

# High protein dietary patterns and Type 2 diabetes

A thesis submitted by

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## Table of Contents

LIST OF FIGURES	iv
LIST OF TABLES	v
ABBREVIATIONS	vi
DECLARATION OF ORIGINALITY	x
ACKNOWLEDGEMENTS	xi
ABSTRACT	1
INTRODUCTION	4
CHAPTER 1: General introduction	9
1.1 Diabetes Mellitus	10
1.1.1 The diabetes ‘epidemic’ and impact on society	10
1.1.2 Defining Type 2 diabetes	11
1.1.2.1 Risk factors for the development of Diabetes Mellitus	12
1.1.3 Diagnostic criteria for diabetes	14
1.1.4 Measurement of blood glucose	15
1.1.4.1 Management of diabetes – normalizing glycemia	17
1.1.4.1.1 The impact of hyperglycemia on macrovascular complications	17
1.1.4.1.2 The impact of hyperglycemia on microvascular complications	20
1.1.4.1.3 Biochemical consequences of hyperglycemia	26
1.2 Weight loss	27
1.2.1 BMI the risk of type 2 diabetes	27
1.2.2 Prevalence: obesity and type 2 diabetes	29
1.2.3 Epidemiology, weight gain and risk of type 2 diabetes	29
1.2.4 Intervention studies, IGT and progression to type 2 diabetes	30
1.2.5 Intervention studies and type 2 diabetes	32
1.2.6 Physical activity	33
1.2.6.1 Observational and prospective studies	35
1.2.6.2 Intervention studies, IGT and progression to type 2 diabetes	34
1.2.6.3 Intervention studies and type 2 diabetes	35
1.2.6.4 Surgery, IGT and type 2 diabetes	35
1.3 Diet and type 2 diabetes	36
1.3.1 Overview	36
1.3.2 Diet composition	37
1.3.3 Dietary Protein	38
1.3.3.1 Definition of a high protein diet	38
1.3.3.2 Satiety	38
1.3.3.3 Epidemiological studies and the risk of diabetes	40
1.3.3.4 Energy balance and type 2 diabetes	41
1.3.3.5 Weight loss	42
1.3.3.5.1 Ad libitum studies in obese and insulin resistant individuals	42
1.3.3.5.2 Energy restriction	45
1.3.3.5.3 Body composition	45
1.3.3.5.4 Glycemic control in insulin resistance or type 2 diabetes	46
1.3.3.5.5 Blood lipids in insulin resistance or type 2 diabetes	51
1.3.3.5.6 Limitations to study comparison	52
1.3.3.6 Hypertension	52
1.3.3.7 Potential adverse effects of protein diets	52

1.3.3.7.1 Diabetic nephropathy	52
1.3.3.7.1.1 Defining diabetic nephropathy	52
1.3.3.7.1.2 Prevalence	54
1.3.3.7.1.2 Optimum targets for diabetic nephropathy	55
1.3.3.7.2 Calcium loss	58
1.3.4 Dietary Fat	58
1.3.4.1 Total dietary fat intake	58
1.3.4.1.1 Epidemiological studies, IGT and progression to type 2 diabetes	58
1.3.4.1.2 Intervention studies, obese individuals and total fat intake	59
1.3.4.2 Type of fat	60
1.3.4.2.1 Epidemiological studies, IGT and progression to type 2 diabetes	60
1.3.4.2.2 Intervention studies, IGT and type 2 diabetes	62
1.3.5 Dietary Fibre	66
1.3.5.1 Epidemiological studies and progression to type 2 diabetes	66
1.3.5.2 Intervention studies and type 2 diabetes	67
1.3.6 Carbohydrates	68
1.3.6.1 Epidemiological studies and progression to type 2 diabetes	69
1.3.6.2 Intervention studies type 2 diabetes	70
1.3.6.3 Simple sugars and type 2 diabetes	70
1.3.6.7 Other Dietary Factors	71
1.3.6.7.1 Dietary alcohol	71
1.3.6.7.2 Coffee consumption	71
1.3.6.7.3 Micronutrients, vitamins and the risk of diabetes	72
1.3.6.7.4 Magnesium, grain and type 2 diabetes	72
1.3.6.7.5 Chromium and type 2 diabetes	73
1.4 Summary	74
1.5 Research arising from this review	76
1.5.1 Thesis aims and hypothesis	76
CHAPTER 2: Effect of carbohydrate distribution on post prandial glucose peaks using continuous glucose monitoring in type 2 diabetes	79
2.1 Abstract	82
2.2 Introduction	83
2.3 Subjects and Methods	86
2.4 Results	93
2.5 Discussion	97
CHAPTER 3: Consistency of diurnal glucose control over time in individuals with type 2 diabetes	102
3.1 Abstract	103
3.2 Introduction	104
3.3 Subjects and Methods	105
3.4 Results	107
3.5 Discussion	108
CHAPTER 4: Determinants of the change in HbA <sub>1c</sub> under conditions of energy restriction	112
4.1 Abstract	114
4.2 Introduction	115
4.3 Methods	117
4.4 Results	123

4.5 Discussion	126
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	131
5.1 Abstract	134
5.2 Introduction	135
5.3 Methods	136
5.4 Results	143
5.5 Discussion	149
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	153
6.1 Abstract	155
6.2 Introduction	156
6.3 Materials and Methods	158
6.4 Results	163
6.5 Discussion	170
CHAPTER 7: The effect of a high protein energy restricted diet on renal function in individuals with type 2 diabetes	175
7.1 Abstract	177
7.2 Introduction	178
7.3 Subjects and Methods	179
7.4 Results	181
7.5 Discussion	185
CHAPTER 8: Summary and Conclusion	189
8.1 Thesis overview	190
8.2 The aims and hypothesis of the studies described in the thesis	190
8.3 Thesis outcomes	192
8.3.1. Glycemic control	192
8.3.1.1 Measurement of glycemic control	192
8.3.1.2 Glucose control in energy balance	193
8.3.1.3 Glucose control in energy restriction	194
8.3.1.4 Measures of microvascular change	196
8.3.1.5 Measures of macrovascular risk	197
8.3.1.6 Weight loss	197
8.3.1.7 Body composition	198
8.4 Limitations	198
8.5 Future work	199
8.6 Conclusion	202
Appendix 1: Even briefer assessment scale for depression (EBAS DEP)	203
Appendix 2: Baecke Physical Activity Questionnaire	205
Bibliography	209

## LIST OF FIGURES

Figure 1.1 Individuals with similar HbA <sub>1c</sub> may exhibit different glucose variability throughout the day.	15
Figure 1.2 Relationship between HbA <sub>1c</sub> and microvascular or macrovascular disease.	24
Figure 1.3 Mechanisms for weight loss after consumption of a moderate protein diet	40
Figure 1.4 Insulin signalling cascade regulated by dietary protein	50
Figure 2.1-5 Diurnal glucose values	95
Figure 3.1 Blood glucose data	108
Figure 4.1. Weight loss and change in FBG over 8 weeks	129
Figure 5.1-6 Cognitive outcomes	146

## LIST OF TABLES

Table 1.1 Plasma venous diagnostic criterion for diabetes	14
Table 1.2 Glycemic control in type 2 diabetes and CV risk.	20
Table 1.3 Studies evaluating the role of high protein diets under conditions of energy balance in type 2 diabetes.	44
Table 1.4 Studies evaluating the role of dietary protein under conditions of energy restriction in individuals with insulin resistance and type 2 diabetes.	48
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	61
Table 2.1 Baseline characteristics	87
Table 2.2 Sample menu of foods and carbohydrate distribution over the day	90
Table 4.1. Subject characteristics at baseline	118
Table 4.2. Macronutrient profile	119
Table 5.1 Baseline characteristics	137
Table 5.2 Macronutrient profile	141
Table 6.1 Subject characteristics at baseline	160
Table 6.2 Macronutrient profile	165
Table 6.3. Lipid, cardiovascular, glycemic and nutritional plasma markers	168
Table 7.1. Subject characteristics at baseline	182
Table 7.2. Dietary intake	182
Table 7.3. Renal function markers	185

## **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 <sub>1c</sub>	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 <sub>fall</sub>	study conducted in the fall

T <sub>spring</sub>	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<sub>1c</sub>, 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<sub>1c</sub> 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<sub>max</sub> and AUC<sub>24</sub>.

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.