diastolic blood pressure (DBP). Decreases in HbA1C (-0.6 ± 0.1%), SBP (-7.5 ± 1.5mmHg), DBP (-4.0 ± 1.8mmHg), Crcl (-23.4 ± 9.2mL/min) was significant ($p<0.001$), which became insignificant when adjusted for weight loss ($p=0.4$). The decrease in eGFR (-0.7 ± 0.75mL/min/1.73m^2) over time was not significant ($p=0.5$).

We concluded that the changes observed in Crcl and eGFR in individuals with type 2 diabetes were due to weight loss and not the high protein weight loss dietary pattern.

Pearce, K.L., Noakes, M. & Clifton, P.M. (2008) The effect of a high protein energy restricted diet on renal function in individuals with type 2 diabetes.
The American Journal of Clinical Nutrition, submitted

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Chapter 8: Summary and Conclusions

8.1 Thesis overview

The overall aim of this thesis was to investigate the role of high protein, moderate carbohydrate (HPMC) dietary patterns in energy balance on acute glucose fluctuations (chapter 2 and 3) and in energy restriction in optimising weight loss, glycemic and lipid profiles for obese individuals with type 2 diabetes, and to evaluate the role of such diets in reducing or slowing the progression of diabetic complications such as cognitive dysfunction, renal function and risk markers for CVD (chapters 4-7). As there is increasing evidence of the effects of high protein low fat (HPLF) diets compared to high carbohydrate, low fat (HCLF) diets on weight loss and glycemic control, this thesis focused on the role of high protein, moderate carbohydrate dietary patterns with respect to weight loss, glycemic and lipid profiles and the prevention of diabetic complications. Continuous glucose monitors were employed to gain extremely detailed blood glucose profiles in free living individuals. As a secondary outcome the role of eggs as an alternative protein source in HPMC diets was also evaluated in Chapters 5 & 6.

8.2 The aims and hypothesis of the studies described in the thesis:

Chapter 2: This chapter comprehensively assessed diurnal glucose profiles in free living individuals with type 2 diabetes using CGMS, when consuming a HPMC diet in energy balance, while carbohydrate distribution at meals was variably distributed, but total carbohydrate remained the same. We examined HbA_1c, FBG and assessed diurnal blood glucose profiles as G_{max}, time>12 mmol/L and AUC_{20}. We hypothesised that an even distribution of carbohydrates across the day may be an optimum pattern

compared to carbohydrate loaded at breakfast, lunch or dinner for attenuating PPG excursions.

Chapter 3: The aim of this chapter was to confirm, in the same free living subjects with type 2 diabetes, the acute measures of glycemic control over time using a CGMS, while consuming a controlled HPMC diet in which the carbohydrates were evenly distributed across the day in free living subjects with type 2 diabetes. We examined HbA_1c, FBG and assessed diurnal blood glucose profiles as G_{max}, T>12 and AUC_{20}. We hypothesised that all measures of acute blood glucose control would remain constant over time.

Chapter 4: The aim of this chapter was to determine the contribution of the postprandial glucose response as assessed by G_{max}, T>12 and AUC to HbA_1c, the most common measure of glycemic control in type 2 diabetes. As it is generally accepted that weight management is one of most important factors in achieving glycemic control in individuals with type 2 diabetes, we examined diurnal glucose profiles on a HPMC diet during weight reduction in free living individuals with type 2 diabetes. We hypothesised that postprandial measures of glycemia, in addition to fasting glucose, would correlate with HbA_1c.

Chapter 5: This chapter aimed to explore the relationship between modest weight loss induced by 8 weeks of an energy restricted HPMC regime in obese individuals with type 2 diabetes and its consequential effects on cognition, and to investigate whether these changes could be related to changes in blood glucose levels. The effect of eggs as a dietary source of cholesterol on cognitive function was also evaluated. We hypothesized that daily consumption of an additional 400mg of dietary cholesterol

(2eggs/day) compared to an equivalent animal protein, low in both saturated fat and dietary cholesterol, would result in similar weight loss and similar improvements in cognitive function compared to baseline values (ie dietary cholesterol would have no adverse effects). Cognitive functioning was assessed using short term memory, working memory, speed of processing, psychomotor speed and executive function. Simultaneous glucose levels were attained using CGMS. Glycemic control was measured by FBG, HbA1c, G_{max}, T>12, and AUC_{24}.

Chapter 6: This chapter aimed to investigate the effect of a hypocaloric HPMC diet, either high or low in dietary cholesterol, on blood glucose and lipids profiles and cardiovascular risk markers in individuals with type 2 diabetes. We hypothesized both HP dietary patterns would similarly improve glycemic control, lipid profiles and cardiovascular risk markers.

Chapter 7: The aim of this chapter was to investigate the effect of a weight loss HPMC diet on renal function in individuals with type 2 diabetes. We hypothesized that a hypocaloric HPMC diet would not alter renal function in individuals with normal renal function.

8.3 Thesis outcomes

8.3.1 Glycemic control

8.3.1.1 Measurement of glycemic control

Fundamental to this research was use of continuous glucose monitoring systems (CGMS) as a non invasive tool to assess glycemic control. Traditional self monitoring blood glucose (SMBG) techniques have been shown to be prone to human error [784],

expensive [785], labour intensive [785] and, at best, would only have been capable of yielding a fraction of the 288 readings/day gained from the CGMS sensors while participants were performing their normal daily activities. Hence, CGMS enabled very detailed postprandial glucose profiles to be obtained.

8.3.1.2 Glucose control in energy balance

Nuttal and Gannon comprehensively examined the role of moderate protein diets in the context of 5 week, energy balanced, mixed meal studies on glycemic control in individuals with type 2 diabetes [786]. Briefly, they demonstrated that a lifestyle intervention in which the carbohydrate from a more traditional HCLF diet was replaced with protein induced significant improvements in blood glucose profiles (as assessed by incremental glucose AUC, incremental insulin AUC and HbA_1c) [50] and yielded similar results to those achieved using medication [786]. Comparable results were also achieved when dietary carbohydrate was replaced with fat, suggesting that decreasing carbohydrate content could significantly improve glycemic control independent of energy restriction or weight loss [786].

If the overall amount of carbohydrate profoundly influences glycemic control, it seems plausible that the way in which carbohydrate is distributed across the day may subtly impact on diurnal glycemic control. This thesis was the first to show that the distribution of carbohydrates can impact on postprandial glucose control in individuals with type 2 diabetes. This challenges the common recommendation that individuals with type 2 diabetes evenly distribute their carbohydrates across the day.

Instead, these individuals may be better advised to shift their carbohydrates from breakfast to lunch to facilitate lower diurnal glucose excursions.

The amount and type of carbohydrate (measured as GL) are significant in a diabetic diet [82]. This thesis has also demonstrated that in the context of a HPMC dietary pattern, carbohydrate amount and meal GL was only weakly associated with meal G_{max} and they accounted for only 16-17% of the variance in G_{max} (chapter 2).

We found that when diet was identical, and exercise, daily temperatures and lifestyle activities were not significantly different over two treatment periods, the measures of HbA_1c , FBG, T>12 and AUC_{20} were reproducible. The magnitude of postprandial "spikes" (G_{max}), however varied; there was a suggestion that this may be due to the amount of sunlight (chapter 3). We also detected lag times for G_{max} in our sample population of up to 105 minutes with the use of CGMS sensors (chapter 2). Importantly, if G_{max} was sought at the standard 2 hour time point after food consumption, the G_{max} value would have been grossly underestimated in many cases. This finding also impacts on any postprandial glucose measurement based over time such as the 2 hour glucose tolerance test or 2 hour GI measurement.

8.3.1.3 Glucose control in energy restriction

HbA_1c, a measure of mean glycemia over an 8-12 week period [124, 682], is the gold standard for long term assessment of glycemic control and many large clinical trials have demonstrated a relationship between HbA_1c and vascular complications [787]. Over the years there has been much debate on the role of fasting [139, 683, 684] and

postprandial blood glucose [139, 683] as determinants of HbA_1c, although in these studies glycemic control was achieved through the use of medications. Lifestyle interventions (chapter 4) demonstrated that when glycemic control was accompanied by weight loss in relatively well controlled individuals (initial HbA_1c of 6.9%), the reduction in energy intake, and both the change in FBG and the time glucose was above 12 mmol/L (T>12) all contributed to change in HbA_1c. Under conditions of energy restriction, the contribution of G_{max}, probably because of the short duration of the peak, is not reflected in HbA_1c. These findings emphasize the need to measure both fasting and postprandial glucose levels to obtain a clear picture of glucose control and reduce the risk of vascular complications in addition to regular HbA_1c measurements. Professional support to determine the timing of G_{max} in individuals taking medications that vary in their action is required when SMBG methods are employed.

Our results support those of previous studies finding that glycemic control could be improved with a dietary pattern higher in protein and lower in carbohydrate. Results documented in chapter 4 show that an 11% reduction in HbA_1c and 9% in FBG could be achieved using a 5000-6000kj/day HPMC dietary pattern over 8 weeks. This study uniquely demonstrated acute improvements in glycemia relative to baseline that were observed as a reduction of 67% in T>12, 23% in AUC, and 10% in G_{max}. Reanalysis of the data selecting for poorly controlled individuals (FBG>7) suggested that these individuals were more responsive to changes in HbA_1c, FBG, T>12 and AUC, but not G_{max}, again supporting the need for G_{max} to be routinely monitored.

Similarly, almost double the number of participants consuming the same dietary patterns for 12 weeks (chapter 6) showed overall reductions in HbA$_1$c and FBG, of 9% and 4% respectively. Most importantly, β-cell function and insulin sensitivity improved significantly by 27% and 40% respectively with low, but stable levels of physical activity. The improvements in insulin sensitivity were also consistent with an improvement of 18% in the postprandial response to glucose as measured by 2 hour oral glucose tolerance test. Fasting insulin levels also decreased overall by 10%. One would expect that if the HPMC dietary regime was combined with a higher level of physical activity, that greater improvements in overall glycemia would be observed.

8.3.1.4 Measures of microvascular change

Creatinine clearance and microalbuminuria are both measures of kidney function. The weight loss study outlined in chapter 7 indicated that microalbuminuria remained stable and the decreased creatinine clearance was due to weight loss and not impaired kidney function. This suggests that the use of HPMC dietary patterns in individuals with relatively well controlled diabetes and normal renal function does not adversely affect kidney function over the short term.

Chapter 5 looked at the effect of blood glucose levels on cognitive function. Although a strong relationship was observed between FBG and working and short term memory performance, the intervention did not observe any change (either positive or negative) in cognitive function. However, it is possible that the study was not long enough to observe any change. We calculated a drop of at least 1mmol/L in blood glucose, as the

minium level to detect change in working memory and we achieved only a 0.6 mmol/l drop. This should be incorporated into any future study designs.

8.3.1.5 Measures of macrovascular risk

The study outlined in chapter 7 showed that energy restricted HPMC dietary patterns did not alter LDL-C, but decreased triglycerides over a 12 week period. Apo-B, non-HDL-C and the total cholesterol: HDL-C ratio, all predictors of CVD, were observed to decrease on HPMC patterns either high or low in dietary cholesterol. The results of this study suggest that HPMC may decrease CV risk, in support of the majority of studies (although limited in number) outlined in chapter 1, Table 1.3. As there is still only a paucity of information on the effect of HPMC's on blood lipid, and this is one of the few studies to have evaluated CV risk parameters such as apo-B and CRP in type 2 diabetes with this dietary pattern, there is a need for more research in this area.

Furthermore, this study also highlighted the fact that dietary cholesterol consumed as 2 eggs/day improved HLD-C in individuals with type 2 diabetes more so than a diet low in dietary cholesterol. However it is not clear if a dietary cholesterol induced rise in HDL-C is beneficial. Confirmation of this result through further research would suggest the current guidelines to reduce dietary cholesterol <200mg/day be reviewed.

8.3.1.6 Weight loss

Our studies suggest that energy restricted (5000-6,000kj/day) HPMC diets facilitate weight loss of 6% over 8 weeks (chapter 4) and 12 weeks (chapter 6). Just 8 weeks on this dietary regime was required to achieve the minimum weight loss to reduce

mortality and co-morbidity risk in obese individuals [687] and was consistent with that reported by other studies over a similar time frame in subjects with type 2 diabetes [414, 688, 689].

8.3.1.7 Body composition

Previous research, although limited in volume, has shown that carbohydrate restriction through the use of HP diets more effectively promote loss of abdominal fat, particularly in overweight or hyperinsulinemic women. Our results have also shown a significant decrease in fat mass with the use of HPMC diets with no difference in gender (chapter 6). Future studies evaluating metabolic control in individuals with diabetes should also incorporate measures of body composition, as loss of abdominal fat mass is important in reducing insulin resistance.

8.4 Limitations

One of the shortcomings of this thesis was the lack of control groups. Future studies should compare the effects observed with HPMC diets to those obtained from the consumption of other dietary patterns, although dietary patterns high in fats may lead to increased energy consumption over the long term and less likely to be suitable for individuals with diabetes.

These studies have only been conducted on Caucasian participants; HPMC dietary patterns should also be trialled in populations genetically susceptible to diabetes such as the Australian Aborigines, Asians [213], Pima Indians [214, 215], African Americans [216, 217], Pacific Islanders [218] and Israeli Jews of non Ashkenazi origin [219]. The subjects recruited in this thesis specifically had type 2 diabetes and

the study designs were of short duration. The applicability of the HPMC to individuals with obesity and metabolic syndrome (both key features of prediabetes) and studies conducted over longer time frames would also require investigation.

Limitations to the study include the small number of participants and the varying types of medication. Larger studies enabling sufficiently powered sub analysis with respect to the varying types of medications are required. Meta analysis of pooled results from previously published studies of similar duration and study design is also another approach that can be taken to overcome the limitation of small population sizes.

Difficulties were also experienced in recruiting participants for energy balanced studies. As it is necessary to evaluate the efficacy of HPMC dietary patterns in the context of both weight-loss and weight-maintenance, additional strategies (in addition to the provision of all food) are required to both entice and maintain participants in weight-maintenance studies.

Eggs were not provided to participants, therefore subtle differences in cholesterol levels may have occurred in the purchase of different brands of eggs. Dietary consultations with dieticians monitored egg intake on a fortnightly basis and ensured that participants were consuming the whole egg and not just the egg white.

8.5 Future work

This thesis was the first to evaluate the effect of carbohydrate distribution on acute postprandial blood glucose profiles (as assessed by AUC20, T>12 and G_{max})

(chapter2) in obese individuals with type 2 diabetes. Even though the postprandial parameters were confirmed though a very small study, the finding that carbohydrates loaded at lunch improved diurnal glucose profiles would need to be trialled in diets with varying macronutrient profiles. Similarly, this thesis was the first to show that consumption of HPMC energy restricted dietary patterns high in dietary cholesterol in individuals with type 2 diabetes improved HDL-C. Furthermore, diets either high or low in dietary cholesterol improved lipid profiles and CV risk markers; renal function was not affected in individuals with normal renal function over the short term.

Cognitive function has the potential to impact on how well individuals with diabetes manage their disease. Future studies designs should also incorporate measures of cognitive function and be designed to result in a drop in blood glucose levels of 1mmol/L. In addition, future studies should also incorporate measures of renal function and cardiovascular risk markers to establish a body of knowledge in this area.

Future research work involving postprandial glucose measurements would benefit from the use of CGMS to obtain detailed glucose profiles. The role of glucose variability has not been extensively researched, however there is evidence to suggest that postprandial and inter prandial glucose fluctuations (positive and negative fluctuations about a mean value) trigger oxidative stress [788]. The use of CGMS will also overcome the variability in timing that makes G_{max} assessment difficult and provide the option to assess other postprandial parameters such as T>12. Future work using CGMS should also seek to assess trend analysis as well as glycemic variability and evaluate the impact of these fluctuations on oxidative stress and endothelial damage.

The use of time blinded CGMS monitors (monitors in which the participants are not able to read the blood glucose values as the occur in 'real time') in clinical trials would be advantageous rather than the newer real time monitors. (Time blinded monitors prevent the wearer from seeing blood glucose measurements as they occur). From our experience, the majority of participants do not regularly check their blood glucose levels and are really not aware of their diurnal glucose profiles. Several of our participants became alarmed at CGMS blood glucose readings; providing them with visual access to their glycemic profiles outside of a clinical setting would only serve to alarm them in a free living setting in the first instance, which could subsequently result in frequent phone calls to a study coordinator. Furthermore adjustments to medical therapy based on CGMS alone are not recommended by the U.S. Food and Drug Administration without training to analyse trend data [789].

Short term studies outlined in chapters 4, 5 & 6 have shown good compliance, with the studies in chapters 2 & 3 demonstrating exceptional compliance. Longer studies either with a traditional HC approach or using HP dietary patterns have traditionally shown poor compliance [414, 790]. Future longer term lifestyle interventions should contain elements to enhance retention and study compliance irrespective of the dietary patterns used. This may require a pilot study to first evaluate some of the drivers to affect behavioural change such as motivation, ability and opportunity [791] and psychological problems related to the dieting process [792].

8.6 Conclusion

Traditionally, physicians and clinicians have focused on weight loss and lowering of HbA$_1$c and FBG as key strategies in the treatment of type 2 diabetes. The studies outlined in this thesis suggest that more emphasis should also be placed on the control of postprandial glucose and in the short term. HPMC, low saturated fat (<8%), low GI dietary patterns offer a lifestyle strategy to facilitate weight loss and improvements in overall glycemic control, including postprandial control. Furthermore, encouraging individuals to reduce their carbohydrates at breakfast and shift them to lunch may result in further postprandial glucose reductions. In addition, the inclusion of eggs in weight reducing HPMC dietary patterns may increase HDL-C levels (without increasing LDL-C) and reduce triglycerides, apo-B, non-HDL-C and the total cholesterol to HDL-C ratio, potentially reducing the risk of CV related outcomes. Furthermore, over the shorter term, hypocaloric HPMC dietary patterns either high or low in dietary cholesterol did not adversely affect cognitive function or renal function in individuals with normal renal function.

In conclusion, the use of high protein, moderate carbohydrate diets in energy balance improve glycemic profiles more so when loaded in the lunch meal and energy restriction over the short term improve glycemic and lipid profiles and CV risk markers in individuals with type 2 diabetes and do not alter cognitive function or renal function in individuals without established kidney dysfunction.

Appendix 1: Even briefer assessment scale for

depression (EBAS DEP)

Volunteer ID……………………………..   Date………………

Question	Response	Positive response	Negative response
1. Do you worry? In the past month?	Admits to worrying in past month.	1	0
2. Have you been sad or depressed in the past month?	Has had sad or depressed mood during the past month	1	0
3. During the past month have you ever felt that life was not worth living?	Has felt that life was not worth living at some time during the past month	1	0
4. How do you feel about your future? What are your hopes for the future?	Pessimistic about the future or has empty Expectations (ie nothing to look forward to).	1	0
5. During the past month have you at any time felt you would rather be dead?	Has wished to be dead at any time during past month.	1	0
6. Do you enjoy things as much as you used to – say like you did a year ago?.	Less enjoyment in activities than a year ago	1	0
If question 6 rated 0, then rate 0 for question 7 and skip to question 8.			
7. Is it because you are depressed or nervous that you don't enjoy things as much?	Loss of enjoyment because of depression/nervousness.	1	0
8. Are you – very happy, fairly happy, not very happy, not happy at all?	Not very happy or not happy at all.	1	0

Total score 8. A score of 3 or greater indicates the probable presence of a depressive

disorder which may need treatment and the patient should be assessed in more detail

or referred for psychiatric evaluation [699].

Appendix 2: Baecke Physical Activity Questionnaire

Volunteer ID……………………..   Date………………………

Please answer the following questions based on your activity levels during the previous **3 months**. Please **circle your response** to multiple choice questions.

		Please circle your response	Office use
1.	What is your main occupation?		1-3-5
2.	At work I sit:	never seldom sometimes often always	1-2-3-4-5
3.	At work I stand:	never seldom sometimes often always	1-2-3-4-5
4.	At work I walk:	never seldom sometimes often always	1-2-3-4-5
5.	At work I lift heavy loads:	never seldom sometimes often always	1-2-3-4-5
6.	At work I sweat:	very often often sometimes seldom never	5-4-3-2-1
7.	After work I am tired:	very often often sometimes seldom never	5-4-3-2-1
8.	In comparison with others my own age I think my work is physically:	much lighter lighter as heavy heavier much heavier	1-2-3-4-5
9.	Do you play sport?	Yes/ No	
	If yes, which sport do you play most frequently?		0.76–1.26–1.76
	How many hours a week?	Less than 1 1-2 2-3 3-4 >4	0.05-1.5-2.5-3.5-4.5
	How many months per year?	Less than 1 1-3 4-6 7-9 >9	0.04-0.17-0.42-0.67 - 0.92
	If you play a second sport, which sport is it?		0.76–1.26–1.76
	How many hours a week?	Less than 1 1-2 2-3 3-4 >4	0.05-1.5-2.5-3.5-4.5
	How many months per year?	Less than 1 1-3 4-6 7-9 >9	0.04-0.17-0.42-0.67 - 0.92
10.	In comparison wit others of my own age I think my physical activity during leisure time is:	much less less the same more much more	1-2-3-4-5
11.	During leisure time I sweat:	very often often sometimes seldom never	1-2-3-4-5
12.	During leisure time I play sport:	never seldom sometimes often always	1-2-3-4-5
13.	During leisure time I watch television:	never seldom sometimes often always	1-2-3-4-5

14.	During leisure time I walk:	never seldom sometimes often always	1-2-3-4-5
15.	During leisure time I cycle:	never seldom sometimes often always	1-2-3-4-5
16.	How many minutes per day do you walk and/ or cycle to and from work, school or shopping?	Less than 5 5-15 15-30 30-45 greater than 45 minutes	1-2-3-4-5

The Baecke questionnaire [680] provides an index of routine physical activity over the past 12 months. The subject's responses on 5-point Likert scales (never, seldom, sometimes, often, very-often or always) permit calculation of a occupational index (calculated from responses of 7 questions relating to occupational activity including, sedentary and walking activities, lifting loads, and sweating and by classifying the patient into one of three occupational activity levels), a sport index (4 questions including information about the 2 most frequently played sports), a leisure time index excluding sports activities (4 questions about watching television, walking, and cycling), and the total activity index as the sum of the three, which varies between 3 and 15. A score under 9 indicates a sedentary level. The questionnaire is reliable and validated against the doubly labelled water method [681].

Scoring and Calculations

Scoring of the questionnaire was described by Baecke et al.[680] as follows.

Work index = Mean score from occupational Likert scale questions one through eight
Score categories for question 1 are:

1 = "Low level" occupations such as office or clerical work, driving, shopkeeping, teaching, studying, housework, medical practice and occupations requiring a university education

2 = "Middle level" occupations such as factory work, plumbing, or carpentry and farming

3 = "High level" occupations such as dock work or construction work and professional sport

Work index = (Q$_1$ + Q$_2$ + Q$_3$ + Q$_4$ + Q$_5$ + Q$_6$ + Q$_7$ + Q$_8$) / 8

Sport Index = Mean score of questions 9 through 12

Score for question 9 = Sum of [proportion of year of participation x intensity code x time (duration)] for all activities. After calculation of question 9, value is scored according to the following scale:

0 (no sport reported) = 1; 0.01-<4 = 2; 4-<8 = 3; 8-<12 = 4; ≥12 = 5

Where : The sport intensity is divided into 3 levels:

1 = "Low level" including billiards, sailing, bowling, golf etc, with an average energy expenditure of 0.76 MJ/h

2 = "Middle level" including badminton, cycling, dancing, swimming, tennis, with an average energy expenditure of 1.26 MJ/h

3 = "High level" including boxing, basketball, football, rugby, rowing, with an average energy expenditure of 1.76 MJ/h

Sport Index = (Q$_9$ + Q$_{10}$ + Q$_{11}$ + Q$_{12}$) / 4

Non-sports leisure = Mean score for questions 13 through 16

Non-Sports Index = [Q$_{13}$ + Q$_{14}$ + Q$_{15}$ + Q$_{16}$] / 4

Total Score = Work Index + Sports Index + Non-Sports Index

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