Effects Of Energy Restriction And Macronutrient Composition On Weight Loss, Energy Expenditure, And Glucose, Insulin And Lipid Levels In Humans

A thesis submitted to the University of Adelaide by

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APPENDIX

SUMMARY

Weight loss is essential in the management of obesity and obesity related diseases such as Type 2 diabetes mellitus and cardiovascular disease. Moderate energy restriction (~2000 to 4200 kJ less than average daily energy requirements) and a subsequent reduction in weight of as little as 5 to 10% may significantly improve blood pressure, fasting plasma glucose, and fasting serum insulin and lipids. There remains no consensus on the optimal macronutrient composition of weight loss diets apart from recommendations that the saturated fat content be kept low (< 10%). However, there is some concern that high-carbohydrate (50 to 60% of total energy), low-fat (< 30% energy) diets that are traditionally used for weight loss, may raise plasma glucose and serum triacylglycerol concentrations, and may reduce LDL-lipoprotein particle size.

Within the dieting public, there has been a resurgence in the popularity of high-protein, low-carbohydrate weight loss diets. However, their efficacy in the treatment of obesity and Type 2 diabetes remains controversial. Several recent studies suggest that replacing some carbohydrate with protein, in low-fat diets, may blunt the diet-induced decrease in energy expenditure that is often observed after weight loss. Consequently, low-fat, high-protein diets may be more beneficial than low-fat, high-carbohydrate diets for long-term weight management. High-protein diets may also improve insulin sensitivity and thereby ameliorate insulin resistance. Accordingly, the focus of this thesis has been to investigate the effects of energy restriction and dietary macronutrient composition on weight loss and energy expenditure, as well as glucose, insulin and lipid levels, in obese adults with and without Type 2 diabetes.

A major aim of this work was to establish the [^{14}C]-bicarbonate-urea method to measure total energy expenditure (TEE) in free-living subjects. Preliminary studies that evaluated the reproducibility and reliability of the method demonstrated that the intra-individual day-to-day variation in TEE was (mean ± SEM) 4.8 ± 1.0% for a non-obese group of men and 9.7 ± 1.3% in and obese group of men and women. The day-to-day reproducibility of the [^{14}C]-bicarbonate-urea method was comparable to that of doubly labeled water (typically 8 to 14%). The reliability coefficient was high in both subject groups. Seventy-five percent of the non-obese and 73% of the obese individuals reported that the method allowed them to continue their normal lifestyle during the measurement period. These findings indicate that the [^{14}C]-bicarbonate-urea method was well-tolerated by subjects under free-living conditions and is a reproducible and suitable method to measure TEE in normal and obese populations.

Preliminary studies were also conducted to determine the reproducibility and reliability of: 1) the Deltatrac™ Metabolic unit (indirect calorimetry) for measuring resting energy expenditure (REE), respiratory quotient (RQ) and the thermic effect of feeding (TEF), and 2) the Norland™ XR36 densitometer for measuring whole-body composition. In healthy men with a wide weight range (BMI 19.7 to 33.5 kg/m^2) the within-subject day-to-day variation was 1.7 ± 0.41% and 3.1 ± 0.8% for fasting REE and RQ respectively, and 7.8 ± 1.5% for the TEF measured over 2 hours. The reliability coefficient for REE was 0.97. For the RQ, a low reliability coefficient (0.35) may have reflected small differences in the composition of meals eaten the day prior to the study measurements, and it may also have reflect the high sensitivity of the Deltatrac for detecting small changes in RQ. These findings indicate that the Deltatrac metabolic unit was a reproducible and reliable instrument for measuring REE, RQ and TEF.

A separate study demonstrated that the measurements of total lean mass, total fat mass and body fat percentage using dual-energy X-ray absorptiometry had day-to-day variations of 2.05 ± 0.30%, 2.34 ± 0.73%, and 2.55 ± 0.81% respectively, in healthy men and women. The index of reliability was 0.99 for all body composition parameters. These findings indicate that the Norland™ XR36 densitometer is a reproducible and reliable method for measuring total body fat and lean mass in individuals that have a wide range of body weight. Subsequently, the above methods were used in three weight loss studies.

Resting energy expenditure is the major determinant of TEE in sedentary people. A small decrease in REE during energy restriction can lead to substantial decreases in daily energy-balance and consequently weight gain may occur. Relatively few studies have been conducted that assess, simultaneously, the impact of diet-induced weight loss on free-living TEE and its' components. The aim of the first weight loss study was to evaluate the effect of energy restriction on TEE and REE, the TEF, energy expenditure due to physical activity (PAEE) and RQ, after body weight is stabilized at a reduced level. Weight loss was induced using a combination of 'Modifast™' formula and one small meal per day (~3.3 MJ/day), in 6 men and 5 women who were overweight and obese. After 8 weeks of energy restriction and 2 weeks of weight maintenance, body weight was reduced 12.2 ± 1.6 kg of which 8.4 ± 1.0 kg was fat mass. Lean mass was reduced 3.8 ± 0.7 kg. Resting energy expenditure was reduced 5.6 ± 1.3% (500 ± 128 kJ/day) ($p < 0.002$). Decreases in TEE (0.18 ± 3.7%) and the TEF (1.4 ± 0.9%), and the increase in PAEE (18.6 ± 21.4%)

were not significant. After the stabilization of the reduced body weight, the fasting and postprandial RQ remained unchanged. These findings suggest that after the stabilization of a moderately reduced body weight, REE but not TEE decreases. However, it is possible that decreases in TEE within the range of 0.1 to 10% were not detected because of the large degree of variability in the response, between-subjects.

Since the 1960s, high-protein diets with emphasis on some degree of carbohydrate restriction have been popular with the dieting public. The efficacy of high-protein diets for facilitating weight loss and ameliorating insulin resistance, in subjects with type 2 diabetes and in those with hyperinsulinemia, remains unclear. The overall aim of both the second and third studies was to compare a high-protein diet (30% of energy) [HP diet] with an isocaloric diet that had 15% of energy as protein [SP diet], during 8 (study 2) to 12 (study 3) weeks of moderate energy restriction (6.7 MJ/day and 6.4 MJ/day, respectively) and 4 weeks of energy-balance. Dietary protein was supplied as red meat, poultry and diary foods. The diets were compared in 54 obese subjects (19 men/ 35 women) with Type 2 diabetes (study 2) and in 57 obese subjects (14 men/ 43 women) with hyperinsulinemia (study 3). Body weight and fasting glucose, insulin, and lipids were assessed at weeks 0, 4, 8 and 12 (in study 3 only). At both week 0 and week 12 (for study 2) or week 16 (for study 3), body composition and postprandial glucose and insulin concentrations were measured after an oral glucose tolerance test (in study 2) or after a meal tolerance test that was representative of the study diet (in study 3). In addition, 26 subjects (11 men/ 15 women) in study 2 and 36 subjects (10 men/ 13 women) in study 3 had measurements for REE, TEF, and RQ made. The 36 subjects in study 3 also had TEE measured. Both study 2 and study 3 showed that energy restriction is the major determinant of weight loss, at least over the short-term (12 to 16 weeks). However, women with type 2 diabetes, that were on the HP diet lost more total body fat (5.3 vs 2.8 kg, $p = 0.009$) and abdominal fat (1.3 vs 0.7 kg, $p = 0.006$) than the women on the SP diet. For the women with hyperinsulinemia, there was no difference in total or abdominal fat loss between diets; however, total lean mass was preserved more on the HP than on the SP diet in the women with hyperinsulinemia. In both study populations, the TEF was greatest after the HP than SP meal; however, it was not associated with weight loss. After weight loss, an increased ratio of protein-to-carbohydrate did not significantly blunt the decrease in REE or alter the TEF. In the subjects with hyperinsulinemia, there was no change in TEE after weight loss (TEE was not measured in the diabetic population). In both study 2 and 3, insulin sensitivity (as depicted by a significant reduction in the HOMA index) increased in all subjects, however, the increase was not dependent on diet composition ($p < 0.001$). In the subjects with hyperinsulinemia, the glycaemic response to the HP meal was less than to the SP meal at weeks 0 and 16 ($p = 0.027$), and the decrease in glycaemic response after weight loss was greater in the high-protein group ($p = 0.049$). Despite improvements in insulin sensitivity in the diabetic subjects, there was no overall change in RQ after weight loss. In the subjects with hyperinsulinemia, fasting RQ also remained unchanged, and the small increase in postprandial RQ was not physiologically significant and was not related to the improvements in insulin sensitivity. There were some benefits of substituting protein for carbohydrate on the plasma lipid profile; the HP diet reduced total and LDL-cholesterol more than the SP diet in subjects with type 2 diabetes, and the triacylglycerol concentrations were reduced more on the HP diet in the subjects with hyperinsulinemia. No adverse effects of the increased protein content were observed on markers of bone turnover, blood pressure, or urinary protein, in either study population. The findings from studies 2 and 3 indicate that caloric restriction, rather than the macronutrient composition of the diet is the most important determinant of weight loss. Replacing some carbohydrate with protein however, may lower the incidence hyperglycaemia and improve lipid levels in individuals with Type 2 diabetes or in those with hyperinsulinemia.

In summary, the studies reported in this thesis demonstrate that: 1) after the stabilization of a moderately reduced body weight, REE but not TEE decreases, although there is substantial variability between individuals for the effect of diet-induced weight loss on TEE when measurements are made in the free-living environment, 2) the reduction in REE and a reduced capacity to enhance fat oxidation after weight loss may be the main mechanisms that may predispose individuals to weight regain on resumption of a normal diet, and 3) the macronutrient composition of diets have no benefits over and above energy restriction on weight loss and energy expenditure. Improvements in insulin sensitivity following a meal containing a high-protein content, combined with improvements in fasting glucose and insulin homeostasis that were a consequence of weight loss, suggest that HP diets may be a suitable diet choice for people with Type 2 diabetes as well as for obese adults who are at risk of developing diabetes. A diet with an increased protein-to-carbohydrate ratio may also reduce the risk of cardiovascular disease, in individuals with dyslipidaemia. These observations will contribute to advances in basic energy metabolism and clinically to dietary interventions in the treatment of obesity and Type 2 diabetes mellitus.

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Ms Barbara Parker (Department of Physiology, University of Adelaide) collected the body composition, glycaemic control, and plasma lipids data reported in Chapter 8 and submitted this work as part of her Honor's thesis (University of Adelaide, 2000).

Ms Emma Farnsworth (Department of Physiology, University of Adelaide) collected the body composition, glycaemic control, and plasma lipids data reported in Chapter 9 and submitted this work as part of her Honor's thesis (University of Adelaide, 2001).

All data collected by Barbara and Emma was re-analysed and presented in a way that followed the aims and structure of this thesis.

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DECLARATION OF ORIGINALITY

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 any other person; except, in part, in the studies described in Chapters 8 and 9. The studies described in these two chapters were collaborative studies funded by a National Health and Medical Research Council grant and a large number of persons were involved in the data collection. Due reference has been made to the persons who significantly contributed to the collection of this data in the acknowledgement section. All data, however, was re-analysed and presented in a way that followed the aims and structure of this thesis.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Submitted for examination on the 22nd November 2002.
Amendments made in response to examiners comments and thesis re-submitted for graduation.

Signed: -------------

Natalie Deanne Luscombe

Date: 11/07/2003

PUBLICATIONS AND PRIZES ARISING FROM THIS THESIS

Publications

1. Luscombe N.D., Wittert G., Noakes M., Parker B, Clifton P.M. Effects of energy-restricted diets containing increased protein on weight loss, resting energy expenditure, and the thermic effect of feeding in Type 2 diabetes. *Diabetes Care 2002; April 25(4):652-657.*

2. Parker B., Luscombe N.D., Noakes M., Clifton P.M. The effects of a high-protein, high monounsaturated fat weight loss diet on glycemic control and lipid levels in Type 2 diabetes. *Diabetes Care 2002; March 25(3): 425-430.*

3. Luscombe N.D., Wittert G., Noakes M., Farnsworth E, Clifton P.M. Effect of a high-protein, energy restricted diet on weight loss and energy expenditure after weight stabilisation in hyperinsulinemic subjects. (Accepted for publication in the *International Journal of Obesity, October 2002*).

4. Farnsworth E, Luscombe N.D., Noakes M., Wittert G., Argyriou E, Clifton P.M. Effect of a high-protein, energy restricted diet on body composition, glycaemic control and lipid levels in hyperinsulinemic subjects. (Accepted for publication in the *American Journal of Clinical Nutrition, September 2002*).

5. Luscombe N.D., Kirkwood I., Bellon M., Tsopelas C., Clifton P, Wittert G. Measurement of energy expenditure in overweight men and women using [^{14}C]-bicarbonate-urea before and after weight loss. (Submitted to American Journal of Physiology 2002)

Prizes

Award for Best Oral Presentation

Luscombe N.D., Kirkwood I., Bellon M., Tsopelas C., Wittert G. *Measurement of energy expenditure in overweight men and women using [^{14}C]-bicarbonate-urea before and after weight loss.*

The Australasian Society for the Study of Obesity

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LIST OF COMMONLY USED ABBREVIATIONS

WHO	World Health Organisation
CVD	Cardiovascular disease
CHD	Coronary heart disease
TEE	Total energy expenditure
REE	Resting energy expenditure
TEF	Thermic effect of feeding
PAEE	Energy expenditure due to physical activity
PA	Physical activity
RQ	Respiratory quotient
DEXA	Dual-energy X-ray absorptiometry
BIA	Bioelectrical impedance analysis
BMI	Body mass index
sBP	Systolic blood pressure
dBP	Diastolic blood pressure
HP	High-protein diet
SP	Standard protein diet
SFA	Saturated fatty acid
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
FQ	Food quotient
RQ/FQ	Respiratory quotient to food quotient ratio
OGTT	Oral glucose tolerance test
MTT	Meal tolerance test
AUC	Area under the curve
HOMA	Homeostasis model of insulin resistance
FFA	Free-fatty acids
LDL	Low density lipoprotein
HDL	High density lipoprotein
VLDL	Very low density lipoprotein