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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November 2011

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Declaration of originality

I, Eva Pedersen certify that this work contains no material which has been submitted or accepted for the award of any other degree or diploma in any university or other tertiary institution and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Signed............................................ Date........................................
Acknowledgements

I would like to sincerely thank my supervisor Professor Peter Clifton for giving me the chance to pursue this challenging but rewarding project. Thank you for always being there and for your encouragement, motivation and patience. Thank you to my supervisors Professors Manny Noakes and Gary Wittert for your support throughout my candidature.

I would also like to thank Ass Prof Jennifer Keogh for your friendship and fruitful conversations.

This thesis would not have been possible without the help of the volunteers, clinic staff: Julia Weaver, Lindy Lawson, Rosemary McArthur, Pennie Taylor, Xenia Cleanthous and David Jesudason for their assistance with project management, taking blood samples and assisting with dietary counselling, and for your friendship, I am deeply grateful. Thank you to Kylie Lange for patiently guiding me through the statistical challenge. I also thank Vanessa Russell for analysis of samples and with helping me understand the analysis methods. Thank you to Kathryn Bastiaans for teaching me how to manage the huge amount of data in a rational way. A special thanks to Karma Pearce for sharing your knowledge of CGMS with me and for your support.

I am indebted to Dr Erin Symonds for guiding me through and helping me make sense of the gastric emptying study, your help was patiently and selflessly given. Thank you to the Centre for Paediatric and Adolescent Gastroenterology, Women and Children’s hospital for analyzing the GE breath-tests.

Thank you to my fellow students Carly Moores, Razinah Sharif, Penelope Main, Kacie Dickinson and to Dr Sasja Beestra-Hill for your support and for listening to me when I needed it.

Thank you to friends and family who patiently supported me and most of all thank you to Kim, Mette and Marc for being interested and for your ongoing support.

Most importantly, thank you Steen for believing in me and pushing me forward even when it meant putting “life” on hold. Thank you for showing such pride in me, that means a lot.

I acknowledge the scholarship from The Centre of Clinical Research Excellence for funding my tuition and the acute study.
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACCORD</td>
<td>The Action to Control Cardiovascular Risk in Diabetes</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin Converting Enzyme</td>
</tr>
<tr>
<td>ACEi</td>
<td>Angiotensin Converting Enzyme inhibitor</td>
</tr>
<tr>
<td>AER</td>
<td>Albumin Excretion Rate</td>
</tr>
<tr>
<td>AFM</td>
<td>Abdominal Fat Mass</td>
</tr>
<tr>
<td>Alb/cr</td>
<td>Albumin to creatinine ratio</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>ANalysis Of COVariance between groups</td>
</tr>
<tr>
<td>ANOVA</td>
<td>ANalysis Of VAriance between groups</td>
</tr>
<tr>
<td>ARB</td>
<td>ATII Receptor Blocker</td>
</tr>
<tr>
<td>ATII</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BF</td>
<td>Body Fat</td>
</tr>
<tr>
<td>BG</td>
<td>Blood Glucose</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BMR</td>
<td>Basal Metabolic Rate</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>BW</td>
<td>Body Weight</td>
</tr>
<tr>
<td>CCK</td>
<td>CholeCystoKinin</td>
</tr>
<tr>
<td>CHO</td>
<td>Carbohydrate</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>Cr</td>
<td>Creatinine</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine Clearance</td>
</tr>
<tr>
<td>CRF</td>
<td>Chronic Renal Failure</td>
</tr>
<tr>
<td>Da Qing</td>
<td>The Da Qing IGT and Diabetes Study</td>
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</tbody>
</table>
DBP  Diastolic Blood Pressure
DCCT  The Diabetes Control and Complication Trial
DCCT  Diabetes Epidemiology: COllaborative analysis of
DECODE  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
GLP₁  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 AI 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.