High protein diets, weight loss, glycaemic control and renal function in type 2 diabetes mellitus

A thesis submitted for the degree of doctor of philosophy by

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Table of content

Table of tables

Table of figures

Declaration of originality

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Abbreviations

ACCORD	The Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin Converting Enzyme
ACEi	Angiotensin Converting Enzyme inhibitor
AER	Albumin Excretion Rate
AFM	Abdominal Fat Mass
Alb/cr	Albumin to creatinine ratio
ANCOVA	ANalysis Of COVAriance between groups
ANOVA	ANalysis Of VAriance between groups
ARB	ATII Receptor Blocker
ATII	Angiotensin II
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BF	Body Fat
BG	Blood Glucose
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BP	Blood Pressure
BW	Body Weight
CCK	CholeCystoKinin
CHO	Carbohydrate
CKD	Chronic Kidney Disease
Cr	Creatinine
CrCl	Creatinine Clearance
CRF	Chronic Renal Failure
Da Qing	The Da Qing IGT and Diabetes Study

DBP	Diastolic Blood Pressure
DCCT	The Diabetes Control and Complication Trial
DECODE	Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe
DXA	Dual-Energy X-ray Absorptiometry
DITE	Diet Induced Thermic Effect
DOB	Date of birth
eGFR	estimated GFR
ESRD	End Stage Renal Disease
FBG	Fasting Blood Glucose
FFM	Fat Free Mass
FFQ	Food Frequency Questionnaire
GE	Gastric Emptying
GFR	Glomerular Filtration Rate
GI	Glycaemic index
GLP_1	Glucagon Like Peptide 1
Gmax	Peak BG
HbA1c	Glycated haemoglobin A1c
HCLF	High Carbohydrate, Low fat diets
HDL	High Density Lipoprotein
HPD	High Protein Diet
HR	Hazard Ratio
IBW	Ideal Body Weight
IDF	International Diabetes Federation
IGF	Impaired Fasting blood Glucose
iGFR	isotope tracer GFR

IGT	Impaired Glucose Tolerance
IHD	Ischemic Heart Disease
KD	Kidney Disease
KDOQI	Kidney Disease Outcomes Quality Initiative
kJ	kilo Joule
LBM	Lean Body Mass
LDL	Low Density Lipoproteins
Look AHEAD	The Action for HEAlth and Diabetes
LPD	Low Protein Diet
LPh	Low Phosphorus
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in renal disease
MI	Myocardial Infarction
Mo	Month
MUFA	Monounsaturated Fatty Acids
NHANES	The National Health and Nutrition Examination Survey
NOCHO	No Carbohydrate
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PA	Physical Activity
PPG	PostPrandial blood Glucose
PREVEND	The Prevention iof Renal and Vascular End Stage Disease
PUFA	Polyunsaturated Fatty Acids
RAAS	Renin-Angiotensin Aldosterone System
RCT	Randomized Controlled Trials
REE	Resting Energy Expenditure

RENAAL	Reduction of Endpoints in NIDDM with the AII Antagonist Losartan
RMR	Resting Metabolic Rate
RR	Relative Risk
SAFA	Saturated Fatty Acids
SBP	Systolic Blood Pressure
sLPD	supplemented (with keto acids) LPD
SNGFR	Single Nephron Glomerular Filtration Rate
SPD	Standard Protein Diet
sVLPD	supplemented Very Low Protein Diet
T>10	Time spent with a BG above 10 mmol/L
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
T-Chol	Total Cholesterol
TE	Total Energy
TEE	Total Energy Expenditure
TG	TriGlycerides
T_x	Time
UKPDS	United Kingdom Prospective Diabetes Study
UPD	Usual Protein Diet
USRDS	The United States Renal Data System Coordinating Centre
UUE	Urinary Urea Excretion
VAS	Visual Analogue Scale
VLPD	Very Low Protein Diets
WHO	World Health Organization

Abstract

The evidence for the efficacy of weight loss diets with a higher protein to carbohydrate (CHO) ratio has increased. However, the long-term effect of higher protein diets (HPD) on renal function in individuals with type 2 diabetes is lacking.

The studies in this thesis focus on the effect of altering the macronutrient composition towards a higher protein to carbohydrate ratio on renal function, HbA1c and lipids in individuals with type 2 diabetes mellitus (T2DM) and microalbuminuria.

The main study was a 12 month randomized weight loss study in 56 volunteers. A 6 MJ high protein diet (HPD: protein 30% total energy (TE) equal to 90-120g/d, carbohydrate [CHO] 40%TE, fat 30%TE) was contrasted with a 6 MJ standard protein diet (SPD: protein 20%TE equal to 55-70g/d, CHO 50%TE, fat 30%TE).

This study showed a significant decrease in weight (-10.5kg HPD and -7.5kg SPD), fat mass (-9% HPD and -8% SPD) and increased fat free mass (+6% in both groups) with no significant difference between diets.

Renal function, measured as isotope GFR, calculated GFR and serum cystatin C, was unaffected by either diet. Microalbuminuria was reduced in HPD (AER: -12.0±9.1 µg/min and + 1.0±17.0 µg/min in SPD) with a borderline significant treatment effect after adjustment for baseline values (p=0.059). Glycaemic control (HbA1c -0.9 HPD and -0.5 SPD), high density lipoprotein cholesterol (+ 0.1 mmol/L in both groups), and triglycerides (HPD -0.8 and SPD -0.5mmol/L), improved similarly in both groups. There was a decreased diastolic BP in the HPD group (-2.5 mmHg) and an increase in SPD (+5.2 mmHg; p=0.03).

The major contributor to diabetes nephropathy is hyperglycaemia. In study 2 (a sub-study to the main study) and study 3, a short term meal intervention study, we investigated the effect of changing macronutrient composition and CHO timing on glycaemic control using a continuous glucose monitoring system.

These studies showed a significant decrease in time spent with blood glucose (BG) above 10 mmol/L, maximal BG level and area under the BG curve indicating an overall beneficial effect of altering the CHO to protein ratio on

glycaemic control. Changing the CHO content of breakfast had no effect on lunch glucose levels.

In conclusion:

This study is the first to examine the long-term efficacy and safety of higher protein diets in individuals with T2DM and microalbuminuria. Both diets had positive effects on cardiovascular risk factors with no changes in renal function.