High protein dietary patterns and Type 2 diabetes

A thesis submitted by

Karma Louise Pearce

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Department of Physiology
Faculty of Health Sciences,
School of Molecular and Biomedical Science
University of Adelaide

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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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SIGNED…… DATE……

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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_1c 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.