DIETARY MANAGEMENT OF POLYCYSTIC OVARY SYNDROME

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DECLARATION

This thesis contains no material which has been 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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Moran LJ, Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ. 2006, Short term meal replacements followed by dietary macronutrient restriction enhance weight loss in Polycystic Ovary Syndrome. The American Journal of Clinical Nutrition; 84(1):77–87.

Moran LJ, Noakes M, Clifton PM, Wittert G, Tomlinson L, Galletly C, Luscombe N, Tomlinson L, Norman RJ. 2004, Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. Journal of Clinical Endocrinology and Metabolism, 89(7):3337–44.

Moran LJ, Noakes M, Clifton P, Wittert GA, Norman RJ. 2007, Weight loss, CRP and adiponectin in overweight women with and without Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology and Metabolism, in press.

SIGNED..... DATED……

DESCRIPTION OF THESIS

Chapters 2–6 were submitted for publication prior to the completion of this thesis. Chapters 2 and 4 have been accepted and published, Chapters 3 has been accepted and is in press and Chapter 5 is currently under review. For this reason, this thesis was prepared in a similar style to a Thesis by Publication. The bulk of the study methodology is included within the relevant chapters conforming to the style of the relevant journal to which the chapters were submitted. Additional methodological information is provided in Appendix 2. Where new information pertinent to the topic of the chapter has been published after the relevant paper, it is discussed in the final conclusion as opposed to the Chapter/Paper discussion being amended. Paper co-authors are acknowledged in the Acknowledgement Section and Appendix 3 contains the published papers.

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ABSTRACT

Background

Polycystic ovary syndrome (PCOS) is a common endocrine condition in women associated with obesity, reproductive and metabolic abnormalities. It improves with weight loss, however currently no specific dietary recommendations exist and there may be abnormalities in appetite regulation in PCOS that contribute to difficulty in weight management.

Aims

To assess the effect of 1) short and long-term weight loss and weight maintenance strategies on weight loss, reproductive and metabolic parameters in overweight women with PCOS and to 2) assess the relative effect of weight loss on cardiovascular risk factors and 3) post-prandial appetite, appetite hormones (ghrelin, CCK, PYY) and food intake in overweight women with and without PCOS.

Results

Overweight women with PCOS followed an 8-week weight loss (2 meal replacements/day, 4904.4±127 kJ, n=32) followed by a 6 month carbohydrate (<120 g/day) or fat restricted (<50 g/day) weight maintenance regime (n=23). Reductions in weight (5.6±2.4 kg) and improvements in body composition, insulin, reproductive hormones and menstrual cyclicity occurred and were sustained equivalently for both diet groups. We then assessed the effect of weight loss (4.2±0.7 kg over 8 weeks as described above) in overweight women with (n=15) and without (n=17) PCOS on cardiovascular risk factors. All subjects had similar improvements in body composition, triglycerides, reproductive hormones and fasting and post-prandial insulin. C-reactive protein decreased with weight loss for non-PCOS women (-1.2±0.5 mg/L, P=0.025) but not for PCOS women.

We finally assessed appetite regulation in PCOS. Women with (n=20) and without (n=12) PCOS followed a standard protein (55% carbohydrate, 15% protein) or high protein diet (40% carbohydrate, 30% protein) for 16 weeks (~6000 kJ/day). Non-PCOS subjects were more satiated (P=0.001) and less hungry (P=0.007) after the test meals and had a 70% higher fasting baseline ghrelin (P=0.011), a greater increase in fasting ghrelin (57.5 versus 34.0%, P=0.033), a greater post-prandial ghrelin decrease at week 16 (113.5±46.3 versus 49.3±12.2 pg/mL, P=0.05) and a greater maximal decrease in post-prandial ghrelin (-144.1±58.4 versus -28.9±14.2 pg/mL, P=0.02) following weight loss than subjects with PCOS. Lastly, women with (n=14) and without (n=14) PCOS undertook an 8-week weight loss regime (4.2±0.7 kg as described above). At week 0 and 8, women with PCOS again displayed lower ghrelin levels (P=0.01 and P=0.097 respectively) and a lesser post-prandial ghrelin decrease (P=0.048 and P=0.069 respectively) but similar post-prandial appetite, buffet consumption and fasting or post-prandial peptide YY and cholecystokinin compared to women without PCOS.

Conclusion

Meal replacements and moderate macronutrient restriction are effective strategies for the dietary management of PCOS. Equivalent weight losses improved cardiovascular risk factors similarly for overweight women with and without PCOS with the exception of CRP which did not decrease with weight loss for overweight women with PCOS. PCOS status is associated with altered fasting and post-prandial ghrelin levels but is not consistently associated with other impairments in post-prandial gut peptides or food intake. Further investigation is required to assess if appetite regulation is impaired in PCOS and the optimal strategies and amount of weight loss for improvement of reproductive and metabolic parameters in PCOS.

PUBLICATIONS ARISING FROM THIS THESIS

Moran LJ, Noakes M, Brinkworth G, Norman RJ. 2006, Diet, Nutrition and Exercise in Reproduction. Reproductive BioMedicine Online, 12(5):569–578

Moran LJ, Noakes M, Clifton P, Wittert GA, Le Roux C, Ghatei M, Bloom S, Norman RJ. 2006, Post-prandial ghrelin, cholecystokinin, PYY, appetite and food consumption before and after weight loss in overweight women with and without Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology and Metabolism, (Submitted 23rd January 2007).

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Norman RJ, Homan G, **Moran L**, Noakes M. 2005, Lifestyle choices, diet and insulin sensitisers in polycystic ovary syndrome. Endocrine, in press.

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Moran LJ, Norman RJ. 2002, The obese patient with infertility: a practical approach to diagnosis and treatment. Nutrition in Clinical Care, 5(6): 290–9.

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Norman RJ, **Moran L**, Davies MJ. 2001, Nutritional aspects of polycystic ovary syndrome. Reproductive Medicine Reviews, 9(2):91–107.

Conference proceedings

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Moran LJ, Noakes M, Wittert GA, Clifton PM, Norman RJ. 2004, Short term energy restriction (using meal replacements) improves reproductive parameters in polycystic ovary syndrome. Asia Pac J Clin Nutr, 13 Suppl:S88.

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PRESENTATIONS ARISING FROM THIS THESIS

Oral presentations

2006:

Androgen Excess Society International Meeting, Athens, Greece

'Obesity and Polycystic Ovary Syndrome'. **Moran LJ** and Norman RJ.

International Congress of Obesity, Sydney, Australia

'Post-prandial ghrelin, cholecystokinin, PYY, appetite and food consumption before and after weight loss in overweight women with and without Polycystic Ovary Syndrome', **Moran LJ**, Noakes M, Clifton P, Wittert GA, Le Roux C, Ghatei M, Bloom S, Norman RJ.

2005:

Dietetics Association of Australia State Conference, Adelaide, Australia

'Diet and Polycystic Ovary Syndrome', **Moran LJ**.

Poster presentations

2006:

International Congress of Obesity, Sydney, Australia

'Weight loss does not lower CRP in overweight women with Polycystic Ovary Syndrome', **Moran LJ**, Noakes M, Clifton P, Wittert GA, Norman RJ.

2005:

North American Society for the Study of Obesity International Conference,

Vancouver, Canada

Australasian Society for the Study of Obesity National Conference, Adelaide, South Australia

Nutrition Society of Australia National Conference, Melbourne, Victoria

‘Effective weight loss and maintenance strategies in polycystic ovary syndrome’, **Moran LJ,** Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ.

2004:

Nutrition Society of Australia National Conference, Brisbane, Queensland

Australasian Society for the Study of Obesity, Brisbane, Queensland

‘Short term meal replacements followed by dietary macronutrient restriction enhance weight loss in Polycystic Ovary Syndrome’, **Moran LJ,** Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ.

2003:

Endocrine Society of Australia National Conference, Melbourne, Victoria

Australian Medical Research Council National Conference, Adelaide, South Australia

Nutrition Society of Australia National Conference, Hobart, Tasmania

Dietetics Association of Australia State Conference, Adelaide, South Australia

‘Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition’, **Moran LJ**, Noakes M, Clifton PM, Wittert G, Tomlinson L, Galletly C, Luscombe N, Tomlinson L, Norman RJ.

ABBREVIATIONS

α-MSH: α-melanocyte stimulating hormone

ADP: Adenosine diphosphate

AgRP: Agouti-related peptide

AI: Adequate intake

AMH: Anti-mullerian hormone

Apo A-IV: Apolipoprotein A-IV

ATP: Adenosine triphosphate

AUC: Area under the curve

BIA: Bioelectrical impedance analysis

BMI: Body mass index

BNRP: Bombesin/bombesin related peptides

CART: Cocaine and amphetamine regulated transcript

CC: Carbohydrate counting

CCK: Cholecystokinin

CHO: Carbohydrate

CIGMA: Continuous infusion of glucose with model assessment

CRF: Corticotropin-releasing factor

CRP: C-reactive protein

CV: Coefficient of variation

CVD: Cardiovascular disease

DBP: Diastolic blood pressure

DEXA: Dual X-ray absorptiometry

DHEA: Dehydroepiandrosterone

DHEAS: Dehydroepiandrosteronesulfate

5α-DHT: 5α- Dihydrotestosterone

DHT: Dihydrotestosterone

ER: Energy restriction

FAI: Free androgen index

FC: Fat counting

FFA: Free fatty acid

FSH: Follicle-stimulating hormone

FSIVGTT: Frequently sampled intravenous glucose tolerance test

hCG: Human chorionic gonadotrophin

GH: Growth hormone

GHRH: Growth hormone releasing hormone

GHS-R: Growth hormone secretagogue receptor

GI: Glycaemic index

GL: Glycaemic load

GLP-1: Glucagon-like peptide 1

Glucose-6-P: Glucose-6 phosphate

GLUT4: Glucose transporter 4

GnRH: Gonadotrophin releasing hormone

HA: Hyperandrogenism

HDL-C: High density lipoprotein cholesterol

HOMA: Homeostasis model assessment

HP: High protein

3βHSD: 3β-hydroxysteroid dehydrogenase

17βHSD: 17β-hydroxysteroid dehydrogenase

20αHSD: 20α-hydroxysteroid dehydrogenase

HSD: Hydroxysteroid dehydrogenase

IGF: Insulin-like growth factor

IGFBP: Insulin-like growth factor binding proteins

IGT: Impaired glucose tolerance

IL: Interleukin

IR: Insulin resistance

IRS: Insulin receptor substrate

IST: Insulin sensitivity test

ITT: Insulin tolerance test

IVF: In vitro fertilization

LDL-C: Low-density lipoprotein cholesterol

LH: Luteinising hormone

LP: Low protein

MAPK: Mitogen activated protein kinase

MCH: Melanin-concentrating hormone

MTT: Meal tolerance test

MUFA: Monounsaturated fatty acid

NIH: National Institute of Health

NPY: Neuropeptide Y

OGTT: Oral glucose tolerance test

OXM: Oxyntomodulin

P450AR: Cytochrome P450 aromatase

P450cscc: Cytochrome P450 side chain cleavage

P450c11AS: Cytochrome P45011 aldosterone synthetase

P450c11B: Cytochrome P450 11-hydroxylase

P450c17α: Cytochrome P450 17 α hydroxylase

P450c17,20: Cytochrome P450 17,20 lyase

P450c21: Cytochrome P450 21-hydroxylase

PAI-1: Plasminogen-activator inhibitor activity

PCO: Polycystic Ovary Syndrome

PCOS: Polycystic Ovary Syndrome

PI3-K: Phosphatidlyinositol 3-kinase

POMC: Pro-opiomelanocortin

PP: Pancreatic polypeptide

PPAR: Peroxisome proliferator activator receptor

PUFA: Polyunsaturated fatty acid

PVN: Paraventricular nucleus

PYY: Peptide YY

QUICKI: Quantitative insulin sensitivity check index

RDI: Recommended dietary intake

REE: Resting energy expenditure

RR: Relative risk

RQ: Respiratory quotient

SFA: Saturated fatty acid

SHBG: Sex-hormone binding globulin

SP: Standard protein

StAR: Steroidogenic acute regulatory protein.

T2DM: Type II diabetes mellitus

TFM: Total fat mass

TFFM: Total fat free mass

TNF-α: Tumour necrosis factor α

TSH: Thyroid stimulating hormone

VAS: Visual analogue scores

VLCD: Very low calorie diets

VLDL: Very low density lipoprotein

VO_{2max} : Maximal oxygen consumption

WHR: Waist-hip ratio

WM: Weight maintenance