Lifestyle Intervention Strategies for Type 2 Diabetes Management

A thesis submitted to the University of Adelaide for the degree of Doctor of Philosophy

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SUMMARY

In parallel with the world wide increase in obesity there has been a dramatic rise in the prevalence of type 2 diabetes (T2DM) which is associated with a number of micro- and macro-vascular complications and increases the risk of coronary heart disease. Lifestyle intervention incorporating a hypocaloric weight loss diet and exercise training is currently recommended as the cornerstone of diabetes management and has been demonstrated to improve glycemic control and reduce cardiovascular disease (CVD) risk factors in individuals with T2DM.

Previous research suggests that manipulating the dietary macronutrient composition may enhance the weight loss and improve the health status in patients undertaking a hypocaloric, weight-reducing diet. Within a low fat caloric restricted diet replacing a portion of carbohydrate with protein has been demonstrated to provide beneficial effects for weight loss, body composition, and cardiometabolic risk outcomes in overweight and obese individuals including patients with T2DM. Moreover combining a high protein, low fat hypocaloric diet with exercise training may provide additive benefits, however the efficacy of this strategy in patients with T2DM who may achieve the greatest benefits has been largely unexplored.

The first study in this thesis was a randomised-controlled clinical study which investigated the effects of a high protein, low fat hypocaloric diet combined with exercise training compared to an isocaloric high protein, low fat diet without exercise training or an isocaloric standard protein, low fat diet with or without exercise training on weight loss, body composition and cardiometabolic risk markers in overweight and obese patients with T2DM. The results showed that compared to caloric restriction alone participation in
exercise training during caloric restriction produced greater reductions in body weight and total body fat mass (FM) and increases in muscular strength. Additionally, replacement of some carbohydrate with protein further magnified these effects resulting in participants who consumed the high protein diet and participated in resistance exercise training experiencing the greatest reductions in weight, total body FM, abdominal FM and insulin levels. All treatments had similar improvements in glycemic control and CVD risk factors. These results suggest a lifestyle modification program that combines a calorie restricted high protein diet and exercise training appears to be a preferred treatment strategy in overweight/obese patients with T2DM.

A separate line of evidence suggests manipulating the timing of protein intake in relation to exercise training (consuming protein adjacent to exercise training compared to a delayed intake) stimulates greater muscle protein synthesis and hypertrophy. This strategy may therefore promote greater muscle tissue retention and improvements in body composition during calorie-restricted induced weight loss. This hypothesis was tested in the second study in this thesis. However, this study showed in overweight and obese patients with T2DM undertaking a 16 week hypocaloric high protein, low fat diet plus exercise training lifestyle intervention program, that altering the timing of protein ingestion relative to exercise (by consuming a 21g protein supplement immediately before exercise compared to delaying ingestion 2 hours post-exercise) provided no additional benefit to weight loss and changes in body composition or cardiometabolic risk.

The sustainability of the benefits obtained from intensive short-term research-based lifestyle intervention programs which incorporate an energy restricted diet and exercise is often poor, with a rebound frequently occurring following the cessation of the intensive support. The final study in this thesis followed up participants 1-year after the
commencement of a 16-week research-based intensive lifestyle (diet and exercise) intervention program and reported factors identified by those participants as enhancing or impeding post-intervention program sustainability. Participants identified multiple reasons for the discontinuation of program components including; a desire for increased diet variety, a desire for increased portion size, limited access to appropriate exercise programs and facilities, the cost of gym membership and the withdrawal of professionals to motivate them. The main factors identified that would have facilitated continuation included having continued supervision or having to report to someone, having regular recorded weight checks and diet visits and access to affordable and appropriate exercise facilities.

The findings of this thesis provide information that can be used by health professionals and policy makers for the development of evidence based recommendations and programs for the management of T2DM through diet and exercise based lifestyle intervention.
DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or 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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AUTHOR STATEMENTS

Publication 1:
A high protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes

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The authors’ responsibilities were as follows:
Th omas Wycherley was responsible for the conception and design of the study (including developing the scientific basis for the research, formulating of the ethics proposal; identification of outcome testing methodology; development of the exercise training protocol; establishment of desired macronutrient compositions of the study diets and relative protein quantities; preparation of data record forms, information and results sheets), recruitment and screening of the participants, co-coordinated the study (troubleshoot participant concerns, personal training for exercise groups), performed data collection (strength assessment, blood pressure assessment, DEXA analysis, auto-analyser biochemical analysis), managed the study data files, performed data analyses, interpreted the data and coordinated the writing of the manuscript.
Manny Noakes contributed to the conception and design of the study, data interpretation and the writing of the manuscript and designed the experimental diets.

Peter Clifton was responsible for the medical monitoring of the research participants and contributed to the data interpretation and writing of the manuscript.

Xenia Cleanthous designed the experimental diets, coordinated the implementation of the dietary protocols and contributed to the writing of the manuscript.

Jennifer Keogh assisted in the design of the experimental diets, contributed to the conception and design of the study, and contributed to the manuscript.

Grant Brinkworth was responsible for the conception and design of the study, co-coordinated the study, interpreted the data and coordinated and contributed to the writing of the manuscript.

All authors agreed on the final version of the manuscript. None of the authors had a conflict of interest in relation to this manuscript.

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I agree with the author contributions for the manuscript “A high protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes”, and give permission for the use of this manuscript in the thesis.

Thomas Wycherley ......... ...........................................
Publication 2:

Timing of protein ingestion relative to resistance exercise training does not influence body composition, energy expenditure, glycemic control or cardiometabolic risk factors in a hypocaloric, high protein, low fat diet in patients with type 2 diabetes.

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Manny Noakes contributed to the conception and design of the study, data interpretation and the writing of the manuscript and designed the experimental diets.

Peter Clifton was responsible for the medical monitoring of the research participants and contributed to the data interpretation and writing of the manuscript.

Xenia Cleanthous designed the experimental diets, coordinated the implementation of the dietary protocols and contributed to the writing of the manuscript.

Jennifer Keogh assisted in the design of the experimental diets and contributed to the writing of the manuscript.

Grant Brinkworth was responsible for the conception and design of the study, co-coordinated the study, interpreted the data and coordinated and contributed to the writing of the manuscript.

All authors agreed on the final version of the manuscript. None of the authors had a conflict of interest in relation to this manuscript.

Authors Signatures:

I agree with the author contributions for the manuscript “Timing of protein ingestion relative to resistance exercise training does not influence body composition, energy expenditure, glycemic control or cardiometabolic risk factors in a hypocaloric, high protein, low fat diet in patients with type 2 diabetes”, and give permission for the use of this manuscript in the thesis.

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Publication 3:

Self-reported facilitators of and impediments to maintenance of healthy lifestyle behaviours following a supervised research-based lifestyle intervention program in patients with type 2 diabetes.

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Philip Mohr was responsible for the conception and design of the study, interpreted the data and contributed to the writing of the manuscript

Manny Noakes contributed to the conception and design of the study, data interpretation and the writing of the manuscript and designed the experimental diets.
**Peter Clifton** was responsible for the medical monitoring of the research participants and contributed to the data interpretation and writing of the manuscript.

**Grant Brinkworth** was responsible for the conception and design of the study, co-coordinated the study, interpreted the data and coordinated and contributed to the writing of the manuscript.

All authors agreed on the final version of the manuscript. None of the authors had a conflict of interest in relation to this manuscript.

**Authors Signatures:**

I agree with the author contributions for the manuscript “Self-reported facilitators of and impediments to maintenance of healthy lifestyle behaviours following a supervised research-based lifestyle intervention program in patients with type 2 diabetes”, and give permission for the use of this manuscript in the thesis.

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OTHER PUBLICATIONS ARISING DURING CANDIDATURE


Submitted for Journal Review


CONFERENCE PRESENTATIONS DURING CANDIDATURE

International

2009  The Obesity Society’s 2009 Annual Scientific Meeting, Tuesday October 27th 2009, Washington DC, USA.

**Poster presentation:** Caloric restriction with or without resistance exercise improves emotional distress and quality of life in overweight and obese patients with type 2 diabetes.

2009  International Diabetes Federation, 20th World Diabetes Congress, Tuesday October 20th 2009, Montreal, Canada.

**Oral presentation:** A high protein diet with resistance exercise improves weight loss and body composition in overweight and obese patients with type 2 diabetes.

National

2010  Nutrition Society of Australia Annual Scientific Meeting, Wednesday December 1st 2010, Perth, Western Australia.

**Student award:** Best oral presentation ($500).

**Oral presentation:** Timing of protein ingestion relative to resistance exercise training does not influence body composition, energy expenditure, glycaemic control or cardiometabolic risk factors in a hypocaloric, high protein, low fat diet in patients with type 2 diabetes.
Oral presentation: A high protein diet with resistance exercise improves weight loss and body composition in overweight and obese patients with type 2 diabetes.


Oral presentation: A high protein diet with resistance exercise improves weight loss and body composition in overweight and obese patients with type 2 diabetes.

Australian Diabetes Society & Australian Diabetes Educators Association Annual Scientific Meeting, Wednesday August 26th 2009, Adelaide, South Australia

Oral presentation: A high protein diet with resistance exercise improves weight loss and body composition in overweight and obese patients with type 2 diabetes.

Oral presentation: Long term effects of weight loss from a very-low-carbohydrate diet on endothelial function in subjects with abdominal obesity.

Nutrition Society of Australia Annual Scientific Meeting, Monday December 1st 2008, Glenelg, South Australia.
ABBREVIATIONS

Chapter 1 & Chapter 5

Action for Health in Diabetes (AHEAD)

Australian Diabetes, Obesity and Lifestyle Study (AusDiab)

Body mass index (BMI)

Cardiovascular disease (CVD)

Cardiovascular disease (CVD)

Fat mass (FM)

Fat-free mass (FFM)

Glycosolated Hemoglobin (HbA1c)

Resting energy expenditure (REE)

Type 2 diabetes (T2DM)

Chapter 2

Analysis of variance (ANOVA)

Body mass index (BMI)

Cardiovascular disease (CVD)

Commonwealth Scientific and Industrial Research Organisation (CSIRO)

Dual-energy X-ray absorptiometry (DXA)

Fat-free mass (FFM)

Glycosolated Hemoglobin (A1c)

High protein (HP)

One repetition maximum (1RM)

Resistance exercise training (RT)
Chapter 3

Type 2 diabetes (T2DM)
Glycosolated Hemoglobin (HbA1c)
Resistance exercise training (RT)
High protein (HP)
Fat-free mass (FFM)
Resting energy expenditure (REE)
Commonwealth Scientific and Industrial Research Organisation (CSIRO)
One repetition maximum (1RM)
Fat mass (FM)
Computerised homeostatic model assessment – insulin resistance (HOMA2-IR)
Analysis of variance (ANOVA)

Chapter 4

Type 2 diabetes (T2DM)
Commonwealth Scientific and Industrial Research Organisation (CSIRO)
Research-based supervised lifestyle intervention program (RLP)
CHAPTER 1: RESEARCH BACKGROUND

1.1. Obesity Prevalence

Obesity is now considered a global epidemic. In 2005, the World Health Organisation estimated that 1.6 billion of the world’s population (age ≥15 years) were overweight (body mass index [BMI] ≥25 kg/m²) and at least 400 million were obese (BMI ≥30 kg/m²) (1). The condition continues to rapidly increase in prevalence with conservative estimates projecting that by 2030, approximately 2.16 billion adults (38% of the world’s population) and 1.12 billion (20%) will be overweight and obese, respectively (2). This would equate to an overall global prevalence of overweight and obesity of 3.3 billion people (57.8%), a 44% and 45% increase in overweight and obesity respectively since 2005 (2). In Australia the prevalence of overweight and obesity is one of the highest in the western world. Australian data obtained from the ‘2007-08 National Health Survey’ estimated using self-reported height and weight data, that 37% of adults (≥18 years) were overweight and 25% were obese (3). Furthermore, although traditionally considered a condition associated with higher income countries, obesity is now rapidly increasing in low and middle income countries, particularly in urban areas (1,2).

Obesity is fundamentally caused by a chronic disruption of energy balance in which energy intake exceeds total energy expenditure (derived from a combination of physical activity, basal metabolism, and adaptive thermogenesis) (4). Although genetic factors that affect appetite and metabolism can play a role in determining a person’s susceptibility to obesity, even with a genetic predisposition obesogenic environmental factors (that promote excessive calorie intake and discourage physical activity) are usually required for phenotypic expression (5). Therefore the increase in obesity prevalence can be primarily
attributed to environmental/lifestyle factors; the World Health Organization have identified fundamental causes of the obesity epidemic as increased intake of energy-dense foods and decreased physical activity due to changing modes of transportation, sedentary work environments and increased urbanization (1,6).

The major concern with obesity is that the condition is associated with a number of cardiometabolic health consequences including hyperlipidaemia, hypertension and insulin resistance (7). It is in fact the most critical factor underlying insulin resistance and therefore plays a major role in the pathogenesis of type 2 diabetes (T2DM) (8,9). Obesity directly impairs insulin action by up regulating several pathological mechanisms for insulin resistance that originate in adipocytes (9,10). Adipose tissue modulates metabolism by releasing free fatty acids and glycerol, hormones and proinflammatory cytokines (9). Of these, free fatty acids may be the single most critical factor in modulating insulin sensitivity (9). Free fatty acids are increased in obesity, as a result of increased adipocyte lipolysis, and induce chronic insulin resistance and impair β-cell function (9,10). The bodily distribution of adipose tissue also plays an important role in modulating insulin resistance with central adiposity more strongly associated with insulin resistance than peripheral adiposity (9,11). Although the precise mechanism/s for this mode of action is/are not entirely clear, it is possible that intra-abdominal adipocytes are more lipolytically active and promote greater increases in free fatty acid and free fatty acid flux (rate of breakdown and uptake) (12). Greater free fatty acid flux appears to be an important factor in mediating insulin resistance (13) since increasing free fatty acid flux (via a lipid plus heparin infusion) has been shown to induce insulin resistance in lean individuals (14).
It is clearly evident that obesity is an enormous global problem underpinning many cardiometabolic health issues; subsequently it is imperative to develop effective strategies to combat the growing epidemic.

1.2. Type 2 Diabetes Pathogenesis

T2DM is a metabolic disorder characterised by insulin resistance and/or abnormal insulin secretion (impaired β-cell function) (10,15-17). T2DM occurs through a continuum of reductions in tolerance to glucose, beginning with normal glucose tolerance and progressing through to insulin resistance and compensatory hyperinsulinemia, impaired glucose tolerance, and eventually T2DM (17).

In individuals with normal glucose tolerance, the relationship between insulin secretion and insulin action is hyperbolic (Figure 1) (18), meaning β-cells (which produce and release insulin) respond to a normal change in insulin action by adjusting insulin secretion to maintain normal glucose tolerance (9,10,17). If progressive increases in insulin resistance occur (e.g. as a result of obesity), initially there is a chronic compensatory increase in fasting (2.0-2.5 fold) and glucose stimulated plasma insulin concentrations (17). Eventually, however, with sustained insulin resistance, β-cells are unable to maintain an elevated rate of insulin secretion (i.e. β-cell dysfunction occurs) and the fasting insulin concentration declines precipitously (17). When β-cell function is inadequately low for a specific degree of insulin sensitivity, deviation from the insulin action, insulin secretion hyperbola occurs (Figure 1), and glucose tolerance is compromised (e.g. impaired glucose tolerance and T2DM) (9-11,16). It has been observed that patients with impaired glucose tolerance have already lost 60-70% of β-cell function (17).
1.2.1. **Figure 1:**

β-cells function (insulin release) and insulin sensitivity relationship. T2DM = type 2 diabetes (red), IGT = impaired glucose tolerance (yellow), Normal = normal glucose tolerance (green). Adapted from Kahn et al. (9).

A number of mechanisms are responsible for the progressive decline in insulin action and/or sensitivity (**Figure 2**), and it is well established that these mechanisms which predispose to T2DM are strongly linked to both genetic and environmental/lifestyle factors (9,10). The genetic factors underlying T2DM are heterogeneous, with multiple genes identified that are associated with insulin sensitivity, β-cell dysfunction, and obesity (including abdominal obesity) predisposition (9,10,19). In particular, the gene **PPARG** encoding the hormone nuclear receptor peroxisome proliferator activated receptor γ, which regulates fatty acid storage and glucose metabolism, has been implicated in the
pathogenesis of obesity and T2DM and is the gene variant most commonly associated with insulin sensitivity (9,20-22).

Despite the role of genetic factors, environmental/lifestyle factors are considered primarily responsible for the increasing incidence of T2DM (9). As previously mentioned, obesity is the most critical factor underlying insulin resistance (9), however insulin sensitivity is also influenced by a number of other non-genetic factors. These include physical activity and fitness, dietary intake, body fat distribution, ageing (which is associated with a natural progressive decline in insulin sensitivity (23)) and some medications (corticosteroids, growth hormone, nicotinic acid) (11). The mechanisms whereby physical activity regulates insulin sensitivity are less well understood than those previously discussed that relate to obesity (10). It is postulated that the physical activity specific mechanisms may be indirectly associated with induced changes in body composition (i.e. reduced fat mass [FM] and increased lean mass) and/or may be related to adaptations in skeletal muscle fuel utilisation (24). Compared to individuals with normal glucose tolerance, patients with T2DM have decreased insulin-stimulated glucose uptake in skeletal muscle (25). Physical activity is known to up-regulate translocation of insulin stimulated glucose transporter type 4 (GLUT-4) in skeletal muscle from intracellular storage sites to the plasma membrane and thereby facilitate glucose uptake in muscle tissue (26).

In individuals with normal glucose tolerance, insulin secretion decreases the glucose output of the liver, increases skeletal muscle glucose uptake and suppresses fatty acid release from fat tissue (10). Consequently, environmental/lifestyle and genetic factors that lead to impaired glucose tolerance affect the insulin secretion of the pancreatic β-cells and/or the action of insulin in fat tissue, skeletal muscle and the liver. This in turn promotes both hyperglycaemia and increased circulating fatty acids (10). Subsequently, prolonged
hyperglycemia (glucotoxicity) and chronically elevated free fatty acids (lipotoxicity) can create a feedback cycle that further worsens insulin action and insulin secretion (Figure 2) (9,10,16).

1.2. Figure 2:
Pathophysiology of hyperglycaemia and increased circulating fatty acids in type 2 diabetes.
Adapted from Stumvoll et al. (10).

1.3. Type 2 Diabetes Diagnosis
The diagnosis for diabetes (both type 1 and 2) is based on glucose criteria as follows (one or more of)* (27):

1. Glycosolated Hemoglobin (HbA1c) ≥6.5% (USA only)
2. Fasting plasma glucose ≥7.0 mmol.L⁻¹ (no caloric intake for at least 8 hours)
3. 2-hour plasma glucose ≥11.1 mmol.L⁻¹ during a 75 gram oral glucose tolerance test
4. A random plasma glucose $\geq 11.1$ mmol.L$^{-1}$ (in a patient with classic symptoms of hyperglycemia or hyperglycemia crisis)

* Criteria 2 & 4 confirmed by repeat testing in the absence of unequivocal hyperglycemia.

Since hyperglycemia develops gradually, there are individuals whose glucose levels do not meet the criteria for diabetes but are higher than those considered normal (27). Individuals in this intermediate stage of diabetes progression (pre-diabetes or impaired glucose tolerance), whereby either fasting glucose or glucose tolerance are impaired have already experienced considerable $\beta$-cell dysfunction (17) and have a relatively high risk for developing diabetes in the future (27). Diagnostic criteria for pre-diabetes are as follows:

The diagnosis for pre-diabetes are the presence of one or more of the following (27):

1. Fasting plasma glucose 5.7 mmol.L$^{-1}$ to 6.9 mmol.L$^{-1}$ (impaired fasting glucose)
2. 2-hour plasma glucose in the 75 gram oral glucose tolerance test 7.8 mmol.L$^{-1}$ to 11 mmol.L$^{-1}$ (impaired glucose tolerance)
3. $\text{HbA1c} \ 5.7\%$ to $6.4\%$ (USA only)

N.B. HbA1c is a marker of chronic glycemia, reflecting average blood glucose levels over a 2- to 3-month time period (27).

1.4. Type 2 Diabetes Prevalence

Due to the fundamental role of obesity in the pathogenesis of insulin resistance it is not surprising that in sequence with the world wide increase in obesity there has been a parallel rise in the prevalence of T2DM (which accounts for ~90-95% of all diabetes cases) (27,28). Approximately 80% of new patients with T2DM are overweight at the time of diagnosis (6), with most patients being obese (27). Current estimates predict from the years
2000 to 2030, the total global prevalence of people with diabetes will more than double from 171 million to 366 million (29).

In particular, data obtained from the ‘1999-2000 Australian Diabetes, Obesity and Lifestyle Study’ (AusDiab) (30) which used an oral glucose tolerance test to assess fasting and 2 hour plasma glucose concentrations reported the incidence of T2DM in Australian adults (≥ 25 years) to be 7.4%. This prevalence has more than doubled since 1981 and is one of the highest in the western world (31). Half of the participants in the AusDiab study identified as having diabetes were previously undiagnosed, and a further 16.4% of the study population had pre diabetes (impaired glucose tolerance or impaired fasting glucose) (31). More recent data from the ‘2007-08 National Health Survey’ also estimated that 4.0% of the Australian population reported they had medically diagnosed diabetes mellitus (3).

The increase in T2DM prevalence is attributable to similar environmental/lifestyle factors to those driving the obesity epidemic (increased intake of energy-dense foods and decreased physical activity) as well as a contribution due to population growth and an ageing population (6,9).

1.5. Type 2 Diabetes Consequences and Cost

T2DM is associated with a number of micro- and macro-vascular complications including hypertension, nephropathy, retinopathy, coronary artery disease, peripheral artery disease and cerebrovascular disease (32). T2DM increases the risk of coronary heart disease by 2-4 fold (33), with cardiovascular disease (CVD) accounting for 70-80% of death in patients with T2DM (34). Compared to people without T2DM, patients with T2DM also experience a higher incidence of other health related impediments including a reduced quality of life and increased levels of emotional distress (35). In 2005 the total financial cost of diabetes
in Australia was estimated to be $10.3 billion, including carer costs of $4.4 billion, productivity losses of $4.1 billion and $1.1 billion in costs to the health system (36).

Prospective studies have identified the degree of glycemia in T2DM as the major determinant of microvascular complications (37), sensory neuropathy (38), stroke (39), myocardial infarction (37), diabetes related mortality (37,40) and the prevalence of reduced quality of life and increased distress (35). It is therefore critically important to develop strategies to improve glycemic control and this represents the major goal for reducing the personal burden and financial costs of diabetes and its associated complications (41).

1.6. Interventional Strategies for Type 2 Diabetes

The current target for patients with T2DM to reduce the risk of micro and macro vascular disease is to achieve a HbA1c <7% (42). For patients with T2DM a 1% (absolute) reduction in HbA1c has been associated with a 37% decrease in the risk of microvascular complications and a 21% decrease in diabetes related mortality (37).

In both the treatment and prevention of T2DM, pharmaceutical agents reduce hyperglycemia by increasing the action of insulin (e.g. metformin), increasing insulin secretion (e.g. sulfonylureas), or in later stages of β-cell dysfunction providing an exogenous source of insulin (10). However, pharmacotherapy also carry high costs and often unwanted side effects including weight gain (10). Alternatively, lifestyle modification that incorporates an energy reduced diet and exercise training represents the cornerstone of T2DM management (43,44). Several studies have demonstrated the benefits of lifestyle modification for both the prevention of T2DM onset (primary prevention), and improving weight status, glycemic control and CVD risk factors in patients with T2DM
(secondary prevention) (45-51). Reductions in total body FM through lifestyle modification can improve insulin sensitivity, with improvements most strongly related to reductions in visceral FM (52).

Anderson et al. (51) conducted a meta analysis of 18 studies that assessed lifestyle modification induced weight loss after 12 weeks in patients with T2DM and found that weight loss was associated with improvements in blood pressure, the blood lipid profile and glycemic control.

Data obtained from the ‘Finnish Diabetes Prevention Study’ (49) and the ‘US Diabetes Prevention Program’ (48) have shown intensive lifestyle intervention that combines diet and exercise is at least as effective as pharmacotherapy for reducing weight and CVD risk factors in patients with impaired glucose tolerance. These prospective studies showed a 5-7% loss of initial body weight achieved through diet and exercise based lifestyle intervention reduced the incidence of developing T2DM by 58% (48,49).

In further support for the role of lifestyle modification for T2DM management, the long-term, multi-centre clinical trial ‘Look AHEAD (Action for Health in Diabetes) study’ has demonstrated that compared to a usual care control condition (involving a program of diabetes support and education), intensive lifestyle intervention that incorporates an energy restricted diet and exercise reduced body weight by 8.6% (vs. 0.7%) at 1 year (45) and 4.7% (vs. 1.1%) at 4 years (47,50). In this study, averaged across the 4 years the intensive lifestyle intervention group had greater improvements than the usual care group in physical fitness (12.7% metabolic equivalents vs. 2.0% metabolic equivalents), HbA1c (-0.36% absolute vs. -0.09% absolute), systolic blood pressure (-5.3 mmHg vs. -3.0 mmHg), diastolic blood pressure (-2.9 mmHg vs. -2.5 mmHg), high density lipoprotein cholesterol
Although low-density lipoprotein was reduced to a greater extent with usual care (-0.71 mmol.L\(^{-1}\) vs. -0.62 mmol.L\(^{-1}\)) this difference was no longer significant after adjusting for medication usage (-0.51 mmol.L\(^{-1}\) vs. -0.49 mmol.L\(^{-1}\)) (47).

Additionally, over the longer-term (>1 year), lifestyle intervention for prevention of T2DM has shown greater cost effectiveness compared to pharmacotherapy (53). Although the effectiveness of lifestyle interventions for reducing actual cardiovascular events has yet to be determined (34); the ‘Look AHEAD study’ currently in progress was designed to primarily determine whether cardiovascular morbidity and mortality in people with T2DM can be reduced through intensive lifestyle intervention (54) and on completion (~2014) should provide this data (47).

**1.7. Caloric Restriction for Weight Loss**

A moderate hypocaloric diet is a core component of a lifestyle intervention weight loss program. Over the short-term of a lifestyle intervention weight loss program (incorporating diet plus exercise) the energy deficit achieved through caloric restriction is usually the largest contributor to body weight reduction (55). Over the longer term a study by Sacks et al. (56) also demonstrated that if a reduced calorie diet is sustained (2 years), it is effective for achieving and maintaining a clinically relevant weight loss (~ -4 kg).

Long-term efficacy studies that have induced chronic caloric restriction via bariatric surgery have demonstrated significant long-term loss of weight, recovery from T2DM, improvement in CVD risk factors and reduction in premature mortality (57-59). Adams et al. (58) matched 7925 participants who underwent bariatric surgery with 7925 participants in a usual treatment control group (mean follow up duration was 7.1 years). This study
found that compared to the control group the surgery group had a 40% reduction in mortality as well as reductions in CVD and T2DM. Sjostrom et al. (59) followed over 4000 obese participants who underwent either bariatric surgery or were prescribed a conventional treatment (mean follow up duration was 10.9 years). The study found a 24% reduction in mortality with surgery and after 15 years participant’s weight loss from baseline was 13-27% for those who underwent surgery (weight changes varied depending on the type of bariatric procedure used) and 2% for those in the control group. Despite the apparent success of surgical treatment, lifestyle modification remains the primary therapeutic approach and bariatric surgery is usually only conducted in severely obese individuals (BMI $\geq 40 \text{ kg.m}^{-2}$) and usually only as a secondary approach in the event that lifestyle medication is unsuccessful; but it is not without the risk of death or major complications (57).

### 1.8. Fat-Free Mass and Weight Loss

The location and type of tissue loss during weight reduction (i.e. the quality of the weight loss) is also an important consideration. In terms of tissue location, visceral fat tissue is an important factor modulating insulin resistance (9,11,12) and reductions in visceral FM, as opposed to subcutaneous FM are most strongly related to improvements in insulin sensitivity (52). In regards to tissue type, despite the usual goal of dietary interventions to achieve weight loss via reductions in FM an accompanying loss of fat-free mass (FFM) is frequently observed (60) and typically accounts for $\sim 1.2$ kg of every 6 kg (20%) of total weight loss (61). FFM consists of two distinct moieties; highly metabolically active muscle and organs, and low metabolic rate tissues such as bone and extra cellular mass. (62). FFM is strongly correlated with resting energy expenditure (REE) (63-65) which is responsible for approximately 60-70% of daily energy expenditure. REE is commonly reduced with weight (FFM) loss, whereas maintenance of REE through preservation of FFM maybe
desirable for minimising the risk of long term weight regain (60). A meta-review showed that REE was 3-5% lower for formerly obese patients compared to controls, with low REE likely to contribute to a high rate of weight regain (66). Increased risk of weight gain with low REE has also been demonstrated in several individual studies (67,68). In addition, since skeletal muscle represents the largest mass of insulin sensitive tissue (69) further importance should be placed on the preservation of FFM for patients with T2DM and other insulin-resistance related metabolic conditions to assist in improving glycemic control (70).

These important considerations highlight the rationale for developing lifestyle interventions that target improvements in body composition by enhancing fat and visceral fat reductions and maintaining/increasing lean muscle mass during weight loss.

1.9. Current Nutrition Recommendations

Based on the data presented in the sections above, it is well established that caloric restriction is an effective strategy to induce weight loss and formulates a key component of lifestyle intervention programs. However, the dietary macronutrient profile is also an important consideration that can potentially play a significant role in modulating weight loss, weight management and health status (71).

Nutritional macronutrient composition recommendations for patients with T2DM vary slightly between countries but generally promote an intake of approximately 10-20% of energy from protein, 45-65% carbohydrate and <35% fat. Specifically, the Diabetes Australia and the Royal Australian College of General Practitioners ‘Diabetes Management in General Practice 2010/11’ guidelines (72) specify a diet macronutrient composition for patients with T2DM of up to 50% of energy from carbohydrate, <30% fat and 10-20%
protein. Similarly the ‘European Association for the Study of Diabetes’ Diabetes and Nutrition Study group guidelines (73) specify a diet macronutrient composition of 45-60% of energy from carbohydrate, <35% from fat and 10-20% from protein. Diabetes UK provide nutritional recommendations for patients with diabetes (74) that specify a diet macronutrient composition of 45-60% of energy from carbohydrate, <35% from fat and recommend ≤1 g.kg⁻¹.day⁻¹ of protein. The Australia and New Zealand ‘Acceptable Macronutrient Distribution Range’ for lowering chronic disease risk specifies a diet that consists of 45-65% carbohydrate, 20-35% fat and 15-25% protein (75). The current American Diabetes Association nutrition guidelines for the management of T2DM (secondary prevention) do not specify an actual optimal macronutrient profile, but include the following recommendations (41):

- It is unlikely any one optimal macronutrient profile exists for all patients with T2DM
- Include carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk, the average minimum requirement for carbohydrate is 130 g.day⁻¹
- Consume a variety of fiber-containing foods to achieve at least the fiber intake goals set for the general population of 14 g/1,000 kcal; limit saturated fat to <7% of total energy
- Limit daily alcohol intake to a moderate amount (one drink per day or less for women and two drinks per day or less for men)
- There is insufficient evidence to suggest that usual protein intake (15–20% of energy) should be modified and high-protein diets are not recommended as a method for weight loss at this time.
The recommended dietary allowance for protein is to consume $0.8 \, \text{g.kg}^{-1}\text{day}^{-1}$ (total body weight) of good quality protein (from sources with high protein digestibility corrected amino acid pattern scores and provide all nine indispensable amino acids e.g. meat, poultry, fish, eggs, milk, cheese, and soy) (41,75). Since the recommended dietary allowance assumes a standard body weight, for people who are heavier this body weight relative recommended dietary allowance does not correspond with the macronutrient ratio based weight loss diet current dietary recommendations for protein (61,76). For example; a moderate energy restricted diet (~7000 kJ.day$^{-1}$) with 10-20% of energy from protein that provides 41 – 82 g.day$^{-1}$ maybe inadequate for delivering $0.8 \, \text{g.kg}^{-1}\text{day}^{-1}$ of protein for an overweight/obese patient (>~100 kg), with possible negative implications for body composition (61,77). In support, Bopp et al. (77) demonstrated an inadequate protein intake during caloric restriction may be associated with adverse body composition changes. In a 20-week study in overweight and obese postmenopausal women using a calorie restricted diet (1420-1670 kJ.day$^{-1}$ of energy deficit) with a recommended protein macronutrient content of 15-20% energy (carbohydrate 50-60 %, fat 25-30%), an average weight loss of 10.8 kg was achieved of which 32% occurred due to reductions in lean mass. The elevated baseline bodyweight of this group meant absolute protein intake was only 0.47-0.8 g.kg$^{-1}\text{day}^{-1}$ (average 0.62 g.kg$^{-1}\text{day}^{-1}$) and those participants who consumed higher absolute amounts of dietary protein lost less lean mass, even after adjusting for body size.

1.10. **High Protein, Low Fat Diets**

Despite the current nutrition recommendations of leading health authorities an abundance of scientific debate still exists regarding the optimal macronutrient composition for patients with T2DM (78). This has largely arisen due to:
1) Emerging evidence recognising the modification of dietary macronutrient composition can play a significant role in weight loss, weight management and health status (71).

2) Obese individuals generally experience difficulty in achieving weight loss and body weight maintenance (71).

3) Observation of an increased popularity and use of alternative dietary patterns (contrary to current recommendations) that offer hope to individuals seeking effective weight loss and health improvements (78).

A central focus of the ‘optimal diet macronutrient profile’ debate is the level of dietary protein and whether altering the macronutrient profile to favour an increased protein intake (i.e. a ‘high protein diet’) can offer additional benefits (78). Standard protein intake is 12%-18% of total energy whilst a high protein diet is usually considered 25%-35% of total energy (79) and notably lies outside the Australia and New Zealand ‘Acceptable Macronutrient Distribution Range’ (75). High protein diets can come in a variety of forms with the two most prominent categories of high protein diets as follows (79):

1) Replacing a portion of carbohydrate with protein whilst maintaining a low level of fat (<30%) and saturated fat.

2) Replacing the majority of carbohydrate with protein and fat.

High protein diets may also differ in the method of controlling energy intake and can be either ‘controlled’, whereby total energy intake, food types and serving sizes are prescribed to achieve a specific level of caloric restriction and macronutrient profile, or they can be ‘ad libitum’ (usually more applicable to high protein diets that are very low in carbohydrate) whereby participants follow a set of food intake rules without any particular prescription of energy intake (e.g. the Atkins diet (80)).

It is difficult to determine the role of protein per se within ‘Atkins style’ very low carbohydrate diets due to the confounding effect of carbohydrate restriction and a high fat intake (81). In this thesis a ‘high protein diet’ unless otherwise specified refers to a diet
that increases protein intake through altering the carbohydrate to protein ratio of a low fat diet.

1.11. High Protein Diets and Health

A growing body of evidence suggests that during caloric restriction, a high protein diet compared to a conventional higher carbohydrate diet may provide a number of advantages (71). Specifically, for overweight and obese subjects including patients with T2DM the benefits may include attenuating the loss of FFM (61,82,83), attenuating the reduction in REE (84,85), increasing body fat loss (61,86,87), increasing satiety (82,87), improving an array of CVD risk factors (insulin sensitivity, glucose homeostasis (84,87) and improving the blood lipid profile (86-89)). Table 1 provides a summary of the changes in body weight, FFM and REE from short term (≤4 months) randomised controlled trials which compare a hypocaloric high protein diet and a standard protein diet. Furthermore, under weight stable conditions, compared to a usual diet control a eucaloric high protein diet has also been shown to improve glycemic control in patients with T2DM (90,91), and lower blood pressure in hypertensive patients (92).

Multiple randomised controlled studies have reported a beneficial effect of an energy restricted high protein diet compared to an isocaloric standard protein diet for improving body composition (82,83,86,87,93). Leidy et al. (82) showed during a 12 week hypocaloric weight loss intervention that a higher protein intake preserves FFM and induced satiety in pre obese and obese women. This study showed that whilst mean weight loss was ~9 kg in both groups, FFM was only reduced by 1.5 kg in the high protein diet group (30% protein, 1.4 g.kg⁻¹.day⁻¹) compared to 2.8 kg in the isocaloric control group (18% protein, 0.8 g.kg⁻¹.day⁻¹). Farnsworth et al. (83) also showed that a high protein diet preserved FFM in hyperinsulinemic females, but not males, following 12 weeks of energy restriction and 4
weeks of energy balance. In females, the mean weight loss was 7 kg but FFM was reduced by -0.1 kg in the high protein diet group (30% protein, ~1.24 g.kg\(^{-1}\).day\(^{-1}\) during weight loss phase) compared to -1.5 kg in the standard protein group (15% protein, ~0.68 g.kg\(^{-1}\).day\(^{-1}\)). In the males, the overall weight loss was 10.5 kg and FFM reduced similarly in both groups (high protein diet group 2.5 kg, standard protein diet group 1.9 kg). The exact reason for the absence of a differential preservation in FFM between the dietary patterns in the male subjects remains unclear. However, it is noteworthy in this study that due to the higher baseline body weights of the males, the differential body weight relative protein contents of the weight loss dietary interventions were markedly less than that of the females (high protein diet ~1.02 g.kg\(^{-1}\).day\(^{-1}\) vs. standard protein diet ~0.55 g.kg\(^{-1}\).day\(^{-1}\)) and may provide some explanation for the differential gender response. Despite this, the complete subject cohort (males and females combined) showed the reduction in glycemic response and triglycerides was greater in the high protein diet group. A separate study also showed in obese women undergoing caloric restriction that compared to participants consuming a standard protein diet (18%, ~0.64 g.kg\(^{-1}\).day\(^{-1}\)) those with high serum triacylglycerol (>1.5 mmol.L\(^{-1}\)) consuming a isocaloric high protein diet (31%, ~1.12 g.kg\(^{-1}\).day\(^{-1}\)) lost more weight (7.9 vs. 5.8 kg) and FM (6.4 vs. 3.4 kg) and had a greater decrease in triacylglycerol concentrations (-0.59 vs. -0.03 mmol.L\(^{-1}\)) (86). However, no differences between the diets for participants with serum triacylglycerol ≤1.5 mmol.L\(^{-1}\) or in the combined whole group analysis were evident, in which the overall weight loss and reductions in blood lipids, glucose, insulin and lean mass (-1.5 kg on the high protein diet vs. -1.8 kg on the standard protein diet) were similar. A 12-week weight loss study by Parker et al. (93) compared a high protein diet (28%, ~1.23 g.kg\(^{-1}\).day\(^{-1}\)) with an isocaloric standard protein diet (16%, ~0.68 g.kg\(^{-1}\).day\(^{-1}\)) in overweight or obese patients with T2DM. Following the intervention there were similar overall reductions in both diet groups for weight (~4.8 kg on the standard protein diet vs. ~5.5 kg on the high protein diet) and lean
mass (-1.35 kg on the standard protein diet vs. -0.52 kg on the high protein diet), however females on the high protein diet lost significantly more total (5.3 vs. 2.8 kg) and abdominal (1.3 vs. 0.7 kg) FM. In a study by Layman et al. (87) although there were no significant differences between diets in changes in actual body weight, FM or lean mass, they showed that compared to the energy restricted standard protein diet group (16%, 0.8 g.kg\(^{-1}\).day\(^{-1}\)) participants in the isocaloric high protein diet group (30%, 1.5 g.kg\(^{-1}\).day\(^{-1}\)) had an increased ratio of fat loss to lean loss. Skov et al. (94) examined the effects of replacing some carbohydrate with protein in a low fat (<30%) diet for 6 months, although the diets used in the study were consumed *ad libitum* participants in each group were required to maintain a specified macronutrient profile and fat intake. Compared to participants who consumed a high carbohydrate diet (12% protein [70.4 g.day\(^{-1}\), 58% carbohydrate, 30% fat), participants who consumed a high protein diet (25% protein [107.8 g.day\(^{-1}\), 45% carbohydrate, 30% fat) lost more total weight (8.7 vs. 5.0kg), FM (7.6 vs. 4.3kg) and intra abdominal FM (33 vs. 16.8 cm\(^2\)). In this study it is interesting to note that both groups achieved weight loss with an *ad libitum* energy intake which was attributed to the participants high level of motivation to lose weight. The authors postulated that the mechanisms responsible for the superior body composition changes with the high protein diet were a lower reported energy intake in this group (~2 MJ.day\(^{-1}\) difference) and possibly the greater thermogenic effect of protein.

Although beneficial effects on body composition have not been observed in all individual studies (95,96) a recent meta-analysis (61) supports the concept that compared with standard protein diets, high protein diets may provide body composition benefits during weight reduction. This analysis showed the degree of FFM retention during weight loss tended to increase with each successive quartile of protein intake (≤0.70 g.kg\(^{-1}\).day\(^{-1}\), >0.70 ≤1.05 g.kg\(^{-1}\).day\(^{-1}\), >1.05 ≤1.20 g.kg\(^{-1}\).day\(^{-1}\) and >1.20 g.kg\(^{-1}\).day\(^{-1}\)) with significant
differences between the upper 2 quartiles compared to the lowest quartile. The analysis identified that protein intakes above 1.05 g.kg\(^{-1}\).day\(^{-1}\) may improve FFM retention during weight loss induced by caloric restriction.

Previous research has also suggested that REE may also be maintained to a greater extent with high protein diets (84,85). It is possible this may occur due to several reasons including an elevated post-prandial increase in energy expenditure (thermogenesis) associated with increased protein intake, a protein sparing effect on lean mass during weight loss and/or protein intake influencing hormone levels (e.g. catecholamines and thyroid hormones) (85). Two small studies showed REE reduced to a lesser extent with a hypocaloric high-protein diet than with an isocaloric conventional diet (84,85). Whitehead et al. (85) showed in overweight men and women who underwent a short term caloric restriction period (7 days, 4200 kJ.day\(^{-1}\)) that compared to a diet with a low absolute protein intake (15% protein [38 g.day\(^{-1}\)], 53% carbohydrate, 32% fat), maintaining protein intake (36% protein [87 g.day\(^{-1}\)], 32% carbohydrate, 32% fat) lessened the reduction in 24 hour energy expenditure (-285 kJ.day\(^{-1}\) vs. -541 kJ.day\(^{-1}\)) and sleeping energy expenditure (-207 kJ.day\(^{-1}\) vs. -479 kJ.day\(^{-1}\)), despite similar reductions in body weight in both groups (~2 kg). Similarly Baba et al. (84) also observed a lesser reduction in REE with a high protein diet (45% protein [~198 g.day\(^{-1}\)], 25% carbohydrate, 30% fat; -553 kJ.day\(^{-1}\)) compared to a high carbohydrate diet (12% protein [~52 g.day\(^{-1}\)], 58% carbohydrate, 30% fat; -1606 kJ.day\(^{-1}\)), this occurred despite a greater level of weight loss in the high protein diet group (-8.3 vs. 6.0 kg). However these effects have not been consistently observed. In contrast, other slightly longer duration studies (8-12 weeks) have observed similar reductions in REE following diet induced weight loss irrespective of the level of dietary protein intake (95,96).
Macronutrient composition of a hypocaloric diet has also been shown to alter the blood lipid profile, satiety and glycemic control (87,89,93,97). Layman et al. (87,97) showed that following ~7.3 kg of weight loss, compared to participants consuming a hypocaloric high carbohydrate diet, those who consumed a high protein diet had greater levels of satiety (87), improvements in glucose homeostasis (stabilised blood glucose during nonabsorptive periods) (97) and reductions in triacylglycerols (87) and the postprandial insulin response (97). Both diet groups had similar reductions in body weight (~7.3 kg), total cholesterol (~0.57 mmol.L⁻¹) and low density lipoprotein cholesterol (~0.43 mmol.L⁻¹). Clifton et al. (89) conducted a pooled data analysis of three weight loss trials (83,86,98) that each compared a high protein diet (30-40%, 110-136 g.day⁻¹) with a standard protein diet (15-20%, 60-67 g.day⁻¹). The analysis showed no differences between dietary patterns for changes in glucose, insulin, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, total weight loss or body composition, however triacylglycerol levels decreased to a greater extent with a high protein diet (-0.48 vs. -0.27 mmol.L⁻¹). Post-hoc analysis further revealed that participants with an elevated baseline triacylglycerol level (>1.54 mmol.L⁻¹) who consumed a high protein diet lost more body weight (8.5 vs. 6.9 kg) and had greater reductions in FM (-6.17 vs. -4.52 kg), abdominal FM (-1.92 vs. 1.23 kg), total cholesterol (12 vs. 6%) and triacylglycerol (39 vs. 20%). In the previously mentioned study by Parker et al. (93) although lipid levels decreased similarly in both diet groups during the initial 8 week energy restriction phase, following the 4 weeks of weight maintenance the group consuming the high protein diet pattern experienced greater reductions in total and low density lipoprotein cholesterol (-0.35 vs. -0.01 mmol.L⁻¹ and -0.19 vs. 0.09 mmol.L⁻¹ respectively).

Under weight stable conditions, compared to a standard protein diet a eucaloric high protein diet can also provide beneficial effects for glycemic control and blood pressure
Gannon et al. (90) demonstrated in patients with T2DM that compared to participants who followed a 5 week standard protein control diet (15% protein, 55% carbohydrate, 30% fat) those following an isoenergetic high protein diet (30% protein, 40% carbohydrate, 30% fat) had greater decreases in HbA1c (−0.8% vs. -0.3% absolute) which was attributed to a reduction in the postprandial glucose response (Figure 3). Hodgson et al. (92) found in hypertensive patients during a randomised controlled trial that compared to participants who maintained their usual diet (18.6% protein, 31.6% fat) participants who followed an 8 week eucaloric diet which increased protein content (+5.3% of energy) at the expense of carbohydrate had lower systolic blood pressure (-5.2 mmHg).
Mean (± standard error of the mean) glycosylated hemoglobin (%) during 5 weeks of the standard protein control (○) or high protein (●) diet. (* P<0.05 significantly different to standard protein control diet). Adapted from Gannon et al. (90)

To date a limitation of the currently available research is the paucity of long term efficacy studies (>6 months) investigating the longer term effects of a high protein diet compared to a normal protein diet (56,99). A two phase study in overweight and obese participants conducted by Delbridge et al. (99) prescribed either a 12 month high protein diet (30%) or a normal protein diet (15%) (phase 2) to participants who had completed a 3 month very low calorie diet period that resulted in 16.5 kg weight loss (phase 1). Following phase 2, overall weight loss (compared to phase 1 baseline) was similar between the diet groups (high protein diet -14.8 kg, normal protein diet -14.3 kg), i.e. similar weight regain occurred in both groups during phase 2 (high protein diet 3.0 kg, normal protein diet 4.3 kg). CVD risk markers also reduced similarly from the phase 1 baseline in both groups, except for blood pressure which was reduced to a greater extent with the high protein diet. In this study the dietary compliance data revealed that although protein intakes were significantly different between the dietary groups and both groups reported similar fat intakes (~30%), participants in the normal protein group were unable to maintain the prescribed lower protein intake (15%) and actual reported protein intake was ~22%. Participants in the high protein diet group reported ~28% which was close to their prescribed protein intake of 30%. It is therefore possible the smaller differential protein intakes between the experimental groups may explain the absence of any differential changes in weight, body composition and CVD risk markers. Moreover, since the macronutrient manipulation phase of this study was implemented following considerable weight loss it is unknown whether differential outcomes would have been observed if the different dietary regimes were implemented from baseline. A separate study by Sacks et al.
(56) also compared a hypocaloric high protein diet with an isocaloric normal protein diet over a 2 year period in overweight adults. After the intervention, both diet groups achieved similar weight loss (normal protein diet -3.6 kg vs. high protein diet -4.5 kg) and reduction in CVD risk factors, with a trend for a greater reduction in insulin in the high protein diet group (-10% vs. -4%, P=0.07). However, despite the normal protein diet and high protein diet participants being prescribed dietary macronutrient percentage intakes (carbohydrate:protein:fat) of 65:15:20 and 55:25:20 respectively, after 2 years participants were not able to achieve their target levels with actual macronutrient percentage intakes of 53.2:19.6:26.5 and 51.3:20.8:28.4 respectively. Although the participants who did achieve the highest protein intake had greater weight loss (within the high protein diet, weight loss increased with increasing quintiles of protein intake) the overall low compliance with the treatment assignment limits the understanding of the efficacy of these dietary patterns. Therefore although these studies suggest no apparent advantage of consuming a long term high protein diet for weight status or CVD risk factors, further long-term well controlled studies with careful consideration for maintaining the desired protein intake targets are still required before any definitive conclusions can be made.

In summary, taken together data from these prior studies suggest replacing some carbohydrate with protein in a low fat energy restricted diet has at least comparable and in some instances beneficial effects over the shorter term for reducing triacylglycerol levels, particularly in patients with elevated baseline levels (81). Additionally, an energy restricted high protein diet may also provide an advantage over a standard protein diet by increasing satiety, enhancing weight and FM loss, retaining lean mass, improving insulin regulation and offsetting diet-induced energy expenditure reductions (71). Under eucaloric conditions, at least in the short-term, a high protein diet may also decrease blood pressure
(92) and improve glycemic control (90), although the effects over the longer term remain largely unknown.
### 1.11.2. Table 1:
Summary of short term (≤ 4 months) randomised controlled trials investigating changes in body weight, fat-free mass and resting energy expenditure following the consumption of a hypocaloric high protein diet (HP) or an isocaloric standard protein diet (SP).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Study Duration</th>
<th>Diet</th>
<th>Protein Content</th>
<th>Δ Weight</th>
<th>Δ Fat-Free Mass</th>
<th>Δ Resting Energy Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leidy et al. (82)</td>
<td>Overweight and Obese (46 Females)</td>
<td>12 Weeks</td>
<td>HP</td>
<td>30%, 1.4 g.kg⁻¹ day⁻¹</td>
<td>-8.1 kg</td>
<td>-1.5 kg</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SP</td>
<td>18%, 0.8 g.kg⁻¹ day⁻¹</td>
<td>-9.5 kg</td>
<td>-2.8 kg*</td>
<td>NA</td>
</tr>
<tr>
<td>Farnsworth et al. (83) - Females Only</td>
<td>Hyperinsulinemic (43 Females)</td>
<td>16 Weeks</td>
<td>HP</td>
<td>30%, ~1.24 g.kg⁻¹ day⁻¹ (During 12-week weight loss phase)</td>
<td>-6.6 kg</td>
<td>-0.1 kg</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SP</td>
<td>15%, ~0.68 g.kg⁻¹ day⁻¹ (During 12-week weight loss phase)</td>
<td>-7.4 kg</td>
<td>-1.5 kg*</td>
<td>NA</td>
</tr>
<tr>
<td>Farnsworth et al. (83) - Males Only</td>
<td>Hyperinsulinemic (14 Males)</td>
<td>16 Weeks</td>
<td>HP</td>
<td>30%, ~1.02 g.kg⁻¹ day⁻¹ (During 12-week weight loss phase)</td>
<td>-11.4 kg</td>
<td>-2.5 kg</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SP</td>
<td>15%, ~0.55 g.kg⁻¹ day⁻¹ (During 12-week weight loss phase)</td>
<td>-9.6 kg</td>
<td>-1.9 kg</td>
<td>NA</td>
</tr>
<tr>
<td>Parker et al. (93)</td>
<td>Type 2 Diabetes (35 Females, 19 Males)</td>
<td>8 Weeks Hypocaloric 4 Weeks Eucaloric</td>
<td>HP</td>
<td>28%, ~1.23 g.kg⁻¹ day⁻¹ (During 8-week weight loss phase)</td>
<td>-5.5 kg</td>
<td>-0.5 kg</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SP</td>
<td>16%, ~0.68 g.kg⁻¹ day⁻¹ (During 8-week weight loss phase)</td>
<td>-4.8 kg</td>
<td>-1.4 kg</td>
<td>NA</td>
</tr>
<tr>
<td>Noakes et al. (86)</td>
<td>Obese (100 Females)</td>
<td>12 Weeks</td>
<td>HP</td>
<td>31%, ~1.12 g.kg⁻¹ day⁻¹</td>
<td>-7.6 kg</td>
<td>-1.5 kg</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SP</td>
<td>18%, ~0.64 g.kg⁻¹ day⁻¹</td>
<td>-6.9 kg</td>
<td>-1.8 kg</td>
<td>NA</td>
</tr>
</tbody>
</table>

(continued)
### 1.11.3. Table 1: Continued

<table>
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<tr>
<th>Reference</th>
<th>Participants</th>
<th>Study Duration</th>
<th>Diet</th>
<th>Protein Content</th>
<th>Δ Weight</th>
<th>Δ Fat-Free Mass</th>
<th>Δ Resting Energy Expenditure</th>
</tr>
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<tbody>
<tr>
<td>Noakes et al. (86)</td>
<td>High Serum Triacylglycerol (&gt;1.5 mmol L^{-1}) (50 Females)</td>
<td>12 Weeks</td>
<td>HP</td>
<td>31%, -1.15 g kg^{-1} day^{-1}</td>
<td>-7.9 kg</td>
<td>-1.5 kg</td>
<td>NA</td>
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<td></td>
<td></td>
<td></td>
<td>SP</td>
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<td>-5.8 kg *</td>
<td>-2.4 kg</td>
<td>NA</td>
</tr>
<tr>
<td>Layman et al. (87)</td>
<td>Overweight (24 Females)</td>
<td>10 Weeks</td>
<td>HP</td>
<td>30%, 1.5 g kg^{-1} day^{-1}</td>
<td>-7.53 kg</td>
<td>-0.88 kg</td>
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<tr>
<td></td>
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<tr>
<td>Luscombe et al. (95)</td>
<td>Hyperinsulinemic (26 Females, 10 Males)</td>
<td>16 Weeks</td>
<td>HP</td>
<td>27%, 1.09 g kg^{-1} day^{-1} (During 12-week weight loss phase)</td>
<td>-7.9 kg</td>
<td>-1.1 kg</td>
<td>-650 kJ day^{-1}</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>SP</td>
<td>16%, 0.66 g kg^{-1} day^{-1} (During 12-week weight loss phase)</td>
<td>-8.0 kg</td>
<td>-1.2 kg</td>
<td>-780 kJ day^{-1}</td>
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<td>Luscombe et al. (96) - Subgroup of Parker et al. (93)</td>
<td>Type 2 Diabetes (15 Females, 11 Males)</td>
<td>8 Weeks Hypocaloric</td>
<td>HP</td>
<td>28%, 1.16 g kg^{-1} day^{-1} (During 8-week weight loss phase)</td>
<td>-4.9 kg</td>
<td>-0.3 kg</td>
<td>-109 kJ day^{-1}</td>
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<tr>
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<td>4 Weeks Eucaloric</td>
<td>SP</td>
<td>16%, 0.69 g kg^{-1} day^{-1} (During 8-week weight loss phase)</td>
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<td>-0.3 kg</td>
<td>-484 kJ day^{-1}</td>
</tr>
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<td>Whitehead et al. (85)</td>
<td>Overweight (2 Males, 6 Females)</td>
<td>1 Week</td>
<td>HP</td>
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<td>NA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SP</td>
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<td>NA</td>
<td>-479 kJ day^{-1} *</td>
</tr>
<tr>
<td>Baba et al. (84)</td>
<td>Hyperinsulinemic (13 Males)</td>
<td>4 Weeks</td>
<td>HP</td>
<td>45%, 1.75 g kg^{-1} day^{-1}</td>
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<td>-553 kJ day^{-1}</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SP</td>
<td>12%, 0.49 g kg^{-1} day^{-1}</td>
<td>-6.0 kg *</td>
<td>NA</td>
<td>-1606 kJ day^{-1} *</td>
</tr>
</tbody>
</table>

* Significantly different to HP (P <0.05).
1.12. Dietary Protein, Body Composition and Muscle Protein Synthesis

It is possible that the effects previously observed for mitigating reductions of FFM during a hypocaloric high protein diet are mediated by increases in muscle protein synthesis.

Previous studies have shown that muscle protein synthesis is increased with the ingestion of either amino acid mixtures (100) or intact protein (101) although the anabolic effect is greater with the ingestion of essential amino acids compared to an isocaloric quantity of intact protein (102). Bohe et al. (103) first demonstrated a dose response relationship exists between the essential amino acid concentration of the blood and muscle protein synthesis using amino acid infusion. These researchers showed the concentration of extracellular essential amino acids rather than that of intramuscular essential amino acids was the stimulus for muscle protein synthesis. Cuthbertson et al. (100) extended these research findings demonstrating that ~10g of ingested essential amino acids maximally stimulates myofibrillar and sarcoplasmic protein synthesis. A muscle protein synthesis response plateau also appears to follow the ingestion of whole protein with Moore et al. (104) demonstrating that the muscle protein synthesis response (albeit following exercise training) was maximally stimulated following the ingestion of 20g of high quality whole egg protein. Similarly, Symons et al. (105) found 30g of meat protein (113g lean beef) consumed within a meal, induced the same post-prandial protein synthesis response (~50% increase in muscle protein synthesis) as a 90g protein serve (340g lean beef).

The mechanism/s whereby dietary protein may enhance body weight and FM reductions are less well understood; it is plausible that high protein diets have a reduced metabolic efficiency since protein has a reduced energy efficiency for metabolism compared to an equivalent caloric intake of fat or carbohydrate (106).
1.13. Benefits of Physical Activity and Exercise

The other side of the energy balance equation to energy input (caloric intake) is energy expenditure, of which physical activity or exercise plays a major role (4). For patients with T2DM it is well recognised the benefits of participation in regular physical activity independent of weight loss include improved glucose tolerance, increased insulin sensitivity, decreased HbA1c, improvements in CVD risk factors and improved psychological well being (107). Therefore, it is not surprising that participation in regular physical activity is recognised as an important component of current diabetes management recommendations (108).

Numerous studies have demonstrated the benefits of physical activity or exercise on CVD risk factors and glycemic control. A Cochrane review meta-analysis on exercise and T2DM showed that exercise, independent of weight loss, significantly improves glycemic control and reduces visceral adipose tissue and plasma triglycerides (109). These findings are consistent with an earlier meta-analysis that showed exercise training independent of weight loss decreases HbA1c by ~0.66% (absolute) which is an amount that would be expected to reduce the risk of diabetic complications (110). The ‘Cooper Center Longitudinal Study’, formally the ‘Aerobics Center Longitudinal Study’ is an ongoing observational study conducted by the ‘Cooper Institute’ in Dallas, Texas. The study aims to examine prospectively the relationship of physical activity and physical fitness to health in patients examined since 1970 (111). Data from a cohort of 25 714 men in this study who were followed up for approximately 10 years showed low cardiorespiratory fitness (defined in this study as exercise test maximal metabolic equivalents of: <10.5 for those aged 20-39 years, <9.9 for those aged 40-49 years, <8.8 for those aged 50-59 years, and <7.5 for those aged ≥60 years) is a strong independent predictor of CVD and all-cause mortality in normal weight, overweight and obese individuals (112). Low cardiorespiratory
fitness’ associated relative risk for CVD death was 3.1, 4.5 and 5.0 for normal-weight, overweight and obese patients respectively which is comparable to the risk associated with diabetes mellitus, smoking and several other CVD risk factors (including high cholesterol & hypertension) (112). In a sub-cohort of men with T2DM from the ‘Cooper Center Longitudinal Study’, having low cardiorespiratory fitness (defined as being in the least fit 20% of participants) and being physically inactive (participants who did not report walking, jogging, or participating in aerobic exercise programs in the 3 months prior to assessment) were also independent predictors of all-cause mortality (relative risk 2.1 and 1.7 respectively) (113). Physical activity has also been shown to play a pivotal role in long-term weight maintenance. Based on data from the US ‘National Weight Control Registry’ (a pool of over 3000 participants who have maintained at least 30 Lb of weight loss for a minimum of 1 year), participation in regular physical activity (including programmed exercise and increased lifestyle activity) has been identified as a key characteristic of these individuals (114).

### 1.14. Exercise Training during Weight Loss

Regular exercise plays an important role during caloric restriction by providing additional benefits compared to caloric restriction alone for weight loss, body composition, CVD risk reduction and reductions in insulin levels. Several meta analysis reviews and randomised clinical trials have reported that a combination of a caloric restricted diet plus exercise is more effective than caloric restriction diet alone for achieving weight loss over the longer term (55,115,116), improving body composition (117-119) and reducing insulin levels (118). The most recent meta analysis including 18 long term studies (≥6 months duration) comparing caloric restriction alone with caloric restriction plus exercise training found that interventions incorporating caloric restriction plus exercise training resulted in greater long term weight loss compared to caloric restriction alone (-3.34 vs. -1.38 kg respectively)
This difference was greater in studies with a duration of ≥1 year compared to those of a lesser duration. Similar findings were reported in analyses conducted by Miller et al. (55) and Curioni et al. (115) who also incorporated shorter duration studies (study duration ranges of 10-52 weeks and 2-90 weeks respectively). Ballor and Poehlman (117) conducted an earlier meta analysis that used stricter inclusion criteria in order to evaluated body composition changes achieved through caloric restriction or caloric restriction plus exercise. In contrast to the prior studies described (55,115,116) this analysis did not find any differences in the magnitude of body weight reduction between the caloric restriction alone and the caloric restriction plus exercise training groups. However, compared to participants who underwent caloric restriction alone, participation in exercise during caloric restriction reduced the amount of weight loss (by approximately half) that occurred from reductions in FFM. Similar findings were reported in a randomised clinical trial by Rice et al. (118) who assigned 29 obese men to 16-weeks of either caloric restriction alone or caloric restriction plus exercise training. Weight loss (−12.4kg) was similar in all treatment groups, however FFM was preserved with participation in exercise training and reduced (−2.5kg) with caloric restriction only. Post-prandial insulin levels also decreased more with a trend for greater reductions in fasting insulin levels with caloric restriction plus exercise compared to caloric restriction alone. Finally, participation in regular physical activity was also the strongest correlate of weight loss after 1-year for participants in the intensive lifestyle intervention group of the ‘Look AHEAD’ study (120).

1.15. Current Exercise Recommendations

‘Exercise’ is usually categorised as either one or a combination of two main styles; aerobic or resistance. Aerobic exercise refers to exercise training designed to primarily improve the efficiency of the cardio-respiratory system; this type of training has consistently been demonstrated to improve glycemic control, insulin sensitivity and CVD risk factors (121).
It is currently recommended that patients with T2DM perform moderate intensity aerobic exercise (50%–80% of VO$_2$ max) for 20-60 continuous minutes per day, 3–7 days per week or accumulate at least 150 minutes per week of >10 minute bouts of aerobic exercise (107). The American College of Sports Medicine also recommends patients with T2DM participate in 2-3 non-consecutive days per week of resistance exercise training which is exercise training designed to primarily increase strength, power and/or muscular endurance (107). According to the recommendations resistance exercise training should incorporate 8-10 multi-joint exercises that include all major muscle groups and each individual exercise should incorporate 2-3 sets of 8-12 repetitions at 60-80% of single repetition maximum (the heaviest weight that can be lifted once) (107).

Despite the well documented cardiovascular and metabolic health benefits for patients with T2DM participating in aerobic exercise training either alone or in combination with resistance exercise training, for several reasons achieving the recommended aerobic exercise targets is often difficult (122). For example, patients who have been habitually sedentary, are severely obese, have arthritis, have physical disabilities and/or have diabetes related complications may find even low level aerobic exercise challenging (121). Alternatively, resistance exercise represents a relatively safe option for improving cardiometabolic health and glycemic control even in patients at significant risk of a cardiac event (123). Research suggests resistance exercise training alone can produce similar metabolic improvements to that achieved with aerobic exercise and may therefore provide a beneficial alternative form of physical activity for patients with impediments to aerobic exercise and those with T2DM (121,122). Resistance exercise training is also relatively safe with very low myocardial demands associated with even high-intensity resistance exercise training, equivalent to the occasional actions required in daily living activities including climbing stairs, walking up a hill or lifting groceries (123).
1.16. **Benefits of Resistance Exercise Training**

In patients with T2DM resistance exercise training has been shown to improve glycemic control (reduce HbA1c), insulin sensitivity, strength and body composition (through increasing lean tissue mass and promoting total body and abdominal FM loss) and reduce CVD risk factors (122,124-128). Castaneda et al. (124) demonstrated that compared to a non-exercise control group, 16 weeks of resistance exercise training (3 days/week) increased lean mass (1.2 vs. -0.1kg) and reduced HbA1c (-1.1 vs. -0.1%), diabetes medication (-72 vs. 42%), systolic blood pressure (-9.7 vs. 7.7 mmHg) and trunk fat (-0.7 vs. 0.8 kg). Similarly, in a single-arm, non-controlled trial, Ibanez et al. (125) also showed a 16 week resistance exercise training program (2 days/week) decreased percent body fat (-1.3%), abdominal subcutaneous and visceral fat (~11%) and fasting plasma glucose (-0.6 mmol.L⁻¹) and increased upper and lower body strength (10.8 kg [18.1%] and 19.7 kg [17.1%] respectively). HbA1c levels did not change, but baseline levels were considerably lower compared to those subjects in the study by Castaneda et al. (124) (6.2 vs. 8.7%), and were within the recommended range (HbA1c <7% (42)). Several other short term (3-5 month) intervention studies in patients with T2DM and higher baseline HbA1c (7.5-8.8%) have demonstrated that compared to participants in a non-exercise control group those who participated in resistance exercise training reduced HbA1c (127,128). Additionally, strength gains which more often than not occur specifically with resistance exercise training are also associated with a reduced risk of metabolic disease and all-cause mortality (129).

1.17. **Resistance Exercise Training during Weight Loss**

During weight loss there is emerging evidence to support the use of lifestyle intervention programs that combine caloric restriction with resistance exercise training (60). In patients
undergoing caloric restriction the addition of resistance exercise has been shown to enhance FM loss (130), reduce the typical decline or increase FFM (119,131-133), reduce the typical decline or increase REE (131) and improve strength (131,133). However these effects have not been consistently demonstrated with other studies reporting no preservation of FFM (134) or REE (119,132,134) with the addition of resistance exercise training to caloric restriction.

In a randomised study, Kraemer et al. (119) found in overweight men a 12 week hypocaloric diet program (~6200 kJ) incorporating both aerobic and resistance exercise training (3 days.week⁻¹) was superior to caloric restriction alone or caloric restriction plus aerobic exercise training for improving body composition and strength, although weight and absolute REE declined similarly in all groups (~ -9.5kg and ~ -380 kJ.day⁻¹). Similar findings have been reported in obese men and women over 8 weeks by Geliebter et al. (132) who compared three groups; caloric restriction only (~5400 kJ.day⁻¹), caloric restriction plus resistance exercise training (3 days.week⁻¹), and caloric restriction plus aerobic exercise training. Although weight loss was similar in all groups (~9kg) the caloric restriction plus resistance exercise training group lost significantly less FFM (-1.1 kg) compared to the caloric restriction plus aerobic exercise training (- 2.3 kg) and the caloric restriction only (- 2.7 kg) groups; however REE declined similarly in all groups (~ -500 kJ.day⁻¹). Bryner et al. (131) also demonstrated a benefit of resistance exercise training on body composition during weight loss such that after 12 weeks participants following a hypocaloric diet plus resistance exercise program lost less lean mass (-0.8 kg) compared to those who were prescribed a hypocaloric diet plus aerobic exercise training program (-4.1 kg). Participants in the caloric restriction plus resistance exercise program also increased their maximum strength for the shoulder press, bench press, leg press and leg extension (≥23%). This study reported contrary findings for REE compared to the findings of
Kraemer et al. (119) and Geliebter et al. (132) such that although REE decreased in the caloric restriction plus aerobic exercise training group (-880.7 kJ.day\(^{-1}\)) it increased in the caloric restriction plus resistance exercise group (264.6 kJ.day\(^{-1}\)).

Although REE was not measured, Daly et al. (133) conducted a study in patients with T2DM that compared a 6 month hypocaloric diet consumed either alone or in combination with a gymnasium based resistance exercise training program. Compared to the caloric restriction only group, the caloric restriction plus resistance exercise training group tended to increase lean mass (0.5 kg vs. -0.4 kg) whereas reductions were similar in both groups for body weight (~3kg) and FM. Upper and lower body muscle strength improved in the caloric restriction plus resistance exercise training group (43 and 33% respectively) and did not change in the caloric restriction only group (1.5 and 5.0%, respectively). Over a longer duration study, Wadden et al (134) compared 48 weeks of caloric restriction alone, caloric restriction plus resistance exercise training (2 days.week\(^{-1}\)), caloric restriction plus aerobic exercise training and caloric restriction plus a combined aerobic and resistance exercise training program in obese women. Similar overall reductions occurred for body weight and REE (-15.1 kg and ~ -670 kJ.day\(^{-1}\)) in all groups, however no differences in body composition were observed between groups which is in contrast to the shorter duration studies (8-26 weeks) by Kraemer et al. (119), Geliebter et al. (132), Bryner et al. (131) and Daly et al. (133). It is unclear why the differences in body composition and/or REE are observed in some studies but not others although it may have something to do with differences in the duration of the study, the acute resistance exercise program variables (weight loads, number of repetitions and sets, rest periods etc.) (135,136) and/or the protein content of the diets (60).
In further support for resistance exercise training during weight loss it may also provide an additional benefit for glycemic control in older patients with T2DM. Dunstan et al. (137) showed that participants who underwent mild caloric restriction (~1400 kJ.day\(^{-1}\)) plus resistance exercise training compared to caloric restriction alone had greater reductions in HbA1c after 6 months (-1.2% vs. 0.4%) although weight loss was relatively small in both groups.

### 1.18. High Protein Hypocaloric Diets and Resistance Exercise Training in Combination

Although prior studies have demonstrated both resistance exercise training and high protein diets separately, can promote maintenance or increases in REE and FFM during calorie-restricted weight loss there is growing speculation that consumption of a high protein diet compared to a standard protein diet may provide additive effects when combined with high-intensity resistance exercise training for FM loss and the maintenance of FFM and REE (60,130). To date however there has been limited research investigating this concept. In 2005, Layman et al. (130) demonstrated that compared to an energy restricted standard protein diet (18%, 0.66 g.kg\(^{-1}\).day\(^{-1}\)) an isocaloric high protein diet (30%, 1.21 g.kg\(^{-1}\).day\(^{-1}\)) combined with exercise training (5 days.week\(^{-1}\) walking and 2 days.week\(^{-1}\) resistance training) additively improved body composition during weight loss in overweight and obese women such that FM loss was greater in women undertaking exercise whilst consuming a calorie restricted high protein diet (-8.8 kg) compared to subjects consuming a caloric restricted high carbohydrate diet with (-5.5 kg) or without (-5.0 kg) exercise or the consumption of an caloric restricted high protein diet alone (-5.9 kg), indicating an additive effect of a high protein diet and exercise (Figure 4). Moreover, there was some evidence (P=0.10) that subjects consuming the high protein dietary pattern lost less lean mass than subjects consuming a high carbohydrate dietary pattern (high
protein diet alone -2.0 kg and high protein diet with exercise -0.4 kg vs. high carbohydrate diet alone -2.7 kg and high carbohydrate diet with exercise -2.0 kg) and had greater reductions in trunk fat (high protein diet alone -3.6 kg and high protein diet with exercise -5.0 kg vs. high carbohydrate diet alone -3.0 kg and high carbohydrate diet with exercise -3.2 kg). The blood lipid profile improved in all treatment groups, however participants consuming the standard protein diet had greater reductions in total cholesterol and low density lipoprotein cholesterol whereas subjects consuming the high protein diet had greater reductions in triacylglycerol and maintained higher concentrations of high density lipoprotein cholesterol.

NOTE: This figure is included on page 37 of the print copy of the thesis held in the University of Adelaide Library.

### 1.18.1. Figure 4:
Mean (±SEM) changes in percent body fat following 16 weeks of consuming an energy restricted high protein (PRO) or standard protein (CHO) diet with or without a supervised
resistance exercise training program (EX). * significant main effect of diet (P<0.05); # significant main effect of exercise (P<0.05). Adapted from Layman et al. (130).

In overweight or obese men and women undergoing weight loss Arciero et al. (138) showed that when combined with an exercise training program (incorporating both aerobic and resistance exercise, 3 days.week$^{-1}$ of each) a moderate/high protein hypocaloric diet (~25% of energy) or a high/very high protein diet (~40% of energy intake) elicited similar reductions in FM and insulin sensitivity and both preserve FFM. However, in both dietary groups the level of energy restriction was mild (daily energy intake ~7800 kJ) and the relative protein intakes well exceeded the 1.05 g.kg$^{-1}$.day$^{-1}$ reported by Krieger et al. (61) to promote a beneficial effect on FFM preservation (moderate protein diet 1.21 g.kg$^{-1}$.day$^{-1}$, high protein diet 2.12 g.kg$^{-1}$.day$^{-1}$). It is therefore possible that the lack of any differential effects between the dietary patterns in this study may have been due to the fact that absolute protein quantity was relatively high in both of the groups and may have provided a similar maximal stimulus for inducing protein stimulated changes in body composition. A limitation of this study is that neither of these relatively high absolute protein quantity lifestyle intervention groups were compared to one with a currently recommended protein intake (10-20% of energy, 0.8 g.kg$^{-1}$.day$^{-1}$). Although, in an earlier study in overweight or obese men and women (139) this research group showed under ad libitum conditions (that reported similar energy intakes between the groups ~6700 kJ.day$^{-1}$) a high protein diet (40% protein [2.1 g.kg$^{-1}$.day$^{-1}$]; 40% carbohydrate; 20% fat) combined with high intensity exercise training (combined aerobic and resistance exercise) resulted in greater improvements in strength and had greater reductions in body weight (-5.2 vs. -2.8 kg) total FM (-5.5 vs. -2.5 kg) and abdominal FM (-0.9 vs. -0.4 kg) compared to a standard protein diet (50-55% carbohydrate:15-20% protein [1.0 g.kg$^{-1}$.day$^{-1}$]; <30% fat) combined with a moderate intensity exercise program. In this study CVD risk markers (fasting glucose,
blood lipids and blood pressure) improved similarly, FFM did not change but interestingly REE increased in both groups.

In a separate 14 week study in sedentary, obese, pre-menopausal women conducted by Kerksick et al. (140) three energy restricted diets (5000-6700 kJ.day\(^{-1}\)) varying in carbohydrate to protein ratio and each combined with an exercise program (Curves\(^{TM}\)) were compared for their effects on body composition, REE and CVD risk outcomes. The study found that a very low carbohydrate, high protein diet (7% carbohydrate, 63% protein \([-1.72-2.30 \text{ g.kg}^{-1}.\text{day}^{-1}], 30\% \text{ fat}\)), a low-carbohydrate moderate protein (50% carbohydrate, 20% protein \([-0.64-0.86 \text{ g.kg}^{-1}.\text{day}^{-1}], 30\% \text{ fat}\)), and a high-carbohydrate, low protein (55% carbohydrate, 15% protein \([-0.50-0.68 \text{ g.kg}^{-1}.\text{day}^{-1}], 30\% \text{ fat}\)) all similarly reduced body weight, FM, FFM, blood lipids, insulin and glucose. REE responded differently with the very low carbohydrate, high protein diet (-155 kJ.day\(^{-1}\)) compared to the high-carbohydrate, low protein diet (376 kJ.day\(^{-1}\)) and low-carbohydrate moderate protein diet, 75 kJ.day\(^{-1}\). However, the findings of this study are limited since the diets were not randomly allocated but rather assigned according to the participant’s response to a pre-study questionnaire that assessed carbohydrate tolerance and that may have contributed to baseline differences between the groups in weight, body mass index and REE.

Meckling and Sherfey (141) also investigated the effect of varying the carbohydrate to protein ratio (3:1 ‘control diet’ vs. 1:1, ‘high protein diet’) of a hypocaloric diet (-2180kJ.day\(^{-1}\)) either with or without exercise training (circuit training 3 days.week\(^{-1}\)) for 12 weeks. Following the intervention, REE, FFM, fasting glucose, insulin and high density lipoprotein cholesterol did not change in any group; however the high protein diet only group lost 2.5kg more weight than the control diet only group (-4.6 kg vs. -2.1 kg) and the
high protein plus exercise group lost 3 kg more than the control plus exercise group (-7.0 kg vs. -4.0 kg). Total cholesterol decreased in the high protein diet only group and the control diet plus exercise group, low density lipoprotein cholesterol decreased in the high protein diet only group and triglycerides decreased in the high protein plus exercise group. However, the interpretation of these results is limited by the poor compliance to the dietary protein intake targets and subsequent lack of dietary pattern differences in the carbohydrate to protein ratio between the treatment groups. The diets were planned to achieve a 3:1 (0.75 g.kg⁻¹.day⁻¹) and 1:1 (1.4 g.kg⁻¹.day⁻¹) carbohydrate to protein ratio in the high protein and control diets respectively, however the actual ratios achieved were dissimilar, particularly within the high protein dietary pattern (control diet only 3:1 [0.71 g.kg⁻¹.day⁻¹], control diet plus exercise 2.7:1 [0.74 g.kg⁻¹.day⁻¹], high protein diet only 1.5:1 [1.0 g.kg⁻¹.day⁻¹], high protein diet plus exercise 0.96:1 [1.34 g.kg⁻¹.day⁻¹]).

It is apparent there remains a paucity of well-controlled studies investigating the effects of a high protein weight loss diet combined with resistance exercise training compared to either an isocaloric high protein diet alone or a high carbohydrate diet with or without resistance exercise training. Furthermore, no studies to date have evaluated these effects in patients with T2DM who may represent a population with increased dietary protein requirements (76,142) since T2DM patients have been shown to have increased proteolysis (potentially reducing net muscle protein balance) under both eucaloric and hypocaloric conditions that is positively associated with the magnitude of hyperglycemia (142-144). In addition, as previously mentioned patients with T2DM may achieve additional benefits in the form of an improvement in glycemic control from the potential preservation of FFM which may be achieved with a hypocaloric high protein diet plus exercise based lifestyle intervention. Chapter 2 of this thesis addresses this research need and investigates the effects in patients with T2DM of a high protein hypocaloric diet combined with resistance
exercise training compared to isocaloric high protein diet alone or an isocaloric standard protein diet with or without resistance exercise training on body composition and cardiometabolic risk markers.

1.19. Timing of Ingestion of Protein Relative to Resistance Exercise on Muscle Protein Synthesis

Apart from a high protein diet combined with exercise training potentiating the beneficial effects of a hypocaloric diet, a separate line of evidence suggests that manipulating the timing of protein intake in relation to resistance exercise training maybe an important consideration to optimise the outcomes by stimulating greater muscle protein synthesis and hypertrophy (145).

Muscle protein synthesis is elevated up to 48-hours following resistance exercise training in untrained participants (146). However, muscle protein synthesis stimulated by elevated plasma amino acid levels maybe confined to the immediate ~60-120 minutes following essential amino acid ingestion (147). Further evidence has shown that consuming a protein source adjacent to exercise (i.e. immediately pre- or post-exercise) increases amino acid delivery to the muscles and additionally stimulates protein synthesis, providing a synergistic effect on net protein balance which may offer the greatest anabolic advantage (148,149).

It has been established that the availability of amino acids rather than energy (in the form of carbohydrate) is the critical factor for stimulating the post-exercise muscle protein synthesis, and positive net protein balance, response (150,151). Levenhagen et al. (150) demonstrated this in an acute feeding study that showed ingestion of a protein rich supplement (10g protein, 8g carbohydrate, 3g fat) immediately following exercise
increased whole body protein balance whilst supplementing with either a calorie-free placebo or an isoenergetic carbohydrate and fat supplement (8g carbohydrate, 3g fat) resulted in a reduction in whole body protein balance. More recently Tang et al. (151) demonstrated the acute effect of a high protein meal (10g protein, 21g carbohydrate) is superior to that of an isocaloric carbohydrate meal (31g carbohydrate) in stimulating muscle protein synthesis following resistance exercise (151).

Acute feeding studies have shown that compared to a delayed ingestion (≥1 hour), ingesting protein adjacent to exercise training increases muscle protein synthesis and muscle protein accretion (152-154). The muscle protein synthesis response has been shown to occur with both amino acid mixtures (153) as well as intact protein (155). Recent dose response studies have quantified the ingested protein stimulus required to maximise the post-exercise muscle protein synthesis response; Moore et al. (104) showed in healthy active males that 20g of intact high-quality protein was sufficient to maximize the anabolic response to resistance exercise with only a non-significant ~15% further increase in muscle protein synthesis when the protein dose was doubled to 40g. This was comparable with earlier research that showed under resting conditions that ~10g of ingested essential amino acids maximally stimulated myofibrillar and sarcoplasmic protein synthesis (100).

Although it is apparent that acute ingestion of protein adjacent to exercise stimulates muscle protein synthesis to a greater extent compared to delayed consumption ≥1 hour, it is not clear whether consumption of a whole protein source either immediately pre exercise or immediate post exercise (both considered proximal to exercise) offers a superior response. A study comparing ingestion of protein immediately pre vs. immediately post exercise showed that net muscle protein balance is greater with immediate pre exercise
ingestion of crystalline amino acids plus carbohydrate (152). However, in a similar experimental design, these researchers showed that the anabolic response increased similarly when actual intact protein was ingested either immediately before or immediately following resistance exercise training (154). This suggests a pre vs. post advantage may not exist with the ingestion of intact protein, possibly due to a slower digestion rate (154).

Collectively, these acute studies investigating the muscle protein synthesis response to protein ingestion and exercise bouts have enabled the identification of optimal protein doses and timing strategies to maximise the muscle anabolic stimulus. However, whether this elevated anabolic response directly translates into chronic muscle accretion is more difficult to determine and has not been conclusively investigated.

### 1.20. Timing of Ingestion of Protein Relative to Resistance Exercise on Muscle Accretion under Eucaloric Conditions

A number of studies have extended the findings from the acute muscle protein synthesis response experiments to assess the chronic effects (8-21 weeks) of ingesting protein adjacent to resistance exercise training in eucaloric conditions on body composition and/or muscle hypertrophy (156-162). However, only some (157-160) but not all of these studies (161,162) have demonstrated a beneficial effect of ingesting protein proximal to exercise training.

Candow et al. (156) extended the acute findings of Tipton et al. (154) by evaluating the chronic effects of immediate pre- vs. post exercise protein ingestion. In this study no differences in body composition were observed between treatment groups when a protein supplement (~25g) was ingested either immediately pre or immediately post resistance exercise training (3 days.week⁻¹) for 12 weeks in older men. Esmark et al. (157)
demonstrated in elderly males that immediate intake of a protein supplement (10g protein, 7g carbohydrate, 3.3g fat) following exercise during a 12 week resistance exercise training (3 days week$^{-1}$) intervention was effective for increasing muscle cross sectional area of the quadriceps femoris and mean fibre area of the vastus lateralis, compared to no change in participants who consumed the protein supplement 2 hours post exercise training. However the differential changes in total body lean mass between the groups (immediate protein ingestion group +1.8 kg vs. delayed protein ingestion group -1.5 kg) did not reach statistical significance. Cribb and Hayes (158) showed after 10 weeks that trained bodybuilders who consumed a protein supplement (1 g kg$^{-1}$ of body weight of a supplement containing 40g protein, 43g carbohydrate, 0.5g fat per 100g) immediately pre- and post exercise training (4 days week$^{-1}$) had greater increases in lean body mass compared to participants who consumed the supplement in the morning and evening (2.5kg vs. 1.5kg). However the supplement used in the study also contained 7g of creatine per 100g which may have at least in part affected the outcome. Hulmi et al. (159) randomised 31 young men into 21 weeks of resistance exercise training (2 days week$^{-1}$) with either a 15g protein supplement or a non-energetic placebo consumed immediately pre- and post-exercise. Overall, macronutrient composition of the participant’s diets were similar in both groups and muscle cross sectional area of the quadriceps femoris increased and body fat percentage reduced similarly in both groups. However vastus lateralis cross-sectional area increased to a greater extent with the protein supplementation. The study also found that immediate ingestion of protein adjacent to exercise training may alter mRNA expression in a manner advantageous for muscle hypertrophy. Andersen et al. (160) showed that participants undergoing resistance exercise training (3 days week$^{-1}$) for 14 weeks who ingested protein (25g) immediately pre- and post exercise increased vastus lateralis muscle fibre cross sectional area whereas those supplementing with carbohydrate (25g) pre- and post exercise had no change. However, these study results were limited by the lack of any
dietary records and whether any difference in overall energy intake or the macronutrient profiles between the treatment groups contributed to the observed effects could not be determined.

In contrast, other studies have reported no additional benefit for promoting muscle accretion by ingesting protein proximal to exercise training. Hoffman et al. (162) compared resistance exercise trained males following 10 weeks of resistance exercise training (4 days.week\(^{-1}\)) with a protein supplement (42g protein, 2g carbohydrate, 0g fat) ingested either in the morning and afternoon or immediately pre- and post exercise training. Following the intervention, no differences between the groups for changes in body composition were observed. However, it is possible that the lack of any group differences could have been caused by the high relative protein intakes achieved in the study (~2.2 g.kg\(^{-1}\).day\(^{-1}\)) that may have masked any additional benefit from supplement timing (163). Burk et al. (161) in an 8 week cross over study design compared participants consuming a protein supplement (35g protein, 0.4g carbohydrate, 0.1g fat) 4-6 hours pre exercise training (4 days.week\(^{-1}\)) and immediately prior to exercise to when participants consumed the supplement 4-6 hours pre exercise training and 2.5 hours following dinner (exercise training was conducted at 4pm). In contrast to the findings of Cribb and Hayes (158) the post dinner supplement group increased FFM (1.1 kg) whereas FFM in the pre exercise supplement group did not change. The authors speculated a potential explanation for the difference between the treatment groups was that the post dinner supplement group experienced greater daily distribution of their protein allocation which may have prolonged the duration of amino acidemia (and hence the chronic anabolic response) and therefore over several weeks this may have lead to an increased protein deposition (FFM). This theory supports observations from a study by Moore et al. (104) that showed an acute anabolic response to protein ingestion can potentially be achieved up to 5-6 times per day,
which may possibly negate any additional synergistic effect of superimposing resistance exercise training and amino acid/protein ingestion on net protein balance (148,149). It was further speculated that these results may have contrasted those of Cribb and Hayes (158) due to differences in duration of training and the type of supplement used (protein composition, carbohydrate content and creatine vs. no creatine). Additionally, as was the case in the study by Hoffman et al. (162) in this study the relative protein intake of both diets was very high (~2.2 g.kg\(^{-1}\).day\(^{-1}\)) and therefore both dietary patterns may have provided a maximal stimulus.

### 1.21. Timing of Ingestion of Protein Relative to Resistance Exercise on Muscle Accretion under Hypocaloric Conditions

Although multiple studies have evaluated the acute and chronic effects of manipulating the timing of protein ingestion relative to the performance of exercise training on body composition changes under eucaloric conditions, there remains a paucity of data examining whether consuming protein proximal to exercise training provides an advantage for ameliorating FFM loss during calorie-restricted induced weight loss (61).

To date, only one known study has chronically examined the effects of manipulating the timing of protein ingestion relative to resistance exercise training during caloric restricted induced weight loss (164). Doi et al. (164) showed that after a 12-week hypocaloric diet plus resistance exercise training intervention FFM did not decrease and resting metabolic rate significantly increased in subjects who consumed a protein supplement immediately following resistance exercise. Despite daily energy and protein intake being similar in both groups, in subjects who did not receive the supplement FFM significantly decreased and REE remained unchanged. This study suggests that protein ingested in close proximity to exercise may be associated with increased total body protein synthesis that may offset
reductions in FFM and REE that typically occur with weight loss. However, this study was performed in young healthy men with relatively normal body weight and levels of adiposity and the degree of energy restriction was only mild (15% deficit). The findings of this study were also limited by the statistical analyses performed in which the conclusion was based on single-arm within group comparisons, using separate within group paired t-tests to compare pre- and post- values rather than by direct between-group comparisons. In fact, no significant differences were observed when direct between-group comparisons were made between the men who ingested a protein supplement proximal to exercise and those who did not (control) with a comparable reduction in FFM between groups (-1.8 kg vs. -2.1 kg respectively).

Further research is required to establish the effect of altering the timing of protein ingestion relative to exercise training. Specifically, it is particularly relevant to establish these effects in overweight and obese patients with established metabolic disease such as patients with T2DM who may obtain multiple benefits from strategies that assist in preserving FFM during weight loss by way of facilitating long term weight loss maintenance and improved glycemic control. *The experiment described in Chapter 3 of this thesis investigates whether in overweight and obese patients with T2DM any additional potential benefit of a high protein diet combined with resistance exercise training on body composition, REE, glycemic control or cardiometabolic risk factors could be further magnified by manipulating the timing of protein ingestion relative to resistance exercise training.*

1.22. **Barriers to Healthy Lifestyle Behaviours**

As previously discussed, intensive lifestyle intervention programs incorporating an energy restricted diet and exercise training are effective for inducing improvements in weight status and metabolic control (45,46,48,49). However, long-term sustainability of these
benefits is often poor with rebound frequently occurring after the intensive support of the program is ceased, even when multiple behavioural change strategies are used (133,165,166). From a social ecological model perspective barriers and facilitators for healthy lifestyle behaviours occur at several levels ranging from intrapersonal skills and choices (e.g. knowledge) to external factors including immediate intrapersonal support (e.g. family and peers), community factors (e.g. food availability, workplace culture) and public policy (e.g. advertising and laws) (167-169). The external factors are of particular importance as although acquiring knowledge enables patients to make informed decisions, the motivation to act is determined by a combination of many additional factors including the ability to adapt to diabetes related stresses, the interpersonal style of the health professional and target setting (170-172). Ultimately, to achieve successful maintenance of weight status and metabolic control, patients are required to establish ongoing healthy lifestyle behaviours. Several key healthy lifestyle behaviours have been identified in individuals that have been successful at maintaining long-term weight loss including the participation in regular physical activity and frequent monitoring of body weight, food/calorie intake and fat intake (114,120,173).

For patients with T2DM, the greatest difficulties for the management of their condition relate to adhering to diet and exercise recommendations with fewer barriers associated with blood glucose monitoring and medication use (174-176). Within the context of diet and exercise a limited number of studies have identified several reasons why people with T2DM do not participate in healthy lifestyle behaviours. For diet, these include the cost, difficulties adhering to portion sizes, support and family issues and quality of life and lifestyle issues (177). For exercise the reasons include difficulty participating, feelings of tiredness, being distracted by something else, a lack of time, a lack of facilities, fear of injury, low self-efficacy in respect of a novel or unfamiliar exercise mode and the
assumption that exercise will lead to increased muscle mass and therefore weight gain (178,179). However, as opposed to factors which prevent change and initial participation in healthy diet and exercise lifestyle behaviours little is known about specific factors that assist or impede people in continuing with healthy lifestyle (diet and exercise) behaviours once established (e.g. through participation in a structured intensive lifestyle intervention program). Currently, only one known study in hypertensive patients has evaluated the dietary factors (180) and one study in patients with T2DM has examined the exercise specific factors (181).

1.23. Barriers and Facilitators for Adherence to a Diet
To understand the specific factors that underlie dietary adherence Vijan et al. (177) investigated barriers to following dietary recommendations in patients with T2DM using a written random postal survey and a mix of urban and suburban focus groups. The results showed that following a moderate diet intervention (sugar and fat reduced with minimal caloric restriction) was more of a burden than taking oral agents but substantially less of a burden than insulin injections. However, a strict diet (sugar and fat reduced plus caloric restriction for weight loss) had a similar burden to taking insulin. Interestingly, patients with T2DM were less likely to adhere to following a moderate diet than to taking oral agents or insulin, despite the higher associated burden. The most commonly identified barrier to following a diet were costs, limited portion size and subsequent hunger, a lack of family support, confusion about the diet prescription, difficulty adhering during holidays/social occasions, emotional aspects of having to follow the diet, a dislike of specific dietary foods and difficulties with the eating schedule.

Jehn et al. (180) also identified similar themes following an investigation of factors that affect continuation of a healthy diet once initiated. This study was a 1 year follow up of
hypertensive patients who had participated in either a 9 week diet and exercise weight loss intervention or a control group. Despite an initial 5.3 kg weight loss in the intervention group, after 1 year post-intervention, participants had regained the majority of their weight loss (-0.5 kg from baseline) whilst participants in the control group had increased their weight slightly (0.9 kg from baseline). The participants identified several self reported barriers to maintaining weight loss including (in order of the number of times they were identified) losing trial structure, an inability to estimate the appropriate portion size, an inability to calculate caloric needs, the recommended diet was too expensive, lack of time to follow the diet, weight loss was not a priority and lack of support from family and friends. But although this study evaluated post-intervention barriers, the interpretability of the findings to patients with T2DM undertaking a holistic lifestyle program are limited since the study was conducted in a non-diabetic population and isolated to an evaluation of dietary factors.

1.24. Barriers and Facilitators to an Exercise Program

Similar to the dietary component of lifestyle interventions, sustainability of exercise is often associated with limited success. Kirk et al. (182) conducted a review on strategies to enhance compliance to physical activity recommendations in patients with insulin resistance. It was determined that long term change is difficult to achieve and the limited research available suggests the core components for sustainability are the development of cognitive behaviour skills, follow-up support and an individualised approach.

The previously described study by Daly et al. (133) that included a 6 month caloric restriction program either alone or combined with a gymnasium based resistance exercise training program, also included a second phase consisting of a one month transition period into a 6 month home-based resistance exercise training program. The objective was to
examine whether any of the initial benefits achieved in phase 1 could be maintained through a subsequent home-based program. During the home based exercise phase, compliance reduced and FM was regained to baseline levels suggesting that even with a transitionary approach towards a prescribed home based program (that included regular phone contact), without personal support structured exercise training may be difficult to achieve.

Thomas et al. (178) used questionnaires distributed at a diabetes clinic to investigate the self perceived factors that prevent patients with diabetes from commencing participation in physical activity. Lack of local facilities, the cost of accessing exercise facilities and a lack of time were identified as the main deterrents. Only one known study to date has reported the self-identified factors that either assist or impede patients with T2DM in continuing a structured exercise program following the completion of an intensive lifestyle intervention program. In that study, Casey et al. (181) conducted a qualitative analysis of the barriers and facilitators to the continuation of exercise following participation in a structured aerobic exercise training program in overweight and obese individuals with T2DM. The key factors identified by the participants for sustaining the exercise were motivation from monitoring, encouragement and accountability provided by the programme staff and to a lesser extent effective transition from supervised programmes to self-directed activities. However, the results of this study are somewhat limited since the lifestyle intervention program used in the study did not incorporate an energy restricted diet; and the exercise program was limited to aerobic exercise which may present different sustainability challenges to those of a resistance exercise training program.

1.25. **Barriers and Facilitators to Continuing an Established Diet and Exercise Based Lifestyle Intervention Program**
To date, no studies have evaluated the barriers and facilitators to the continuation of established holistic healthy lifestyle practices (incorporating both diet and exercise) that have been acquired through prior participation in an intensive weight loss program. Healthy lifestyle practices are of particular importance to overweight and obese patients with T2DM who have the additional concerns of glycemic control as well as the potential additional burden of hypoglycemic medication and diabetes complications. This information would provide a valuable insight to the concerns of patients with T2DM and assist in identifying critical areas to target for support and policy that can be used in turn to achieve long term improvements in the weight and health status of patients with T2DM.

Chapter 4 of this thesis investigates the factors perceived by individuals’ with T2DM that enhance or impede the sustainability of acquired healthy lifestyle behaviours, previously obtained through participation in a research based lifestyle intervention program that achieved considerable weight loss and improvements in glycemic control and CVD risk factors.

1.26. Specific Aims of this Thesis

The aim of this thesis was to evaluate the efficacy of lifestyle intervention weight loss programs that incorporate a high protein diet and exercise training in overweight and obese patients with T2DM and indentify factors that facilitate or impede their long-term sustainability and success by:

1. Comparing a hypocaloric high protein diet with an isocaloric standard protein diet, with or without exercise training on body composition and cardio metabolic outcomes in overweight and obese patients with T2DM.
2. Investigating within a hypocaloric high protein diet plus exercise training whether manipulating the timing of protein intake in relation to exercise training (consuming protein adjacent to exercise training vs. a delayed intake) can provide any additional benefit on the measured outcomes.

3. Conducting a long-term, follow-up exploratory qualitative analysis of participants to identify self perceived barriers and facilitators to sustaining developed healthy lifestyle behaviours in a community setting following participation in a research based lifestyle intervention program that achieved considerable weight loss and improvements in glycemic control and CVD risk factors.
CHAPTER 2:
A HIGH PROTEIN DIET WITH RESISTANCE EXERCISE TRAINING IMPROVES WEIGHT LOSS AND BODY COMPOSITION IN OVERWEIGHT AND OBESE PATIENTS WITH TYPE 2 DIABETES

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Diabetes Care. 2010. May;33(5):969-976
2.1. Summary

The aim of this chapter was to compare the effects of an energy restricted high protein diet and an isocaloric standard protein diet with and without resistance exercise training on weight loss, body composition, CVD risk factors and glycemic control in overweight/obese patients with T2DM.

The results showed that participation in resistance exercise training produced greater weight and FM loss and increases in muscular strength compared to caloric restriction alone. Additionally, replacement of some carbohydrate for protein further magnified these effects resulting in this group achieving the greatest reductions in weight, total body FM, abdominal FM and fasting insulin. All treatments had similar improvements in glycemic control and CVD risk factors.

The findings of this chapter suggest a lifestyle modification program combining a calorie restricted high protein diet and resistance exercise training appears to be a preferred treatment strategy in overweight/obese individuals with T2DM.
Diabetes Care, v. 33 (5), pp. 969-976, May 2010

NOTE: This publication is included on pages 54 – 63 in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

http://dx.doi.org/10.2337/dc09-1974
CHAPTER 3:
TIMING OF PROTEIN INGESTION RELATIVE TO RESISTANCE EXERCISE TRAINING DOES NOT INFLUENCE BODY COMPOSITION, ENERGY EXPENDITURE, GLYCEMIC CONTROL OR CARDIOMETABOLIC RISK FACTORS IN A HYPOCALORIC, HIGH PROTEIN, LOW FAT DIET IN PATIENTS WITH TYPE 2 DIABETES

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Diabetes, Obesity and Metabolism. 2010. Dec;12(12):1097-1105
3.1. Summary

The results of the Chapter 2 study showed in overweight and obese patients with T2DM an energy restricted high protein diet plus resistance exercise training induced clinically relevant greater reductions in body weight and FM compared with either an isocaloric high protein diet alone or a standard protein diet alone or combined with exercise training. The aim of Chapter 3 was to investigate whether additional benefits could be achieved in this ‘superior’ high protein diet plus exercise training lifestyle intervention program by manipulating the timing of ingestion of protein relative to exercise training.

The results showed that in overweight and obese patients with T2DM who were undertaking a hypocaloric high protein diet plus exercise training lifestyle intervention program altering the timing of protein ingestion relative to exercise by consuming a supplement containing 21g of protein immediately before exercise compared to delaying ingestion 2 hours post-exercise has no additional benefit. Both groups achieved substantial weight loss, improvements in strength and glycemic control, and had similar reductions in cardiometabolic risk factors, FFM and REE.

The findings from this chapter re-affirm that for overweight and obese individuals with T2DM participation in a lifestyle modification program combining an energy restricted high protein diet plus resistance exercise training is an effective treatment strategy for reducing body mass and cardiometabolic risk factors and improving glycemic control and muscular strength. However, within this lifestyle intervention program altering the timing of protein ingestion relative to exercise training appears to provide no additional benefit on these outcomes or the attenuation of FFM reductions.

Diabetes, Obesity and Metabolism, v. 12 (12), pp. 1097-1105, December 2010

NOTE: This publication is included on pages 64 – 74 in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

http://dx.doi.org/10.1111/j.1463-1326.2010.01307.x
CHAPTER 4:
SELF-REPORTED FACILITATORS OF AND IMPEDIMENTS TO MAINTENANCE OF HEALTHY LIFESTYLE BEHAVIOURS FOLLOWING A SUPERVISED RESEARCH-BASED LIFESTYLE INTERVENTION PROGRAM IN PATIENTS WITH TYPE 2 DIABETES

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Submitted for Journal Review
4.1. Summary

Chapters 2 and 3 of this thesis demonstrated that a short term (16-week) lifestyle intervention program that incorporated caloric restriction with or without exercise training was effective for reducing body weight and a number of cardiometabolic risk markers. In Chapter 4 the participants who completed the lifestyle intervention programs (described in Chapters 2 & 3) were followed-up one year following the program commencement (36 weeks following program completion). The aim of this study was to identify through a qualitative interview the factors identified by participants as enhancing or impeding the sustainability of lifestyle behaviours adopted throughout the research based lifestyle intervention program.

The results showed that on average participants who attended the follow-up regained some of the body weight lost during the intervention program but still weighed considerably less than baseline. Only a small number of the participants were still maintaining the program in its entirety. Participants identified a number of reasons for the discontinuation of program components including; a desire for increased diet variety, a desire for increased portion size, limited access to appropriate exercise programs and facilities, the high price of gym membership and no longer having a professional to motivate them. The main factors identified that would have facilitated continuation included having continued supervision or having to report to someone, having regular recorded weight checks and diet visits and having access to affordable and appropriate exercise facilities.

The results suggested that in overweight and obese individuals with T2DM the initial success of the lifestyle intervention program was perceived as being primarily due to high levels of professional support and supervision, the discontinuation of which subsequently
presented difficulties. The interview data remind us that intensive programs assembled for research purposes with the emphasis on compliance may not be a realistic model for community intervention.
4.2. Publication 3

Self-reported facilitators of and impediments to maintenance of healthy lifestyle behaviours following a supervised research-based lifestyle intervention program in patients with type 2 diabetes

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4.2.1. ABSTRACT

Introduction: Sustainability of healthy lifestyle behaviours following participation in a research-based supervised lifestyle intervention program (RLP) is often poor. This study aimed to document factors reported by overweight and obese individuals with type 2 diabetes (T2DM) as enhancing or impeding sustainability of lifestyle behaviours following participation in a RLP.

Methods: 30 patients who completed a 16-week RLP, incorporating a structured energy restricted diet with or without supervised resistance exercise training underwent a semi-structured qualitative interview about their experiences in maintaining program components after 1 year.

Results: Participants maintained 8.8±8.9kg of the 13.9±6.6kg weight loss achieved with RLP. Only 23% of participants indicated continuation of the complete diet program. Desire for ‘variety’ (33%) and increased portion size (27%) were the most commonly reported reasons for discontinuation. Participants who undertook supervised exercise training during the RLP indicated access to appropriate programs/facilities (38%), more affordable gym membership (21%) and having a personal trainer/motivator (17%) would have facilitated exercise continuation.

Conclusion: In overweight and obese individuals with T2DM, success of RLP was perceived as being primarily due to high levels of professional support and supervision, the discontinuation of which subsequently presented difficulties. The interview data provide insight into what people experience in the outside world without intensive support of the
research setting and remind us that intensive programs assembled for research purposes with the emphasis on compliance may not be a realistic model for community intervention.

**Key Words:** Obesity, Nutrition

**Abbreviations:**

Commonwealth Scientific and Industrial Research Organisation = CSIRO

Research-based supervised lifestyle intervention program = RLP

Type 2 diabetes = T2DM
4.2.2. INTRODUCTION:

Overweight and obesity are closely linked to the development of type 2 diabetes (T2DM) [1]. Lifestyle modification that combines an energy reduced diet and regular physical activity formulates the cornerstone for obesity and T2DM management [2]. It has been repeatedly demonstrated that research-based supervised lifestyle intervention programs (RLP) incorporating these components promote weight loss, decrease cardiovascular disease risk factors and improve glycemic control, body composition and health related quality of life in overweight and obese patients with T2DM [1, 3-6]. However, long-term sustainability of these healthy lifestyle behaviours, weight maintenance and improved metabolic control following participation in a RLP is often poor without continued support, with a rebound in these outcomes frequently occurring after completion [7, 8].

To date, only one known study in T2DM has examined individuals’ perceptions of factors that assist or impede them in continuing with a lifestyle intervention program following completion of a RLP [9]. In that study, Casey et al. [9] conducted a qualitative analysis of the barriers and facilitators to the continuation of exercise following participation in a structured aerobic exercise training program in overweight and obese T2DM individuals. Motivation from monitoring, encouragement and accountability provided by the programme staff and, to a lesser extent, effective transition from supervised programmes to self-directed activities, were identified as key factors by participants for sustaining the exercise over the long-term following the initial program. However, the RLP used in this study did not incorporate an energy restricted diet, a core component of comprehensive T2DM lifestyle modification [2]. Additionally, the exercise program was limited to aerobic-based exercise; whereas resistance exercise, which is well recognised as an important exercise therapy for T2DM [10], may present different sustainability challenges.
The objective of the present study was to identify factors reported by participants as enhancing or impeding the sustainability of lifestyle behaviours in overweight individuals with T2DM following completion of a RLP incorporating an energy restricted diet with or without a resistance-based exercise program.

4.2.3. METHODS:
This study was conducted as a 1-year follow-up after the commencement of a 16-week RLP incorporating a structured energy restricted diet with or without supervised resistance exercise training in which participants had initially volunteered. The RLP has been described in detail elsewhere [11] and was designed to achieve maximal compliance to assess the efficacy of the specific lifestyle therapies being evaluated. Briefly the structured diet was a moderately energy restricted (females; ~6000 kJ/day, males; ~7000 kJ/day), prescriptive eating plan in which participants received dietary advice and instruction by a qualified dietician at baseline and every 2 weeks during clinic-based visits. The eating plan included specific food quantities that were listed in a quantitative food record completed daily by participants and used by the dieticians to provide feedback to the participants during the clinic visits. This provided participants with clear dietary targets and an opportunity for dietary self-management. Participants were also supplied with key foods (~50% total energy) every 2 weeks of the RLP study to facilitate dietary compliance. Approximately 60% of the enrolled participants also participated in a progressive resistance exercise training program. This involved completing 3 moderate/high intensity whole body resistance exercise training sessions per week (~45-minutes per session), at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) research gymnasium under professional supervision. Pre- and post-RLP, clinical assessments including body weight and composition, waist circumference and cardiometabolic risk markers were assessed and have been previously reported elsewhere [11].
Following the RLP, all participants were given advice on healthy food options and planning strategies for maintaining the diet program without the professional support provided during the study. Participants who did not participate in the resistance exercise training program were also provided with general exercise advice and encouraged to commence a regular exercise program to achieve physical activity recommendations for T2DM [10]. Participants in the diet and exercise group were encouraged to continue the same resistance exercise program with the additional incorporation of moderate aerobic exercise.

Overall, 106 participants commenced and 84 completed the initial 16 week RLP. Of the completers, 81 participants who provided permission for future contact were sent invitation letters to participate in a follow-up visit at 1 year from study commencement. At this visit, participants attended the CSIRO clinic during which body weight was measured using calibrated electronic digital scales (Mercury, AMZ 14, Tokyo, Japan). Within one week of the 1-year follow-up clinical assessment, a semi-structured qualitative phone interview was conducted by an investigator external to the original research team that had conducted the RLP. The interview opened with a brief summary of the original program to remind participants of the circumstances of their participation, followed by a series of open-ended questions. These were designed to identify reasons for the participation in the RLP, difficulties and coping strategies associated with adherence to the RLP components during the initial 16-week study and factors perceived to have impeded or assisted them in maintaining components of the RLP following its completion.

Interview responses were transcribed and content analysed for common themes. The number of times each theme was mentioned by individual participants was tallied and expressed as a percentage of the total number of participants who completed the follow-up
evaluation. Paired t-tests were used to evaluate combined group changes in body weight over time and individual t-tests on the changes in body weight were used to test for differences between the groups. All participants provided written informed consent. The study was approved by the Human Research Ethics Committees of the CSIRO and the University of Adelaide.

4.2.4. RESULTS and DISCUSSION:

4.2.4.1. Weight Loss

Of the 81 participants invited, 30 (37%) completed the 1-year follow-up. This consisted of 6 (19%) and 24 (49%) participants in the initial RLP diet only group and diet and exercise groups, respectively. Overall, these participants maintained 8.8 ± 8.9 kg [mean ± standard deviation] (63%) of the 13.9 ± 6.6 kg weight loss achieved during the RLP such that those who participated weighed 8.1 ± 7.1% less than at Week 0 (P<0.001). Ten participants (33%) maintained a weight loss greater than 10% of initial body weight and 17 participants (57%) maintained a weight loss greater than 5%. Participants who completed the 1-year follow up achieved greater weight loss during the 16-week RLP compared to the non participants (-13.9±6.6kg [-12.8±4.6%] vs -8.4±4.5kg [-8.3±4.2%]); P<0.001) [11].

4.2.4.2. Reasons for participating in the RLP

Participants identified weight loss (63%) and improved diabetes control (40%) as the main reasons for volunteering for the RLP. “I was fairly unhealthy, overweight, with health problems. I wasn’t feeling very well, due to being overweight.” “I’d reached a point in my life where I need a change in my health. This opportunity came along and I took it.” Thirty-seven percent of participants also identified the desire to gain some diet and/or exercise education as a reason for participating: “I needed some guidance and information
on what I’m meant to be eating.” “I wanted to find out how I could go about controlling sugar levels, and more about diet and exercise. Wanted to find out how to manage [T2DM] myself.” It was clear that this was not the first attempt at weight or diabetes management for a number of participants. “I could never lose weight before. People can tell you how to lose weight, but sometimes you need that helping hand.” Overall, comments pointed to both the achievement of improvements to health and the desire for increased education about and mastery over their condition as motivating factors for participation in a RLP.

4.2.4.3. Ease of participation and reasons for persisting

On the subject of their participation in the RLP, the majority of participants (67%) reported they found it relatively easy to comply with and complete the 16-week program. Those parts of the program with which people reported experiencing difficulty were dietary constraints (30%), sticking to alcohol limitations (23%) and dealing with cravings (17%). Among participants assigned to the exercise program, the requirement to undertake moderate to high intensity exercise (8%) and overcoming the initial challenge of doing exercise (8%), were identified as being hard. The main factors identified by participants that helped them to deal with difficult aspects of the RLP were the support, encouragement and troubleshooting efforts of the staff (40%), personal persistence (50%), and to a lesser extent, the motivating effects of having lost weight (13%) and/or achieved improvements in diabetes control (13%). Similarly, a major reason given for completing the study was the support from staff (37%). Other prominent explanations for successful completion were the desire not to let down others or the sponsoring research organisation (30%) and, less specifically, because they had made the commitment (27%). Prominent among participants’ reports of their feelings at the completion of the program were feeling healthier (30%), pride in their achievements (20%) and generally feeling good (30%).” I
had a lot more energy, felt better in myself.” “Participating in this study gave me back more confidence.”

The generally positive responses and the perceived relative ease of completion indicate a high level of acceptability of the RLP in the targeted patient group. However, some of the reasons provided for completing the program suggest that potential impediments for the sustainability of healthy lifestyle behaviours may exist once the RLP has concluded. Participants identified health benefits (weight loss and diabetes control) as key motivators for commencing the study. However, non-health related reasons (not breaking a commitment or not to let down external parties) were also provided for completing the RLP. These responses suggest that health-related outcomes and knowledge alone may be insufficient for maintaining some individuals’ motivation to sustain behaviours for improving diabetes management. This is consistent with previous research that has demonstrated that although knowledge enables patients to make informed decisions, motivation to act is a result of a combination of many factors [12, 13]. In this case, the external parties included the researchers, whose involvement can only ever be transitory. If nothing else, this observation reminds us of a key limitation in the conduct of a short-term clinical program for research purposes as a model for the delivery of an enduring lifestyle intervention.

4.2.4.4. Difficulty in maintaining the dietary plan and routine post-RLP

When participants were asked at the 1-year follow-up what aspects of the diet plan they had continued, 17% nominated breakfast only, 3% said lunch only, and 33% indicated they continued to consume the same breakfast and lunch. Approximately one quarter of participants (23%) indicated that they had continued to follow the entire diet plan, though how scrupulously is not known. The suggestion in these figures that adherence presented
fewer difficulties in the earlier than in the later parts of the day was supported by participants’ own comments. Several participants reported that they had increased the size of the evening meal. “I felt hungrier at night, so I needed a bit more meat”. “The problem is the main meal – portion control….Plate is now full rather than half-full like before“.

Between-meal snacks were also identified as an impediment to adherence. One participant said “I still have the same breakfast and lunches. Fall down at tea time, fall down with snacks – chocolate and crisps. That’s my really bad thing”. Berteus Forslund et al. [14] previously showed that although obese and non-obese women consume similar meals during traditional meal times, obese women consume more meals or snacks in the afternoon and evening/night time periods. Although the exact reason for the weight regain observed during the post-RLP follow up period cannot be determined from the data available, there are reasonable grounds to suspect that increased energy consumption during the latter periods of the day may have been a large contributing factor. If so, weight loss maintenance following a RLP may benefit from strategies focusing on reducing the impact of overeating from snacks and overconsumption in meals, with particular emphasis during the latter half of the day. This could potentially be achieved at least in part by reducing the quantity or the energy density of foods [15], substitution of foods that induce satiety (e.g. high protein foods) [16], and/or altering the daily distribution of food, although further research is required to confirm this.

Another reason participants gave for discontinuing the diet program included the need for ‘variety’ (33%). “I just wanted variety. I didn’t want to stick with the exact diet”. Whether this reflects desire for increased recipe choices using the allocated foods within the dietary plan or alternative foods cannot be determined from the information collected. Irrespective of the specific interpretation of the term ‘variety’, preference for food variety has previously been shown in ad libitum studies to be a predictor of obesity [17] that may
increase energy intake either through greater consumption of energy dense foods or increased absolute food quantity. When food variety is offered either in consecutive courses or within a single meal, hyperphagia and subsequent increased consumption occurs, independent of the energy density and macronutrient composition of the food [14]. Alternatively, ‘liking foods absent in the meal plan’ has been previously identified as an adherence barrier to a prescribed calorie-controlled diet [18]. Therefore, although variety may be an impediment to healthy weight status in ad libitum conditions, it does not follow that a lack of choice will enhance compliance with a weight-control diet. It maybe possible that within a calorie-controlled prescriptive diet, providing increased variety through more recipe ideas and food types (whilst maintaining the desired nutrient composition) may improve dietary satisfaction and increase compliance. In the current study, it is important to consider the diet plan used in RLP may have been more constrained, than might usually be prescribed to achieve sustained dietary adherence, out of necessity to achieve the initial study objectives [11]. Further research is required to investigate the effect of providing greater consideration of individual tastes and food preferences (increased variety) on long-term compliance with a calorie-controlled diet.

Finally, several participants also mentioned factors relating to breaking routine as being an impediment to continuing the dietary plan. These included no longer being monitored. “When discipline is gone, and you don’t have to do it, it’s easy to get back into bad habits.” “I let things get in my way.” This was consistent with a previous study in non-diabetics that reported loss of trial structure and difficulty in determining portion size as the most frequently reported barriers for maintaining long-term weight loss following a short-term diet and exercise weight loss intervention trial [19]. Also mentioned were disrupting personal events, the pressures of social outings, and travel, all circumstances in which people might find their dietary choices diminished by the change of environment or
social pressures. “Going away [on extended travel] from my home environment broke the routine. The loss of structure and being away from the comfort zone of my home environment had a negative impact.” To counteract these disruptions, individualised problem solving strategies may play an important role [20, 21].

4.2.4.5. Strategies used for continuation of the dietary plan post-RLP

When participants were asked how they managed to continue with the diet plan following cessation of RLP, the key factors identified were maintaining portion control (27%): “I cut down on portions. The big thing was realising how much I was eating before.”; continuing the prescribed diet (20%); reducing ‘bad’ or fatty foods (20%): “Anything I’m not supposed to eat, I don’t buy it, so it’s not in the house. If it’s not here, I can’t eat it.”; learning to change dietary habits during the program (17%), and/or being motivated to continue by their improvements in health, weight or diabetes control (23%): “My palate has significantly changed. The long period of time [16 weeks] helped to change my dietary habits. As a result, I continue to feel a sense of flow-on and benefits”. Apparent from these comments was that a number of people had successfully developed new eating habits to replace earlier, less healthy habits.

4.2.4.6. The importance of supervision and monitoring for dietary compliance during the RLP

From many participants’ perspectives, factors contributing to program success included continued supervision or having to report to someone (30%), having regular recorded weight checks and diet visits (30%) and not breaking routine in general (10%). The loss of the structural supports at the program cessation was therefore important. “You go from intensive supervision to no supervision at all at the conclusion of the program. You don’t have regular weigh-ins or anything like that afterwards. The weigh-ins and that sort of
thing are incentives during the study. Left to your own devices, you don’t have that to look forward to, tend to let things slide.” Generally speaking, under the close professional supervision provided by the RLP, participants achieved good compliance with the prescribed eating plan. It is likely that some participants were highly dependent on that support and supervision and had not developed the skills and routines necessary to continue to succeed independently. The ability to self-monitor weight and food intake has been identified as an important characteristic of successful weight loss maintainers [22] that may represent an important educational consideration for achieving successful transition of the RLP components to facilitate self-sustainability.

Over the longer-term, intensive lifestyle intervention has shown greater cost effectiveness compared to pharmacotherapy for preventing type 2 diabetes [23]. Nevertheless, the substantial cost of providing personal support is well documented [23] and this approach may still not be a feasible model for sustainable lifestyle intervention, particularly when costs are borne at a personal level. Further research is still required to investigate alternative cost effective community health services and delivery mechanisms (e.g. internet and phone) to achieve successful outcomes.

4.2.4.7. **Continuation of exercise participation post-RLP**

Of the 24 participants whose RLP involvement included, by random assignment, a supervised, resistance exercise training intervention, 50% reported they were still attending gym sessions at alternative locations. Thirty-three percent of participants did not continue with any aspects of the prescribed exercise program, although several participants (13%) indicated they had commenced other physical activities such as hiking and walking. A key reason given by participants for continuing with exercise was the motivation derived from the general improvements they experienced during the program (25%): “I had this great
sense of achievement with what I’d done with the exercise. I was keen to keep it going”.
One participant stated “Making the commitment to start with, and finding the right facility
and access to the right program, that’s the hard part”. It appears that, for some people at
least, getting involved in a structured exercise program may lead to improvements that may
intrinsically motivate and facilitate exercise participation in the longer term.

Over recent years, strong evidence for the therapeutic benefits of resistance exercise
training for T2DM management has accumulated, and this form of exercise has been
advocated by leading health authorities [24]. Despite this, previous studies in patients with
T2DM have identified the fear of injury, low self-efficacy in respect of a novel or
unfamiliar exercise mode and the assumption that exercise will lead to increased muscle
mass and therefore body weight, as common barriers to participation in resistance exercise
training [25]. None of these factors were evident in the accounts provided by our
participants. It is therefore possible that commonly perceived barriers to resistance exercise
training may be overcome early by initial participation in a carefully supervised resistance
exercise training program, as in this case.

On a separate note, several participants identified exercise participation as a facilitator in
its own right of following a healthy dietary routine. “Without exercise I probably would
have got bored with the program.” Participation in regular physical activity was identified
as a key characteristic of individuals in the ‘National Weight Control Registry’ [22] and
the strongest correlate of weight loss after 1-year of the ‘Look AHEAD’ study [26]. It is
likely that, for some people at least, increased physical activity is important for its
motivational value as well as its physiological effects for weight and diabetes management.
A possible reason is that the immediate feedback available from exercise regimens –
beating a ‘personal best’ for example – is potentially highly rewarding and likely to
encourage more of the activity that led to the feedback. By comparison, the beneficial
effects of improvements to diet can take some time to become apparent, thus causing people to become disheartened.

4.2.4.8. Impediments to exercise participation post-RLP

Participants who did not continue or (in the case of diet-only participants) subsequently did not commence a resistance training based exercise program identified reduced access to gyms, equipment or similar exercise programs (29%) and the expense of public gyms (21%) as major impediments. Participants also suggested that more appropriate or accessible gyms or programs (38%), more affordable gym membership (21%) and having a personal trainer or motivator (17%) would have made the exercise easier to continue over the longer term. “It was difficult to find a similar program to the one [used in the study], with some sort of monitoring. They [commercial gyms] tend to leave you to your own devices, or push a program of their own.” “Access to a convenient gym would have made a big difference. Also have to consider expense of a gym.” It needs to be borne in mind that the majority of interview participants had completed 16 weeks of resistance exercise training in the RLP and thus presumably overcome initial obstacles to participation. Explanations for lack of continuation of exercise training emphasised problems of access and affordability whereas participants’ explanations for lack of continuation of the diet plan invoked factors relating to external support and motivation.

A recent study in T2DM patients [9] identified motivation and to a lesser extent the need for better transition to ‘post-program realities’ of less support and supervision as the most important factors for continuation of exercise participation 18 months following completion of a 24-week RLP; however, factors relating to cost and facilities were not evident. This discrepancy with our results could possibly be explained by the utilisation of an aerobic rather than a resistance based exercise program in the latter study that may not
have the same potential financial or equipment accessibility impediments. Additionally, Casey et al. [9] used a weaning exercise program that gradually reduced the number of weekly supervised sessions during the program from 3 to 1 and provided a high level of transition towards independent unsupervised exercise. In contrast, our study participants attended 3 supervised sessions per week for the entire 16-week duration of the RLP that ceased at the completion of the study. Whether transition from the supervised research-based program to independent exercise may have ameliorated perceived problems of facility access as an exercise impediment is not known. One participant commented “Better to taper off. Start off intensively and then taper off, rather than a sudden conclusion”. Within the general community where this research study was conducted, a number of appropriate exercise facilities and programs are available. This suggests the lack of a transitional component (that includes both the identification and physical re-location to community-based facilities) may have been responsible at least in part for the lack of exercise continuation, rather than the lack of these services per se. On the other hand, Daly et al. [27] conducted a 12-month study that included an initial 6-month gym-based resistance exercise training program and incorporated a one month transition period into a 6-month home-based resistance exercise training program. However, during the home based exercise, compliance reduced and fat mass rebounded to baseline levels suggesting that even with weaning towards a prescribed home based program (with regular phone contact), without personal support structured exercise training may be difficult to achieve. Clearly, to maximise long term exercise participation, matters of cost, facilities, motivation and possibly progressive transition strategies need to be considered for the successful replacement of supervised clinical resistance exercise training programs with independent exercise participation that achieves the recommended guidelines [10].

4.2.4.9. Research Limitation
This is the first known study to assess self-reported impediments to and facilitators of completion and subsequent adherence to a RLP incorporating an energy restricted diet and resistance exercise training in overweight and obese patient with T2DM. However, a limitation of this study is that the individuals who attended the follow-up achieved better outcomes during the RLP, on average, than those who did not. It is therefore possible this subgroup may also have had more success in maintaining their improvements and that the factors identified by those participants may not be generalisable to participants who were less successful or failed to complete the RLP. Nevertheless, this information provides insight into factors perceived by patients with T2DM themselves as facilitating or impeding their ability to maintain lifestyle behaviours following a RLP. Information of this kind is potentially valuable in the development of strategies and programs for this target population.

4.2.5. CONCLUSION

From the participants’ perspective, success of the RLP was perceived to be due largely to high levels of professional support and supervision, and its absence post-program may have reduced their ability to sustain these lifestyle behaviours without an alternative provision of motivation and resources. The interview data provide some insight into what people may experience in the outside world after they depart the research setting with its structure and close monitoring and professional supports. Moreover, they remind us that intensive programs put together for research purposes with the emphasis on compliance may not be a realistic model for community intervention. This is especially evident when it is acknowledged that the success of a research based weight management program may be partially due to participants’ commitment to the research or the researchers. Development of programs for long-term independent behaviour change requires identification of cost-
effective and sustainable means of providing appropriate support and motivation and the availability of affordable and accessible resources.

4.2.6. ACKNOWLEDGEMENTS:
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4.2.7. AUTHOR CONTRIBUTIONS:
The authors’ responsibilities were as follows – Wycherley was responsible for the conception and design of the study, coordinated the study, performed data analyses, interpreted the data and wrote the manuscript. Mohr was responsible for the conception and design of the study, data interpretation and contributed to the writing of the manuscript. Noakes and Clifton contributed to the design of the study and the writing of the manuscript. Brinkworth was responsible for the conception and design of the study, coordinated the study, and contributed to data interpretation and the writing of the manuscript. All authors agreed on the final version of the manuscript. None of the authors had a conflict of interest in relation to this manuscript.

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CHAPTER 5: CONCLUSIONS

As obesity continues to escalate and the mean age of the population increases, it is projected the incidence of T2DM will continue to rise to epidemic proportions. Effective lifestyle intervention strategies that can promote weight loss and improve the maintenance of weight status will aid in stemming the rise in obesity and T2DM prevalence and the subsequent co-morbidities and financial costs to individuals and society. Lifestyle modification that incorporates an energy reduced diet and exercise is effective for improving weight status, glycemic control and CVD risk factors in patients with T2DM and represents the cornerstone of T2DM management (43,44). The work conducted in this thesis aimed to identify strategies that potentiate and sustain the benefits of lifestyle modification that combines a caloric restricted diet and exercise training for overweight/obese patients with T2DM.

Previous research suggests that manipulating the dietary macronutrient composition, and/or participation in exercise training may alter the degree of weight loss and health status in patients undertaking a hypocaloric, weight-reducing diet. A number of lifestyle intervention studies have shown that increasing the dietary macronutrient content of protein in a low fat, hypocaloric diet (by substitution of some carbohydrate with protein) can provide beneficial effects for body composition (by mitigating FFM loss and enhancing the reduction of FM) and cardiometabolic outcomes (82-88,93). Several studies have also demonstrated benefits for these outcomes from participating in exercise training during weight loss (55,115-119). However, to date there has been a paucity of well controlled studies that have investigated the effects of manipulation of the macronutrient
profile of a hypocaloric diet that is consumed as part of a holistic lifestyle intervention program that incorporates exercise training.

Chapter 2 of this thesis demonstrated a 16-week lifestyle intervention program that incorporates a structured energy restricted diet resulted in substantial improvements in CVD risk factors and glycemic control irrespective of dietary macronutrient composition or the addition of resistance exercise training in overweight and obese patients with T2DM. However, an energy restricted high protein diet plus resistance exercise training induced clinically relevant greater reductions in body weight and FM compared with either an isocaloric high protein diet alone or an isocaloric standard protein diet alone or combined with resistance exercise training. Based on these data, it would suggest that a high protein diet plus resistance exercise training program may be a preferred treatment strategy in overweight/obese individuals with T2DM.

Apart from the superior benefits of a high protein diet combined with exercise training for reducing body weight and FM, demonstrated in Chapter 2, a separate line of evidence suggests that manipulating the timing of protein intake in relation to resistance exercise training maybe an important consideration for optimising body composition and cardiometabolic outcomes by stimulating greater muscle protein synthesis and hypertrophy (145). Mitigating the reductions in FFM that commonly occur with weight loss may also mitigate weight loss related reductions in REE and therefore reduce the risk of long term weight regain. In addition since skeletal muscle represents the largest mass of insulin sensitive tissue, in patients with T2DM and other insulin-resistance related metabolic conditions its preservation may benefit glycemic control.
In Chapter 3 of this thesis, it was investigated whether the ‘superior’ benefits of a high protein energy restricted diet plus resistance exercise training lifestyle intervention program (identified in Chapter 2) could be further enhanced by manipulating the timing of protein ingestion relative to resistance exercise. The study compared an energy restricted high protein diet plus resistance exercise training program with a 21g protein load ingested either immediately prior to exercise or 2 hours post exercise. The results of this study showed that both treatments had similar weight loss, reductions in total body FM, FFM and REE and improvements in cardiometabolic risk factors. It is concluded that within an energy reduced high protein diet plus resistance exercise training intervention program altering the timing of ingestion of a 21g protein source relative to resistance exercise training appears to provide no additional benefit over a period of 16 weeks for overweight and obese patients with T2DM.

A limitation of the research studies conducted in Chapters 2 and 3 of this thesis is that these experiments were designed to mainly evaluate the applied outcomes of diet and exercise based interventions. These data provide a valuable assessment of physiological changes achievable with particular intervention strategies and provide insight for the application of lifestyle intervention programs into clinical practice. However, the inclusion of biochemical or genetic outcomes (including plasma amino acid concentrations, gene expression, protein activation and muscle protein synthesis) would have provided a more complex insight to the mechanisms that underpin the observed effects and may also provide a more sensitive outcome measure (e.g. evaluating the muscle protein synthesis response compared to actual changes in FFM). Another limitation of these experiments is that the utilised intervention programs were only of short duration (16-weeks) and therefore it remains unknown whether the beneficial effect of a high protein diet plus resistance exercise program and/or the effect of manipulating the timing of ingestion of
protein relative to exercise training would be altered and/or sustained if the duration of the intervention program was extended over the longer term.

An interesting observation from the results obtained from Chapters 2 and 3 was that despite the lack of any effect of a high protein diet and resistance exercise training program for enhancing reductions in body weight and FM, no additional preservation of FFM or reduction on HBA1c was evident with either manipulation of dietary composition, the addition of resistance exercise training or the manipulation of the timing of protein ingestion relative to exercise. Gannon et al. (90) have previously demonstrated in patients with T2DM that compared to standard protein (15%) eucaloric control diet, those following an isoenergetic high protein (30%) diet had greater reductions in HbA1c (-0.8% vs. -0.3% absolute). Dunstan et al. (137) have previously observed a greater reduction in HBA1c following 6 months of mild caloric restriction plus resistance exercise training compared to caloric restriction alone (-1.2% vs. 0.4%) with participants experiencing only a small reduction in body weight (~ -2.8 kg). It is plausible that with substantial weight loss (as observed in Chapters 2 and 3) the potent hypoglycaemic effects of energy restriction (183) may have masked any separate effects of exercise or diet composition for reducing HbA1c.

For FFM, in addition to the previously discussed considerations of the relative protein quantity prescribed in the high protein diet in Chapters 2 & 3 and the protein amino acid profile of the snack in the Chapter 3 study, it is possible that the participant’s gender, the rate of weight loss and the exercise training volume may have affected the outcome. Leidy et al. (82) and Farnsworth et al. (83) both observed a mitigation in the reduction of FFM in participants consuming a high protein diet, compared to those consuming a standard protein diet. However these findings were reported in female participants only; protein
kinetics are different in males and females, such that women have been observed to oxidize less protein at rest compared to men (184,185). Whether gender differences in protein metabolism equate to measurable differences in body composition outcomes requires further investigation (186). Bryner et al. (131) showed that the addition of a resistance exercise training program to caloric restriction prevented a reduction in FFM, in that study participants in the resistance exercise training group were also mostly female (9 females vs. 1 male) and the prescribed exercise program had a higher training volume than the program used in Chapters 2 and 3 (2-4 sets per exercise vs. 2 sets per exercise). Similarly, Kraemer et al. (119) and Geliebter et al. (132), who showed the addition of a resistance exercise training program to caloric restriction prevented a reduction of FFM, both used a higher volume resistance exercise program (3 sets per exercise). The results of these studies suggest increasing the training volume to amounts greater than those used in Chapters 2 & 3 (>2 sets per exercise) may provide an advantage for muscle hypertrophy (187) and preserve FFM in patients with T2DM undergoing caloric restriction weight loss, although to date this has not been investigated.

Dunstan et al. (137) showed that during 6 months of mild caloric restriction the addition of resistance training to caloric restriction increased FFM in patients with T2DM. However as previously mentioned the weight loss achieved was only mild (~ -2.8 kg) which may have induced a smaller relative FFM reduction (188).

There is some evidence that the branch chain amino acid leucine may be an important independent factor for optimising the muscle protein synthesis response both throughout the day and following exercise, with 7-12 grams per day and 2.5g per meal providing the optimal metabolic response (189). In the Chapter 2 and 3 studies the high protein diet
contained ~9 g.day\(^{-1}\) of leucine (based on absolute protein intake (189)) which, assuming this mechanism, would have been sufficient to maximise the daily muscle protein synthesis response (achievable with 7-12 grams per day of leucine (189)). However, whether the leucine content per meal (i.e. the daily dietary protein distribution) was optimal (>2.5g of leucine per meal (189)) was not determined and is a limitation of the study. Therefore it is possible that despite achieving the planned daily protein intake targets (and sufficient daily leucine dose) without an appropriate daily protein/leucine distribution the chronic muscle protein synthesis response induced by the diet may not have been maximised.

In the Chapter 3 study the snack provided 21g of protein (Sufficient to provide a near maximal muscle protein synthesis response based on a protein dose stimulus (104)), the leucine content of the snack we estimated to be ~1.7g (based on (189)). Although the quantity of leucine utilised in the protein snack was below the optimal (>2.5g per meal) leucine dose identified by Layman et al. (189), a recent study by Glynn et al. (190) showed that when consuming a 10g dose of essential amino acids the muscle protein synthesis response was similar when the amino acid dose contained either 1.8g or 3.5g of leucine. This suggests that ~1.8g of leucine in an amino acid mixture is sufficient to elicit a maximal protein anabolic response. Hence despite the absence of a direct measure of muscle protein synthesis the protein/leucine stimulus provided in the protein snack was likely to have been sufficient to assess the effect of the manipulation of timing of protein ingestion relative to resistance exercise training in Chapter 3. It is unlikely, given that FFM reduced similarly between dietary treatment groups in Chapter 2, that the underlying high protein dietary pattern used in Chapter 3, had maximally stimulated the dietary muscle protein synthesis response and was therefore responsible for a lack of effect of manipulation of timing of protein ingestion.
The lack of any observed effects on FFM combined with its potential importance for facilitating long term weight maintenance and glycemic control poses a significant question for future research; ‘How can FFM be preserved during weight loss?’. 

Future research areas arising from the experiments in this thesis include investigating alternative strategies to preserve FFM during weight loss with lifestyle intervention combinations that that incorporate a hypocaloric high protein diet and resistance exercise training, to identify the program that offers the greatest benefit to overweight and obese patients with T2DM. This research should incorporate mechanistic outcome measures (e.g. gene expression, plasma amino acid concentration, protein activation and muscle protein synthesis) to provide further insight and understanding into the mode of effects. In particular, future research should focus on a number of strategies including the daily distribution of dietary protein, the primary source of protein (dairy vs. soy vs. meat [i.e. essential amino acid content]), the absolute and body weight relative protein intakes prescribed in the diet, the degree of caloric restriction or the characteristics of the exercise training program (muscle groups being exercised, the number of sets, the number of repetitions etc.). Specifically for Chapter 3, it would be of interest to investigate whether using a more rapidly digested protein source adjacent to exercise (e.g. whey protein isolate) would provide any beneficial effect.

Long-term sustainability of the benefits achieved with research-based, intensive lifestyle intervention programs is often poor with rebound frequently occurring after the intensive support of the program has ceased (133,165,166). Within the context of diet and exercise a limited number of studies have identified several reasons why people with T2DM do not participate in healthy lifestyle behaviours. However, self-perceived factors that may
facilitate or impede the continuation of acquired healthy lifestyle behaviours are largely unknown. In Chapter 4 of this thesis, participants involved in the 16-week research-based lifestyle intervention studies described in Chapters 2 & 3 were followed up 1-year after the commencement of these studies to identify self perceived impediments and enablers to maintaining the healthy lifestyle behaviours acquired through participation in the research-based lifestyle intervention programs which incorporated a weight loss diet with or without exercise training. The collection of this data was conducted to provide an understanding of the challenges experienced by individuals with T2DM in maintaining a lifestyle modification program once the intensive support of a research setting has ceased. The results showed that difficulties with the continuation of healthy lifestyle behaviours were primarily due to the loss of external accountability and high levels of professional support and supervision. The data generated in Chapter 4 also reminds us that intensive programs assembled for research purposes with the emphasis on compliance may not be a realistic model for community intervention.

A limitation of the research conducted in Chapter 4 is that although the data provides some insight into factors that facilitate or impede continuation of diet and exercise components in a community setting, since the factors were an expressed opinion whether the availability of the desired resources/support would actually translate into success still remains unknown and requires further exploration.

Although substantial improvements in health markers are achievable with short term, research based, diet and exercise lifestyle intervention there are clearly numerous barriers to overcome if this success is to be sustained long term within a community setting, outside of the research clinic environment. Subsequently future research is required to identify and evaluate effective strategies and support measures that can be achieved within the
constraints of available community resources to assist in the translation of clinical outcomes to sustained community programs. This could be investigated with the use of long term efficacy based studies using community based resources and delivery models.

The overall findings from the research conducted in this thesis provides information that can be used by health professionals and policy makers for the development of evidence based recommendations for the management of T2DM through diet and exercise based lifestyle intervention.
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