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The effects of resistance
training on individuals with
clusters of metabolic risk

**The Effects of Resistance Training on
Individuals with Clusters of Metabolic Risk
Factors: Focus on Functional Capacities,
Clinical Outcomes and Quality of Life**

Submitted by
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Abstract

The prevalence of high numbers of metabolic risk factors (HiMF) associated with the metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) has increased considerably over the past two decades. Lifestyle factors including physical inactivity are major components in the development of HiMF. Middle-aged individuals with HiMF and T2DM are commonly characterised by reductions in muscle strength, muscle mass and also lower capacities to perform activities of daily living (ADL's), compared to individuals with low numbers of metabolic risk factors (LoMF). As such, changes to physical activity levels should improve the functional capacities and clinical profiles for individuals with HiMF.

Study One. The purpose of this study was to investigate differences in some characteristics between individuals with HiMF and LoMF. These included conventional metabolic risk factors: waist circumference, blood pressure, lipids profile and fasting glucose levels and emerging metabolic risk factors: inflammatory markers, the hepatic enzymes gammaglutamyltransferase (GGT) and alanine aminotransferase (ALT) and brain-derived neurotrophic factor (BDNF). This study also examined whether HiMF in the absence of symptomatic heart disease is linked to reductions in capacities to perform ADL's and/or impaired quality of life (QoL). Fifty-five middle-aged (50.8 ± 6.1 yr) men ($n=28$) and women ($n=27$) participated in the study. Each participant was classified as HiMF (n of risk factors ≥ 2) or LoMF (n of risk factors ≤ 1) as defined by the International Diabetes Federation (IDF). Multivariate analysis of variance (MANOVA) was used to assess differences between HiMF and LoMF groups. Spearman Rho correlations were conducted to assess the relationship between selected variables. Participants with HiMF (both men and women) diverged more from healthy clinical profiles than individuals with LoMF. This included both conventional and emerging risk factors. In men, despite the higher numbers of risk factors for HiMF, compared to men with LoMF, no differences between groups were observed for aerobic power, muscle strength relative to body mass, the capacity to perform ADL's or QoL. Women with HiMF however, tended to have lower relative muscle strength (-14%, $p=0.06$) and longer time to complete their ADL's (10%, $p=0.07$), and they also reported higher level of bodily pain ($p=0.02$), compared to women with LoMF. In women, but not in men, the actual number of metabolic risk factors was positively correlated with the time taken to perform ADL's ($r=0.50$, $p=0.01$) and negatively correlated with aerobic power ($r=$ -

0.52, $p < 0.01$), and the physical components of the QoL questionnaire (SF-36) ($p = -0.40$, $p = 0.04$). Muscle strength relative to body mass, was also negatively correlated with the risk profile ($r = -0.50$, $p = 0.01$) for women only. The findings from this study may provide an explanation as to why women are more likely to consult a healthcare practitioner than men. As women's clinical profiles have negative associations with bodily pain and the capacity to perform ADL's, they may be more likely to seek medical intervention before risk factors progress to heart disease, compared to men. In men, impaired functional capacities or reduced QoL may not serve as early warnings of future disease. This emphasises the importance of regular medical check-ups, combined with education and motivation strategies, to promote health outcomes.

Study Two. The purpose of this study was to compare the effects of 10 weeks of resistance exercise training (RT) on the capacity to perform ADL's and QoL for middle-aged individuals with HiMF and LoMF. Following the initial allocation to HiMF or LoMF, (see Study One), participants were randomised to either training or control within their groups, as follows: HiMF training (HiMFT), HiMF non-exercise control (HiMFC), LoMF training (LoMFT) and LoMF non-exercise control (LoMFC). The training data were analysed by the repeated measures ANOVA model. No changes were observed in total energy intake or energy macronutrient composition within or between groups ($p > 0.20$). For both HiMFT and LoMFT, training improved lean body mass (LBM, 2.6% and 2.1%, both $p = 0.03$), total muscle strength (25.0% and 23.7% $p < 0.01$) and the capacity to perform ADL's (9.7% and 8.8% $p < 0.01$), compared to corresponding controls. RT did not reduce whole body fat content or improve aerobic power (VO_{2peak}) for HiMFT, but did improve QoL. In contrast, there was a reduction in whole body fat and improved aerobic power for LoMFT, in the absence of improvements in QoL. Changes to total muscle strength were negatively correlated with changes to total time to complete the ADL's for both HiMF (pooled HiMFT and HiMFC, $r = -0.53$, $p < 0.01$) and LoMF (pooled LoMFT and LoMFC, $r = -0.47$, $p = 0.02$). However, changes to total muscle strength for the HiMF group only (pooled data), correlated with changes to self-reported physical and mental health ($r = 0.59$, $p < 0.01$ and 0.45 , $p = 0.02$ respectively). The main finding of Study Two was that for HiMF, the improvements in the capacity to perform ADL's and improvements to self-perceived QoL were associated with increases in muscle strength, and not related to changes in body fat levels or aerobic capacity.

Study Three. The purpose was to examine the effect of RT on conventional and emerging metabolic risk factors for individuals with HiMF and LoMF. The participants and the randomisation to subgroups (i.e. HiMFT, HiMFC, LoMFT and LoMFC) were identical to Study Two. Ten weeks of RT did not change any metabolic risk factors for HiMF, including blood pressure, lipid profiles, and fasting glucose levels. In addition, training did not change plasma levels of inflammatory markers, hepatic enzymes or BDNF (all $p > 0.05$). For HiMFT, training increased insulin levels compared to baseline (from 46.1 ± 28.5 to 71.2 ± 48.8 $\text{pmol} \cdot \text{L}^{-1}$, $p < 0.05$) and also tended to increase insulin resistance, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) (from 1.6 ± 1.1 to 2.6 ± 2.0 , $p = 0.07$). The data suggest that RT as a single intervention has little or no influence on conventional and emerging metabolic risk factors and may even have an adverse effect on insulin levels and insulin resistance in middle-aged individuals with clusters of metabolic abnormalities in the absence of overt T2DM or CVD. As such, RT may not be sufficiently efficacious as a therapeutic mode of exercise to improve metabolic risk profiles in middle-aged individuals who are yet to develop overt disease. It is possible however, that longer RT duration or the inclusion of aerobic training and/or dietary interventions may be needed in order to elicit improvements in metabolic risk factors in this population.

Study Four. This study was an investigation of the effects of RT on the insulin-signalling proteins, Akt (protein kinase B) and Akt substrate of 160 kDa (AS160), and muscle glycogen stores for individuals with HiMF or LoMF. In addition, correlations of the insulin-signalling proteins with metabolic risk factors were analysed. Thirty-two men ($n = 15$) and women ($n = 17$) who participated in Studies Two and Three also volunteered to undergo muscle biopsies and other anthropometric and clinical measures before and after RT. At baseline, no significant differences were found between HiMF and LoMF groups in regard to glycogen stores, and total and phosphorylated Akt and AS160. At baseline, IL6 and IL8 were negatively correlated with total AS160 ($r = -0.51$ and $r = -0.52$, $p = 0.02$) and phosphorylated AS160 ($r = -0.49$ and $r = -0.45$, $p < 0.05$) and insulin resistance was negatively correlated with phosphorylated Akt ($r = -0.44$, $p = 0.05$) for the total HiMF group, (training and control pooled together). For both HiMFT and LoMFT, training increased muscle glycogen stores, compared to baseline (by 22.3%, $p = 0.06$ and 34.4%, $p = 0.03$, respectively). For HiMFT, training significantly increased total Akt by 25.1% but phosphorylated Akt tended to reduce, compared to the HiMFC

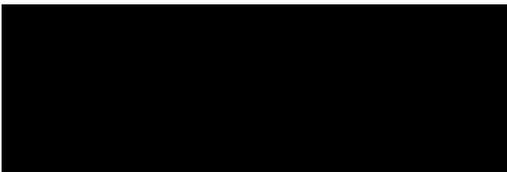
group ($p=0.08$), and phosphorylated AS160 was significantly reduced by 24.8% ($p<0.05$). No significant changes in Akt or AS160 (total or phosphorylated) were observed for LoMF groups (training and control). For HiMFT, the percentage change in phosphorylated AS160 was negatively correlated with the number of metabolic risk factors ($r=-0.81$, $p<0.01$). RT increased skeletal muscle glycogen content, while it reduced phosphorylated Akt and phosphorylated AS160 for HiMFT. The increases in the number of metabolic risk factors and levels of inflammatory markers may serve to inhibit insulin-signalling protein phosphorylation and possibly contribute to the insulin resistance evident in these individuals.

Conclusion. Study One showed that women with HiMF have higher perception of bodily pain, compared to their LoMF peers, and the number of metabolic risk factors is correlated with the capacity to perform ADL's and the physical aspect of the SF-36. Men with HiMF however, have similar capacities to perform ADL's and QoL, compared to men with LoMF. This may partly explain why women are more likely to consult a healthcare practitioner than men, especially early in the disease progression. It may also indicate that functional capacity and self-perceived QoL may not serve as early warnings of future disease in men. As such, routine medical check-ups and adoption of healthier lifestyle are recommended before risk factors progress to symptomatic disease. Study Two showed that RT can improve the capacity to perform ADL's and QoL in individuals with HiMF even in the absence of change in aerobic power or body fat mass. Study Three showed that despite these improvements, RT had limited effects on conventional and emerging metabolic risk factors and Study Four showed that RT can increase muscle glycogen content, but may also adversely affect insulin-signalling. Reductions in phosphorylated AS160 and phosphorylated Akt may also be related to increases in inflammatory marker levels.

The results of this thesis suggest that middle-aged individuals should perform RT as it improves muscle strength, mass, muscle glycogen stores and the capacity to perform ADL's and QoL. However, it appears that in order to target the metabolic risk and improve insulin-signalling proteins (especially the phosphorylated proteins) for individuals with clusters of metabolic risk factors, this form of training may need to be combined with aerobic training and other lifestyle interventions such as diet.

Declaration

I, Itamar Levinger, declare that the PhD thesis entitled “The Effects of Resistance Training on Individuals with Clusters of Metabolic Risk Factors: Focus on Functional Capacities, Clinical Outcomes and Quality of Life” is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this is my own work. Considerable collaboration with other institutions were also involved in this thesis. The Dual-energy X-ray absorptiometry (DXA) measurements were conducted by staff at the Bone Density Unit, Austin Health, Repatriation Campus. Fasting blood samples were collected and analysed by staff from the Austin Health pathology laboratory. Plasma brain-derived neurotrophic factor (BDNF) was analysed at the Baker Heart Institute, Melbourne by Dr. Vance Matthews. Proinflammatory cytokines were analysed at the University of Queensland, School of Human Movement Studies by Dr. Jonathan Peake. The dietary logs were analysed by Ms. Ka Yan Tse, School of Human Movement, Recreation and Performance, Victoria University. Muscle biopsies were conducted by Dr. Andrew Garnham, School of Exercise and Nutrition Sciences, Deakin University. All other analyses of tissue samples and all data analyses other than those described above were performed by the candidate.



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List of publications and conference presentations related to the thesis

All parts of this thesis have been published or accepted for publication in peer reviewed journals and/or peer reviewed conferences proceeding.

Peer reviewed journal publications

1. **Levinger I**, Goodman C, Hare LD, Jerums G, Selig, S. (2007). The effect of resistance training on functional capacity and quality of life in individuals with high and low number of metabolic risk factors. *Diabetes Care*. 30; 2205-2210.
2. **Levinger I**, Goodman C, Matthews V, Hare D, Jerums G, Garnham A, Selig S. (2008). BDNF, risk factors for metabolic syndrome and resistance training in middle-aged individuals. *Medicine and Science in Sports and Exercise*. 40; 535–541.
3. **Levinger I**, Goodman C, Hare D, Jerums G, Toia D, Selig S. The reliability of the 1RM strength test for untrained middle-aged individuals. *Journal of Science and Medicine in Sport*. In Press (Accepted 18 October, 2007).
4. **Levinger I**, Goodman C, Hare LD, Jerums G, Selig, S. Functional capacity and quality of life in middle-age men and women with high and low number metabolic risk factors. *International Journal of Cardiology*. In Press (Accepted 18 November 2007).

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1. **Levinger I**, Goodman CA, Peake J, Hare DL, Jerums G, Garnham A, Selig S. The association between emerging and traditional risk factors for developing metabolic syndrome and type 2 diabetes. Australian Association for Exercise and Sport Science Conference. Melbourne (2008).
2. **Levinger I**, Goodman CA, Peake J, Hare DL, Jerums G, Garnham A, Selig S. The effects of resistance training on emerging metabolic risk factors in individuals with clusters of metabolic risk factors. Australian Association for Exercise and Sport Science Conference. Melbourne (2008).
3. **Levinger I**, Goodman C, Hare LD, Jerums G, Selig, S. Resistance training and metabolic risk profile in individuals with multiple components of the metabolic syndrome. Australian Conference of Science and Medicine in Sport. Adelaide, Australia (2007) (nominated for several prizes in the conference).
4. **Levinger I**, Goodman C, Hare LD, Jerums G, Selig, S. The ability to perform ADL's and quality of life in individuals with high and low metabolic risk profiles. Australian Conference of Science and Medicine in Sport. Adelaide, Australia (2007).
5. Goodman CA, **Levinger I**, Howlett KF, Peake J, Garnham A, Hare DL, Jerums G, Selig S. Resistance training increases total akt, but decreases basal AS160 phosphorylation in individuals with clusters of metabolic risk factors. Joint meeting of the Australian Physiological Society and the Australian Society for Biophysics, Newcastle, Australia (2007).
6. **Levinger I**, Goodman C, Hare LD, Jerums G, Toia, D, Selig, S. The reliability of the one repetition maximum test for untrained middle-aged individuals. International Congress of Obesity. Sydney, Australia (2006).

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List of abbreviation

ACE	angiotensin converting enzyme
ADL's	activities of daily living
Akt	protein kinase B
ALT	alanine aminotransferase
AS160	Akt substrate of 160 kDa
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BP	blood pressure
cm	centimetre
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
DXA	Dual-energy X-ray absorptiometry
FFA	free fatty acid
GGT	gammaglutamyltransferase
GLUT4	glucose transport 4
GSK3	glycogen synthase kinase 3
HbA1c	glycosylated-haemoglobin
HDL	high-density lipoprotein
HiMF	high number of metabolic risk factors
HiMFC	high number metabolic risk factors control group
HiMFT	high number metabolic risk factors training group
HOMA-IR	homeostasis model assessment
HR	heart rate
IDF	International Diabetes Federation
IL	interleukin
IRS	insulin receptor substrate
kg	kilogram
KJ	kilojoule
LBM	lean body mass
LDL	low-density lipoprotein
LoMF	low number of metabolic risk factors

LoMFT	low number of metabolic risk factors training group
LoMFC	low number of metabolic risk factors control group
MAPK	mitogen-activated protein kinase
MetS	metabolic syndrome
OGTT	oral glucose tolerance test
1RM	one repetition maximum
PI3K	phosphatidylinositol 3- kinase
PPT	Physical Performance Test
PVR	peripheral vascular resistance
Q	cardiac output
QoL	quality of life
RMR	resting metabolic rate
RPP	rate pressure product
RT	resistance training
SBP	systolic blood pressure
SDS-PAGE	sodium dodecyl sulfate -polyacrylamide gel electrophoresis
SF-36	Short Form Health Survey 36
T2DM	type 2 diabetes mellitus
TNF- α	tumor necrosis factor alpha
VO _{2peak}	peak aerobic power
W	watts
WHO	World Health Organisation

Chapter 1

1.0 Introduction

1.1 Overview

The prevalence of clusters of metabolic risk factors including central/abdominal obesity, hypertension, dyslipidemias and insulin resistance has proliferated worldwide over the past two decades, accompanied by the obesity epidemic (Elabbassi and Haddad, 2005; Miranda et al., 2005). Previously, clusters of metabolic risk factors were termed metabolic syndrome (MetS). However, as there is little consensus on the classification of risk factors for MetS (Alberti and Zimmet, 1998; ATP III, 2001; Zimmet et al., 2005), or even the syndrome itself, investigators and organisations such as, the American Diabetes Association and the European Association for the Study of Diabetes suggested not to use the term MetS, but rather describe clusters of metabolic risk factors (Grundy, 2006; Kahn et al., 2005; Reaven, 2006). As such, for the purpose of this thesis the term cluster of metabolic risk factors or high number of metabolic risk factors (HiMF) was used to define individuals with several numbers of metabolic risk factors (≥ 2). The conventional and the most common metabolic risk factors that are used in clinical practice to identify individuals with HiMF are over-weight/obesity, hypertension, elevated blood glucose levels and dyslipidaemia, especially elevated levels triglyceride and/or low levels of high-density lipoprotein (HDL). Recently, other metabolic risk factors have been suggested as predictors of future insulin resistance/type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). These include inflammatory markers (such as tumor necrosis factor alpha (TNF- α), interleukin (IL) 6, IL8 and C-reactive protein, CRP) (Rutter et al., 2004), the liver enzymes gammaglutamyltransferase (GGT) and alanine aminotransferase (ALT) (Emdin et al., 2005; Wannamethee et al., 2005) and brain-derived neurotrophic factor (BDNF) (Krabbe et al., 2007).

The pathological changes in the periphery associated with HiMF involve several mechanisms. The insulin resistance and metabolic alterations in this population appear to involve changes in skeletal muscle metabolism and structure including abnormal cellular insulin actions and abnormalities in insulin-signalling proteins such as Akt

(protein kinase B) and Akt substrate of 160 kDa (AS160). These cellular alterations may contribute to the reduction in glycogen synthesis, glycogen content and glucose disposal. (Mandarino, 1999; Perez-Martin et al., 2001).

Physical inactivity and sedentary lifestyle are major components in the development of HiMF (Bray and Popkin, 1998; Hwu et al., 2004; Pi-Sunyer, 2002). Some individuals with HiMF and T2DM suffer from muscle atrophy and strength loss and changes in muscle structure and metabolism (Nyholm et al., 1997; Vaag et al., 1992; Willey and Fiatarone-Singh, 2003; Yki-Jarvinen and Koivisto, 1983). As most individuals with HiMF are middle-aged or older (Ford et al., 2002), these characteristics may not be related solely to the development of the disease but may also be consequences of ageing. Impaired capacity to perform activities of daily living (ADL's) and lower self-perceived physical, emotional and social quality of life (QoL) are also associated with increased cardiovascular risk profiles (Chambers et al., 2002; Doll et al., 2000; Katz et al., 2000; Ko, 2006; Rejeski et al., 2006). However, most studies to date included patients with overt cardiac disease (such as coronary artery disease and/or heart failure). In addition, others have reported that overweight and obese individuals have lower rates of anxiety and depression, compared to normal weight individuals; this is known as the "jolly fat" hypothesis (Crisp and McGuiness, 1976). It remains unclear if individuals with HiMF, in the absence of symptomatic heart disease also have impaired capacities to perform ADL's and lower self-perceived QoL. In addition it is unclear if men and women with HiMF perceive their capacity to perform ADL's and QoL differently, compared to men and women with LoMF, and if alterations in the capacity to perform ADL's and QoL may be used as early warnings of future overt disease.

Lifestyle modifications are considered the cornerstone in the treatment of HiMF and should be the first intervention for preventing and managing HiMF and T2DM (Hu, 2006; Maggio and Pi-Sunyer, 1997; Pi-Sunyer, 2006; Schulze and Hu, 2005; Stone and Saxon, 2005). Aerobic exercise training is the most recommended exercise mode for individuals with HiMF and T2DM (Buemann and Tremblay, 1996; Eriksson, 1999; Hagberg et al., 2000; Pescatello et al., 2004; Rissanen and Fogelholm, 1999). However, this form of exercise has limited effect on preservation of muscle mass and strength or on reversal of muscle wasting (Ballor et al., 1996; Dumortier et al., 2003; Fleg and Lakatta, 1988; Rinder et al., 2004; Segal et al., 1991; Straczkowski et al., 2001) . In addition, the ability of some patients to perform aerobic exercise may be limited due to

musculoskeletal pain and/or low motivation (Focht et al., 2002; Focht et al., 2004; Willey and Fiatarone-Singh, 2003). It has been suggested that training that does not alter skeletal muscle mass and strength, has a limited effect on body composition and sarcopenia (Fiatarone-Singh, 1998), glycaemic control (Dumortier et al., 2003; Eriksson et al., 1997; Ferrier et al., 2004; Houmard et al., 2004; Ligtenberg et al., 1997; Watkins et al., 2003) and lipid profile (Dumortier et al., 2003; Ferrier et al., 2004; Rinder et al., 2004; Watkins et al., 2003).

Compared to aerobic training, few studies (particularly randomized controlled studies) have examined the effect of resistance training (RT) in people with HiMF and insulin resistance/T2DM (Eriksson, 1999; Willey and Fiatarone-Singh, 2003). RT has been shown to increase muscle strength and mass, which are important for the performance of ADL's, in many populations including young, elderly and those who suffer from chronic disease (such as CVD and T2DM) (Abe et al., 2003; Abernethy et al., 1994; Castaneda et al., 2002; King, 2001; Kraemer et al., 2001; Levinger et al., 2005b; Maiorana et al., 2002; Pollock et al., 2000). It is accepted that RT can increase muscle strength and the capacity to perform ADL's. It is unclear however, if RT can improve the QoL in individuals with HiMF but free from overt heart disease as at least one study has reported no improvement in QoL after RT (Perrig-Chiello et al., 1998). There is also a lack of comparative data on the effects of RT on the capacity to perform ADL's and QoL in middle-aged individuals with HiMF, compared to individuals with low number (≤ 1) of metabolic risk factors (LoMF).

Some studies have reported that RT improved fasting blood glucose levels (Balducci et al., 2004; Maiorana et al., 2002), glycosylated-haemoglobin (HbA1c) (Brooks et al., 2007; Dunstan et al., 2002; Maiorana et al., 2002; Sigal et al., 2007), insulin resistance (Brooks et al., 2007; Ishii et al., 1998; Ryan et al., 1996) and blood pressure (both systolic and diastolic) (Blumenthal et al., 1991). However other studies have reported no change in the above metabolic risk factors after RT (Cornelissen and Fagard, 2005; Cuff et al., 2003; Dunstan et al., 1998; Rice et al., 1999; Sigal et al., 2007). It is difficult to assess the role of RT for individuals with HiMF and T2DM, as some of the above studies involved either hybrid exercise training regimens (i.e. combined aerobic and resistance exercise) or double interventions (e.g. including diet). In addition, there have been only few studies that looked at RT as a single intervention and even fewer randomised controlled studies (and these included patients with T2DM). To date, there

are limited data on the effect of RT on the emerging metabolic risk factors, proinflammatory markers, and no information on the effect of RT on BDNF levels or the hepatic enzyme ALT concentration in individuals HiMF. Similarly, only one study (Holten et al. 2004) has reported the effect of RT on GGT levels. This study reported no change in GGT after 6 week of one-leg RT for individuals with T2DM. As such it is not known if RT can elicit metabolic improvements through changes to GGT, ALT and BDNF levels in people with HiMF. Further studies are needed in order to determine the effect of exercise on proinflammatory markers, hepatic enzymes and BDNF levels.

The effect of resistance exercise training on insulin sensitivity and on insulin-signalling proteins is unclear. A limited number of studies have examined the effects of RT on insulin-signalling proteins (such as Akt) and no study has examined the effect of RT on AS160. Recently, Howlett et al. (2007) reported that acute resistance exercise significantly reduced insulin sensitivity and glucose disposal as well as reducing basal Akt and AS160 phosphorylation. The effect of RT on basal insulin resistance and insulin-signalling proteins is not clear as the biopsies were taken up to 24 hours after the last exercise session. By contrast, other studies have reported an improvement in insulin sensitivity and insulin-signalling proteins after RT (Dela et al., 1994; Holten et al., 2004; Krisan et al., 2004). Despite the potential benefits of RT on insulin resistance and glucose disposal, the underlying mechanisms by which training may affect insulin-signalling proteins are unclear (Jessen and Goodyear, 2005). Furthermore, the above studies have reported insulin sensitivity and insulin-signalling protein under insulin load or during contraction stimulation and not in a basal state. As individuals are at rest (basal levels) during most hours of the day, it is important to examine the effects of RT on basal levels of insulin-signalling proteins. Individuals with HiMF are characterised by increased levels of inflammatory markers. It has been reported that inflammatory markers may lead to insulin resistance as they may alter the action of the insulin-signalling proteins (Hotamisligil et al., 1994; Hotamisligil et al., 1996; Kanety et al., 1995; Peraldi et al., 1996). It is not clear however, what is the association between inflammatory markers and Akt and AS160, and if RT can change the inflammatory state of these individuals.

In summary, it is generally accepted that symptomatic heart disease has adverse effects on the patient's capacity to perform ADL's and QoL. However, little is known if the capacity to perform ADL's and self-perceived QoL are affected by HiMF in the absence

of symptomatic disease. In addition, compared to other non-pharmacological interventions for individuals with HiMF (i.e. aerobic exercise training and diet), the benefits from RT are not well understood. It appears that RT may improve muscle strength and body composition that in turn should lead to increases in the capacity to perform ADL's and improvements to QoL. However, it is not clear if individuals with HiMF will benefit more, less or similarly to their healthy age-matched peers with respect to ADL's and QoL. In addition it is not clear if RT can improve metabolic risk factors (both traditional and emerging) and insulin-signalling proteins Akt and AS160 and skeletal muscle glycogen content in individuals with HiMF, compared to individuals with LoMF.

1.2 Purposes and hypotheses of the PhD

The purposes and the hypotheses specific for each study are described in the relevant chapter. Generally, the purpose of this PhD was to increase the body of knowledge in regard to the association of clusters of metabolic risk factors with muscle strength, aerobic power, the capacity to perform ADL's and QoL for middle-aged individuals. This PhD also examined the effects of RT as a single intervention, on muscle strength, functional capacities, QoL and clinical outcomes for individuals with HiMF. The effects of RT in individuals with HiMF were also compared to the effects of RT in individuals with LoMF. Finally, the effects of RT on insulin-signalling proteins (Akt and AS160) were examined in these two populations.

General hypotheses:

- The capacity to perform ADL's and QoL is adversely affected in both men women with HiMF, compared to those with LoMF.
- Emerging (Inflammatory markers, hepatic enzymes and BDNF levels) metabolic risk factors are associated with the traditional metabolic risk factors, and both will be significantly elevated in individuals with HiMF, compared to individuals with LoMF.
- The capacity to perform ADL's and QoL will be improved for individuals with either HiMF or LoMF following RT.

- The metabolic risk profile of individuals with HiMF will be improved after RT
- Total and phosphorylation Akt and AS160 will increase after RT.
- RT improves glycogen content.

1.3 PhD design

This PhD has examined the characteristics of individuals with HiMF compared to individuals with LoMF as well as the effects of RT on functional capacity, QoL and clinical outcomes in these two populations.

The aim of each study is detailed below:

Study One examined the difference characteristics between individuals with HiMF and those with LoMF for MetS and T2DM. These included conventional and emerging metabolic risk factors. This study also examined whether increased metabolic risk profiles in the absence of symptomatic heart disease are linked to reductions in capacities to perform ADL's and/or impaired QoL in this population as a whole, and also according to sex (i.e. men with HiMF versus men with LoMF and women with HiMF versus women with LoMF). Studies Two-to-Four examined the effects of 10 weeks RT on muscle strength, the capacity to perform ADL's and QoL (Study Two), metabolic risk factors (Study Three) and insulin-signalling proteins (Study Four) of middle-aged individuals with HiMF and LoMF.

1.4 Significance of the PhD

The prevalence of obesity and HiMF has increased dramatically over the past two decades. Poor lifestyle and physical inactivity have been recognised as major contributors for the recent epidemic. This thesis has examined the physical characteristics of individuals with HiMF compared to those with LoMF, as well as the capacity to perform ADL's, functional capacities and QoL in those populations. It has also examined the effects of RT on body composition, functional capacities and QoL as well as the effects of RT on metabolic risk factors and insulin-signalling proteins and muscle glycogen content in individuals with HiMF and LoMF. The findings of this thesis may provide novel information in regard to the effects of clusters of metabolic

risk factors on the capacities to perform ADL's and QoL. In addition the findings from this thesis may indicate if the capacity to perform ADL's and self perceived QoL may be used as early warning signs for individuals with HiMF. This thesis may also add important data in regard to the role and benefits of RT as well as the limitations of this form of training for individuals with HiMF.

Chapter 2

2.0 Literature review

2.1 Clusters of metabolic risk factors: Background

Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) are major global health concerns (World Health Organization, 2003a; Zimmet et al., 2003). Investigators have tried to identify the major metabolic risk factors leading to T2DM and CVD. Usually there is no single cause for CVD and T2DM, but rather there are clusters of metabolic risk factors occurring in susceptible individuals. Clusters of metabolic risk factors are termed metabolic syndrome (MetS). MetS are combinations of several metabolic risk factors including obesity (mostly central obesity), hypertension, dyslipidemias and insulin resistance (Alberti and Zimmet, 1998; ATP III, 2001; Brunzell, 2003; Grundy et al., 2004; Tuomilehto, 2005; Zanella et al., 2001). All of these risk factors are also considered to be diseases (Ayodele et al., 2005; Mancia, 2005; Sowers et al., 2001). The American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE), the World Health Organisation (WHO) (Alberti and Zimmet, 1998), National Cholesterol Education Program-Adult Treatment Panel III (ATP III, 2001) and the International Diabetes Federation (Zimmet et al., 2005) have each set diagnostic criteria for the MetS. The major difference between these sets of criteria is that each organisation emphasises different aspects of the MetS in the metabolic risk factor profiles. For instance, according to the WHO a person must have insulin resistance, glucose intolerance or diabetes and two more of the diagnostic factors to be diagnosed with the MetS. WHO uses the body mass index (BMI) as an indicator for obesity. The ATP III and IDF include any three criteria (Table 2.1) in order to be classified as MetS. The major difference between the ATP III and IDF criteria is the differing threshold levels for risk factors.

Table 2.1. Clinical criteria for the diagnosis of metabolic syndrome. WHO (1998), ATP III (2001) and IDF (2005).

Risk factor	WHO (1998)	ATP III (2001)	IDF (2005)
Obesity	Waist to hip ratio: Males > 0.90 Females > 0.85 or BMI > 30 kg·m ⁻²	Waist circumference: >102 cm >88 cm	Waist circumference: >94 cm >80 cm
Triglycerides	≥ 1.7 mmol·L ⁻¹	≥1.7 mmol·L ⁻¹	≥1.7 mmol·L ⁻¹
HDL cholesterol	Males < 0.9 mmol·L ⁻¹ Females < 1.0 mmol·L ⁻¹	<1.04 mmol·L ⁻¹ <1.3 mmol·L	<1.03 mmol·L ⁻¹ <1.3 mmol·L
Blood pressure	SBP≥160 and/or DBP≥ 90 mmHg medications	SBP≥130 and/or DBP≥ 85 mmHg or medications	SBP≥130 and/or DBP≥ 85 mmHg or medications
Fasting glucose	Impaired glucose tolerance, impaired fasting glucose, insulin resistance or diabetes.	≥6.1 mmol·L ⁻¹	≥5.6 mmol·L ⁻¹
Microalbuminuria	Urinary albumin to creatinine ratio ≥ 30 mg·g ⁻¹ or albumin excretion rate ≥ 20 µg·min ⁻¹	-----	-----

HDL (High-density lipoprotein). Adapted from Alberti and Zimmet (1998), ATP III (2001) and Zimmet et al (2005).

Some investigators use alternative terms to MetS to define similar metabolic abnormalities. These include syndrome X (Das, 2002b; Deen, 2004; Reaven, 1988, 1993), the central obesity syndrome (Brunzell and Hokanson, 1999), dyslipidemic syndrome of visceral obesity (Despres, 1994, 1998), the insulin resistance syndrome (Deen, 2004; DeFronzo and Ferrannini, 1991; Despres, 1993) and dyslipidemic hypertension (Onat et al., 2005). Thus, there is little consensus on the classification of metabolic abnormalities for MetS, or even the syndrome itself. Moreover, describing a person as having MetS has “little clinical or pedagogic utility and even can do more harm than good” as each metabolic risk factor should be targeted and treated specifically and not treated as a cluster (Reaven, 2006) (See section 2.7 “Pharmacotherapy for individuals with clusters of metabolic risk factors”). Recently, investigators and organisations such as the American Diabetes Association and the European Association for the Study of Diabetes suggested not to use the term MetS, but

rather describe clusters of metabolic risk factors (Grundy, 2006; Kahn et al., 2005; Reaven, 2006). It has even been suggested that people with two metabolic risk factors are not at lower risk to develop T2DM and CVD compared to people with three or more risk factors (Kahn et al., 2005; Reaven, 2006; Ridker et al., 2003; Ridker et al., 2004; Sattar et al., 2003). For the purpose of this thesis, the term clusters of metabolic risk factors or high numbers of metabolic risk factors (HiMF) was defined as individuals with two or more metabolic risk factors.

2.1.1 Epidemiology

The prevalence of clusters of metabolic risk factors has proliferated worldwide over the past two decades, accompanied by the obesity epidemic (Elabbassi and Haddad, 2005; Miranda et al., 2005). It has been estimated that the prevalence of clusters of metabolic risk factors in individuals with normal fasting blood glucose, but with varying combinations of obesity, dyslipidemia, and hypertension, is between 7% to 16% in Asia (Enkhmaa et al., 2005; Shiwaku et al., 2005; Thomas et al., 2005a) and 15%-35% in the US (Ford and Giles, 2003; Friedman and Fanning, 2004), Europe (Hu et al., 2004b; Ozsahin et al., 2004) and in the middle east (Elabbassi and Haddad, 2005). The prevalence is much higher in individuals with impaired fasting glucose (~50%) and individuals with T2DM (~80%) (Isomaa et al., 2001). In addition, it has been shown that the prevalence is age-dependent (Elabbassi and Haddad, 2005; Ozsahin et al., 2004), increasing from approximately 7% in people aged 20-29 yr to more than 40% in people over the age of 60 yr (Ford et al., 2002).

2.1.2 Clinical outcomes

The characteristics of individuals with clusters of metabolic risk factors are shown in Table 2.2. These individuals are usually overweight/obese (mainly visceral obesity) and generally have high blood pressure (BP), elevated plasma glucose and serum triglyceride levels, and suffer more frequently from chronic kidney disease (Chen et al., 2004; Miranda et al., 2005). In addition, they engage in less physical activity (sedentary lifestyle) (Chen et al., 2004; Lakka et al., 2003) and have poor cardiorespiratory fitness (aerobic capacity) (Lakka et al., 2003), compared to their healthy age-matched peers.

Table 2.2. Common characteristics of individuals with HiMF.

Characteristic
Overweight/obese (mostly visceral obesity)
Hypertension
Hyperinsulinemia
Insulin resistance
High plasma glucose level
Dyslipidemia (high triglyceride and LDL and low HDL)
Impaired glucose tolerance
Endothelial dysfunction
Inflammation
Physical inactivity
Kidney disease

HDL (high-density lipoprotein), LDL (low-density lipoprotein). Adapted from Chen et al. (2004) and Miranda et al. (2005).

The morbidity, mortality and economic consequences of clusters of metabolic risk factors are significant (Ford et al., 2002; Lakka et al., 2002). These individuals have 1.5-5.9 times (depending on the duration of the study) higher risk of developing coronary artery disease (Girman et al., 2004; Isomaa et al., 2001; Wilson et al., 1999) and a threefold increased risk of suffering a stroke (Isomaa et al., 2001). They are also at higher risk of developing left ventricular hypertrophy (Leoncini et al., 2005), possibly leading to heart failure. Moreover, the mortality rate from CVD (particularly coronary artery disease) accelerates (by approximately threefold) in this population (Lakka et al., 2002).

2.2 Conventional metabolic risk factors

There are many possible metabolic disorders that may lead to the development of T2DM and CVD. However, the traditional and the most common used metabolic risk factors to classify and to diagnose individuals at high metabolic risk are obesity, insulin resistance, hypertension and dyslipidaemia.

2.2.1 Obesity

2.2.1.1 Epidemiology and costs

The obesity epidemic is one of the most serious global health concerns, affecting more than 300 million people world wide (World Health Organization, 2003b), with the incidence accelerating (Greenlund et al., 2004; Jackson et al., 2001). Obesity is defined as an excess of adipose tissue resulting from chronic increases in caloric intake, decreases in energy expenditure, or both (Aronne, 1998; Bjorntorp, 1998; Swinburn and Ravussin, 1994).

The most frequently used measure for the classification of overweight and obesity is the body mass index (BMI), calculated by dividing body mass (kg) by the square of the height (m^2). However, the validity of the BMI may be questioned in relation to obesity because the numerator is based on a “one compartment model” that takes no account of muscle, bone or fat contributions to overall mass. That said, the BMI is a very simple and accurate measure to obtain and is widely applied as follows: BMI < 18.5 $kg\cdot m^{-2}$ under weight, 18.5-24.9 $kg\cdot m^{-2}$ normal weight, 25.0 -29.9 $kg\cdot m^{-2}$ overweight, 30-39.9 $kg\cdot m^{-2}$ obesity and BMI > 40 $kg\cdot m^{-2}$ extreme (morbid) obesity (Grundy et al., 1999; Gumbiner, 2001).

Over the 20th century in industrialised countries, mean BMI increased by 5.7 $kg\cdot m^{-2}$ (25%) (Helmchen and Henderson, 2004), and the 21st century is looming as the obesity century (Baur, 2001; Jackson et al., 2001). The prevalence of overweight has increased from 46% to 64.5% and the prevalence of obesity has increased from 14.5% to 30.5% for adults in the USA over the past 3 decades (Flegal et al., 2002; Stein and Colditz, 2004). In Australia, it is estimated that 5 million adults (≥ 25 yr) are overweight and an additional 2 million are obese. Overall, 60% of Australian adults are overweight, and obesity has more than doubled in the past 25 years (AIHW, 2001; Australia Heart

Foundation, 2005; Cameron et al., 2003). Furthermore, it is anticipated that the obesity “epidemic” is continuing unabated (Jackson et al., 2001).

Obesity is associated with huge costs in human and economic terms (Kottke et al., 2003). The burden of obesity on the health care system is enormous (Friedman and Fanning, 2004; Kottke et al., 2003). It has been estimated that the direct cost of obesity for the American National Health Care system is approximately 94 billion dollars per annum, or 9.4% of the national health care expenditure (Colditz, 1999; Manson et al., 2004), and this is likely to accelerate in the coming decades.

The increased prevalence of obesity and particularly central obesity (Carr et al., 2004) has associations with many other conditions/diseases (Dalton et al., 2003; Despres, 1991; Friedman and Fanning, 2004; Lemieux et al., 2000; Pi-Sunyer, 2002; Sowers, 1998). These include dyslipidemia (high blood triglycerides and/or low HDL cholesterol levels) (Dalton et al., 2003; Greenlund et al., 2004; McLaughlin et al., 2003; Must et al., 1999), hypertension (Dalton et al., 2003; Greenlund et al., 2004; Must et al., 1999; Redon, 2001), CVD (Kenchiah et al., 2002; Sowers, 1998; Steinberger and Daniels, 2003), insulin resistance and T2DM (Colditz et al., 1995; Goodpaster et al., 2003; Wilson and Kannel, 2002), cancer, gallbladder and liver diseases (Boland et al., 2002; Bray, 2004; Garfinkel, 1985; Must et al., 1999), increased psychological vulnerability (such as a reduction in self-esteem and increased depression) and social isolation (Bray, 2004; Epel et al., 2000; Franklin, 1977; Ganley, 1989; Kottke et al., 2003; Must et al., 1999; Stein and Colditz, 2004) and the development of osteoarthritis and gout. The increase in fat mass has an effect on musculoskeletal and locomotor systems as it increases the mechanical load on joints and bones (Bray, 2004; Cicuttini et al., 1996; Hills et al., 2002; Manninen et al., 1996; Must et al., 1999). Obesity is also associated with sleep disorders such as sleep apnea (Bray, 2004; Robinson and Grunstein, 2003; Wolk et al., 2003) and is strongly predictive of mortality (Allison et al., 1999; Calle et al., 1999; Lew and Garfinkel, 1979; Manson et al., 1995). It has been estimated that 27% of the deaths among non-smoking individuals are attributed to abdominal obesity (Visscher et al., 2001).

2.2.1.2 Aetiology

Obesity is a multifactorial and complex disease (Bray, 2004; Eckel, 2003; WHO, 1997) with several possible aetiologies. These include environmental (lifestyle) factors superimposed on genetic factors (Bray, 1987; Cameron et al., 2003; Martinez, 2000; Pi-Sunyer, 2002; Stein and Colditz, 2004; Stunkard, 1988).

There is increased evidence for the contribution of heredity and/or gene defects/mutation to body fat and energy balance that may lead to the development of obesity (Bouchard and Tremblay, 1997; Bouchard et al., 1990; Stunkard, 1988; Stunkard et al., 1990; Stunkard et al., 1986). In recent years, several single gene mutations were identified as possible contributors for the heredity of obesity and HiMF (Bouchard and Perusse, 1996; Chouchane et al., 2001; Martinez, 2000; Park et al., 2005; Rosmond, 2002). It has been shown that gene defects/mutations, such as genes involved in formation of leptin (chromosome 6), leptin receptor (chromosome 4) and beta₂-adrenergic receptors are related to energy balance in the body and as such, contribute to obesity, insulin resistance and hypertension (Bray, 1997; Martinez, 2000; Rosmond, 2002). Other studies however, have reported that heredity plays a limited role in the development of obesity and that only up to 25% of the body fat percentage is attributed to biological inheritance (gene transmission). (Bouchard et al., 1988; Stunkard, 1988). It has been speculated that the rapid increase in the prevalence of obesity may indicate that it is mostly the environmental factors that contribute to the epidemic, rather than changes or mutations to the gene pool (Eckel, 2003; Martinez, 2000; Ravussin et al., 1994; Stein and Colditz, 2004).

The two main environmental factors responsible for weight gain are sedentary lifestyle and physical inactivity (low energy expenditure), and high caloric energy intake (Bray and Popkin, 1998; Pi-Sunyer, 2002). Modern technologies have led to sedentary lifestyle becoming almost the norm (Martinez-Gonzalez et al., 1999; Martinez, 2000; Pi-Sunyer, 2002). Cameron et al. (2003), Martinez et al. (1999) and Martinez-Gonzalez (1999) reported inverse associations between BMI and physical activity, suggesting that habitual inactivity is an important factor that may lead to obesity.

Energy expenditure does not depend only on caloric expenditure during physical activity (20-30% of total energy expenditure), but also on the energy an individual utilises at rest, known as the resting metabolic rate (RMR) (60-70% of total energy

expenditure) and the thermic response to food intake (10% of total energy expenditure) (Bouchard and Tremblay, 1997; Pi-Sunyer, 2002; Swinburn and Ravussin, 1994; Williams and Considine, 2001). It has been suggested that RMR is an important factor that can assist in maintaining normal body weight (Martinez, 2000; Pi-Sunyer, 2002; Ravussin and Bogardus, 1989; Swinburn and Ravussin, 1994). Individuals with low 24 h energy expenditure (200 kcal below their predicted value) had a four-fold increased risk of gaining significant body mass, compared to individuals with high 24 h energy expenditure (200 kcal above their predicted value) (Ravussin et al., 1988). During ageing, total energy expenditure is often significantly reduced. The reduction in total energy expenditure with age was mainly due to reductions in RMR (by 42% in males and 46% in females) and physical activity (48% in males and 44% in females) (Elia et al., 2000). There is a strong positive relationship between RMR and lean body mass (LBM) ($r \sim 0.9$) (Bogardus et al., 1986; Illner et al., 2000; Ravussin et al., 1988). It has also been suggested that skeletal muscle mass is an important component of LBM (De Los Reyes et al., 2003; Illner et al., 2000). Therefore, it is possible that a reduction in muscle mass as a result of inactivity (Bloomfield, 1997; Convertino et al., 1997) or ageing (Fleg and Lakatta, 1988; Mishra and Misra, 2003; Rogers and Evans, 1993) contributes to the reduction in RMR, that in turn leads to increased body weight. These data emphasise the importance of skeletal muscle mass in maintaining normal body weight. It also emphasises the importance of specifically targeting skeletal muscle mass in any intervention for obese (and non-obese) individuals.

Modern lifestyle and the accessibility of cheap, high calorie food, may also contribute to the development of obesity (Pi-Sunyer, 2002). Some reports, but not all (Popkin et al., 2001), suggest that average caloric intake has increased significantly in the past 3 decades by 6.5%-15% (Harnack et al., 2000; Wright et al., 2004). However, an extensive review of the literature by Togo et al. (2001), revealed inconsistencies between reports regarding the contribution of food intake to obesity. Only one third of the studies (10 of 30) demonstrated associations between food intake and BMI/obesity (Togo et al., 2001). This suggests that it is the reduction in physical activity (caloric expenditure) that has contributed the most to the current obesity epidemic, rather than increases in caloric intake.

In summary, Figure 2.1 is a schematic of the contributions of environmental and genetic factors in the development of obesity. It appears that both genetic and environmental

factors influence BMI. Genetic factors may determine the susceptibility of an individual to become obese (vulnerability for obesity), that may then be expressed by long term exposure to environmental factors (Astrup and Lundsgaard, 1998; Ravussin et al., 1994; Stunkard, 1988).

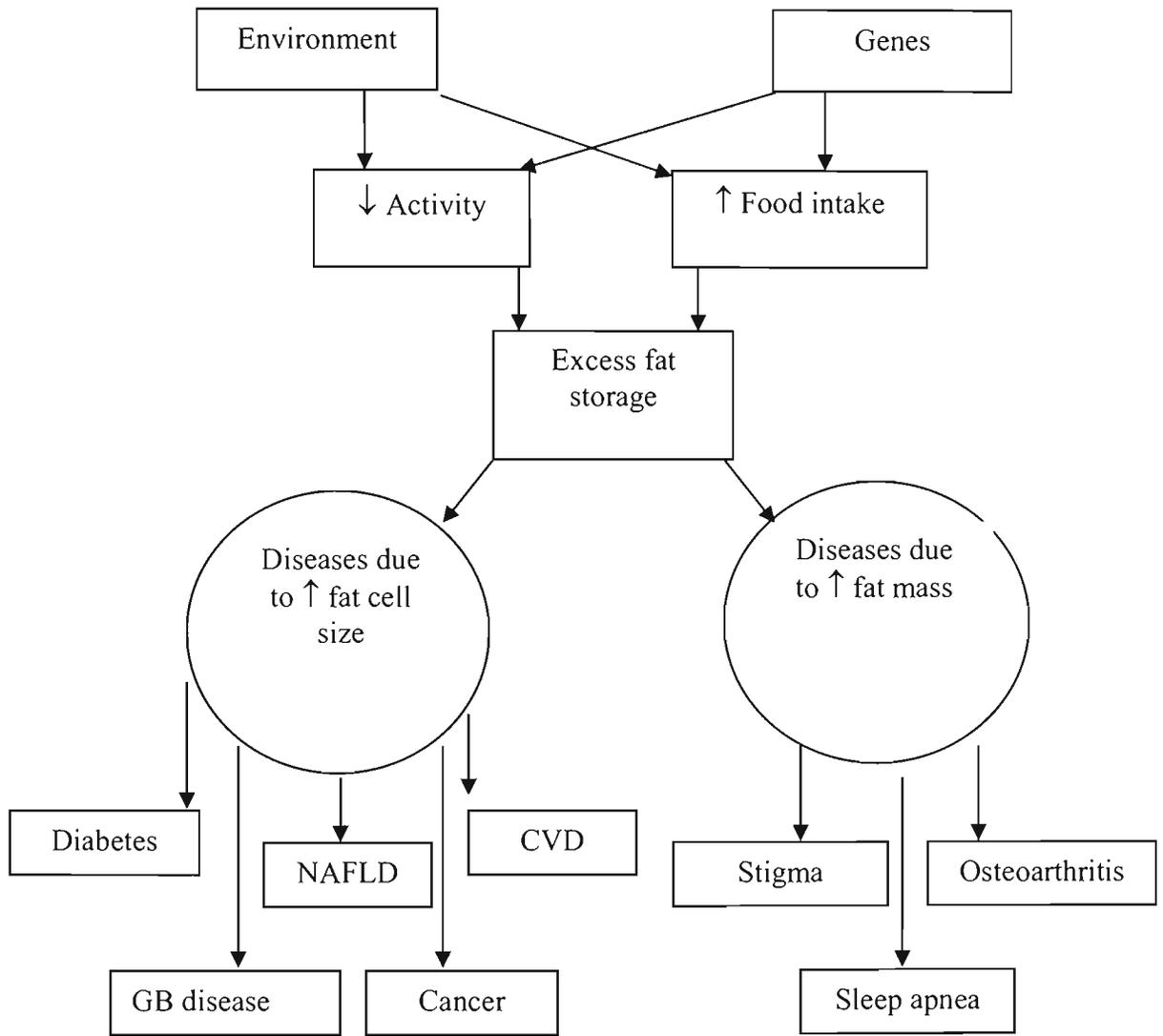


Figure 2.1. Pathogenesis of health problems associated with obesity.

NAFLD (nonalcoholic fatty liver disease), CVD (cardiovascular disease), GB (gallbladder). Adapted from Bray (2004).

2.2.2 Insulin resistance and type 2 diabetes mellitus

2.2.2.1 Overview

Insulin is an anabolic hormone secreted from the pancreatic islet beta cells in response to increased blood glucose levels. Insulin promotes the synthesis of fatty acids and triglycerides in the liver and adipose tissue, glycogen in skeletal muscle and the liver and proteins in a wide variety of tissues (Figure 2.2) (Germann and Stanfield, 2005; Levy and Lightman, 1997; Zorzano and Camps, 1997). Insulin plays a crucial role in glucose metabolism by inhibiting hepatic glucose secretion (Kahn, 1994; Zorzano and Camps, 1997), by increasing the number of glucose transporters 4 (GLUT4) in the cell membrane of skeletal muscle cells and by triggering the movement of GLUT4 from the cell cytoplasm to the membrane (Germann and Stanfield, 2005; Miranda et al., 2005). Insulin also leads to the storage of glucose as glycogen in the liver and skeletal muscle and increases the ability of target cells to take up glucose (Kahn, 1994).

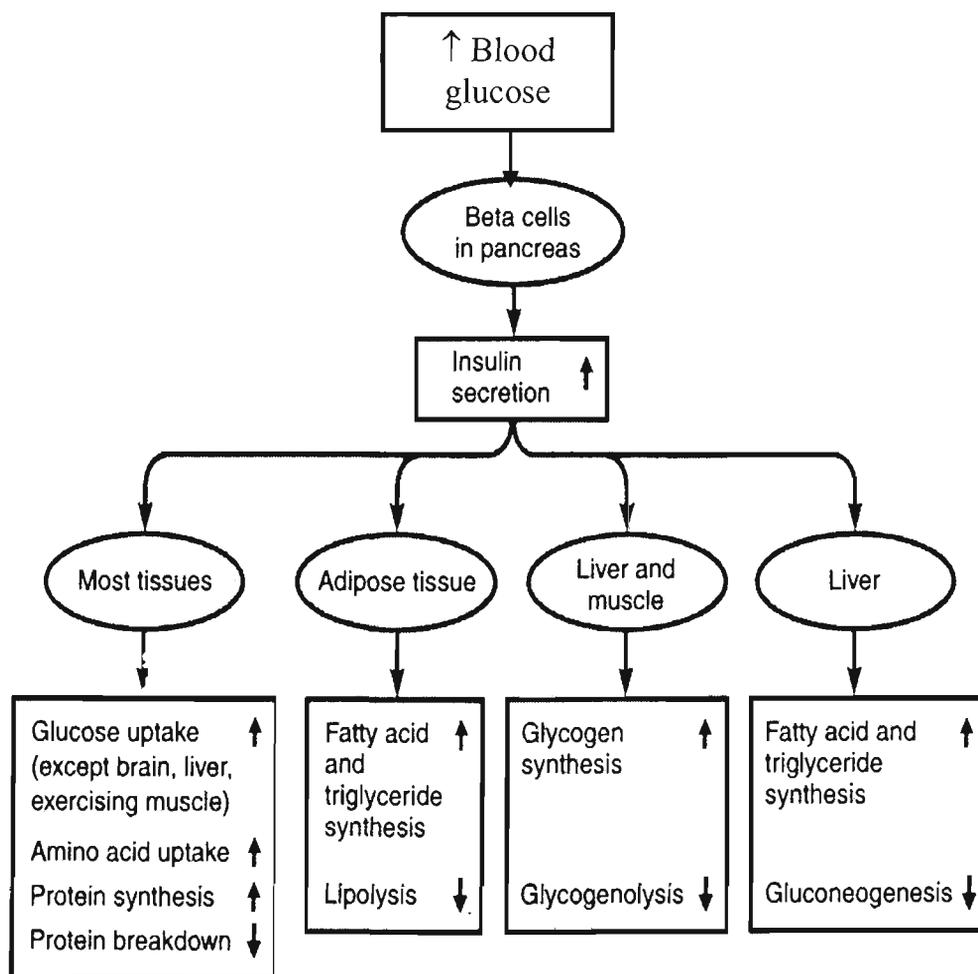


Figure 2.2. Insulin and its action on target tissues.

Adapted from Germann and Stanfield (2005; pp 189).

Insulin resistance is characterised by inability of target tissues to increase glucose uptake in response to insulin due to defects in insulin secretion, insulin action or both (Goodpaster and Wolf, 2004; Groop and Tuomi, 1997; Reaven, 1993; Taylor et al., 1994) (note, the pathophysiology of insulin resistance and T2DM are described in the section of “Clusters of metabolic risk factors: pathophysiology”). As a result, the pancreatic islet beta cells try to compensate by increasing insulin production, this increase insulin level above that seen in normal conditions, is known as hyperinsulinemia (Figure 2.3). Blood glucose levels usually remain normal as long as the hyperinsulinemia is maintained (Reaven, 1988). However, hyperinsulinemia is associated with increased plasma triglyceride levels, hypertension and decreased HDL (Reaven, 1993). As a result, it may lead to CVD (Despres, 1998). When beta cells fail to maintain hyperinsulinemia, blood glucose levels rise (known as hyperglycaemia) (Reaven, 1988; Saltiel, 2000). Non-insulin dependent diabetes mellitus or T2DM is a term used to describe a state of chronic hyperglycaemia (Figure 2.3). Insulin resistance is therefore a major metabolic risk factor for the development of T2DM (Lillioja et al., 1993). It may take up to 10 years for diabetes to evolve in an individual from the time insulin defects are noticeable (insulin resistance and hyperinsulinemia with normal blood glucose) (Martin et al., 1992).

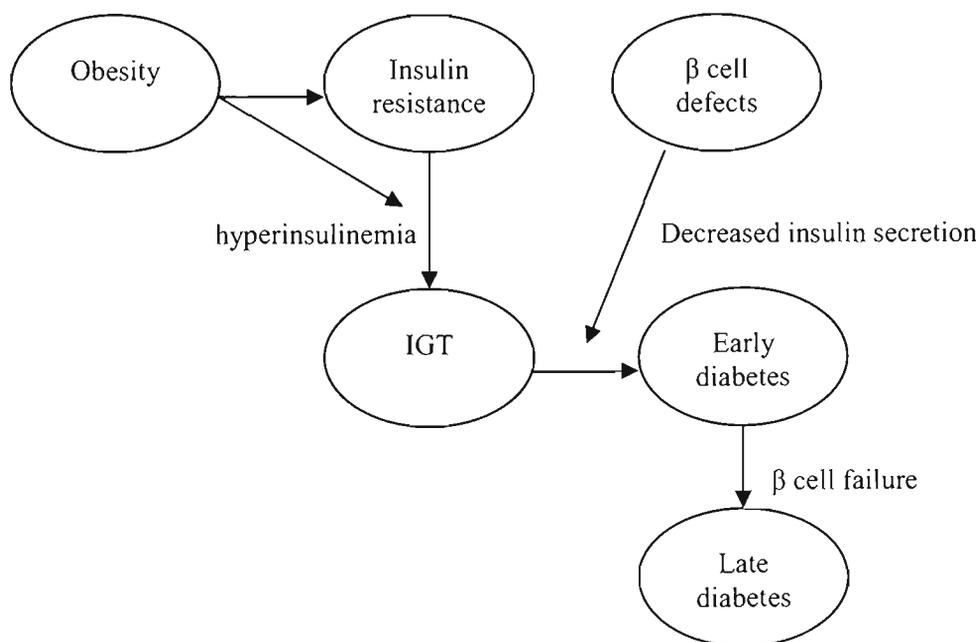


Figure 2.3. Metabolic staging of type 2 diabetes.

IGT (impaired glucose tolerance), adapted from Saltiel (2000).

Both insulin resistance and T2DM are diagnosed according to plasma glucose levels after overnight fasting and/or two hours oral glucose tolerance test (OGTT). The different diagnostic categories are normal plasma glucose, impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) (also known as prediabetes) and diabetes (American Diabetes Association, 2006) (Table 2.3).

Table 2.3. Normal plasma glucose level and categories of hyperglycemia.

Category	Fasting glucose (mmol·L ⁻¹)
Normal	
Fasting	< 5.6
2-h after OGTT	<7.8
Impaired glucose metabolism	
Fasting	5.6-6.9 (IFG)
2-h after OGTT	7.8-11.1 (IGT)
Diabetes mellitus:	
Fasting	≥ 7.0
2-h after OGTT	≥ 11.1

OGTT (oral glucose tolerance test). Adapted from American Diabetes Association (2006).

2.2.2.2 Epidemiology and clinical outcomes

Insulin resistance and T2DM are two of the most prevalent metabolic disorders in obese individuals (Steinberg and Gumbiner, 2001). The prevalence of insulin resistance and T2DM has increased significantly in the past 2 decades, mainly because both phenomena are closely associated with abdominal obesity (Colditz et al., 1995; Despres, 1993; Goodpaster et al., 2003; Greenlund et al., 2004; Leibson et al., 2001; Must et al., 1999; Zimmet et al., 2003). From 1995 to 2000, the prevalence of diabetes increased from 135 million to 151 million world wide (King et al., 1998; Zimmet et al., 2001), with the number increasing further to 189 million by 2003 (Zimmet et al., 2003). It was estimated that the number of people with diabetes will accelerate and by 2025, it will reach 324 million (72% increase from 2003) (Zimmet et al., 2003). In Australia, the number of people diagnosed with T2DM (self reported data) increased two-fold between 1989 and 2000 (Australia Heart Foundation, 2005). It is difficult however, to

estimate how many more people live with undiagnosed T2DM and insulin resistance (Harris, 1993; Mooy et al., 1995; Mykkanen et al., 1993; Thomas et al., 2005b).

The human and the economical impacts of insulin resistance and diabetes are enormous (King et al., 1998; Zimmet et al., 2001). Insulin resistance and diabetes comprise not only a disease but are also considered risk factors for most macro-vascular diseases including hypertension, coronary artery disease and stroke (Benetos et al., 2002; Fontbonne and Eschwege, 1991; Woodward et al., 2003) and many micro-vascular conditions including diabetic retinopathy, diabetic neuropathy and diabetic nephropathy (Brown and Asbury, 1984; Levy and Lightman, 1997; Zimmet et al., 2001). Costs related to diabetes impose heavy burdens on the health care system and on individuals and their families (American Diabetes Association, 1998; Franklin, 1977). In 2002, the direct medical expenditure by the US Health Care System due to diabetes was \$US91.8 billion. Indirect costs (lost workdays, restricted activity days, mortality and permanent disability) added another \$US39.8 billion (Hogan et al., 2003).

2.2.2.3 Aetiology

Similar to the aetiology of obesity, both genetic and environmental factors have been identified as contributing to insulin resistance and T2DM (Groop and Tuomi, 1997; Kahn, 1994). There is substantial evidence suggesting that T2DM involves gene mutation (Andersen et al., 2005; Frayling et al., 2001; Froguel et al., 1992; Morcillo et al., 2005; Vaxillaire et al., 1995) and the disease has heredity aetiology (Barroso, 2005; Froguel et al., 1992; Meigs et al., 2000; Vaag et al., 1992). Offspring have 3.5 times the risk of becoming diabetic if one parent has T2DM. The odds ratio increases to 6.1 if both parents have diabetes (Meigs et al., 2000). Similarly, an individual has a 40% chance to become diabetic during his/her lifetime if one parent has diabetes and his/her chance to become diabetic increases to 70% if both parents have diabetes (Groop and Tuomi, 1997).

However, genetic potential for diabetes is not the sole factor that determines if an individual develops the disease (Groop and Tuomi, 1997; Kahn, 1994). While there are undoubted and important genetic influences in T2DM, the parallel accelerations in both T2DM and obesity in the past two decades provide strong evidence of a causal link between these and suggest that both are almost certainly linked to lifestyle factors.

The increase prevalence of obesity is a major contributor to insulin resistance and T2DM, since 60-80% of individuals with T2DM are obese (Groop and Tuomi, 1997). It was therefore suggested that environmental factors are crucial contributors to the development of the disease and that improvements in lifestyle, particularly diet and physical activity, may reduce the occurrence of diabetes (Colwell, 2003; Hu et al., 2001b; Torgerson et al., 2004; Torjesen et al., 1997; Tuomilehto et al., 2001).

Physical inactivity is a major component in the development of insulin resistance and T2DM (Hwu et al., 2004). Hu et al. (2001a) reported that the time spent watching TV is associated with elevated risk for diabetes, while increased physical activity levels are associated with reduced risk for developing diabetes. Moreover, lifestyle interventions have been shown to reduce the incidence of diabetes by more than 50% (Knowler et al., 2002; Tuomilehto et al., 2001). These data emphasizes the contribution of behavioural factors in the development of T2DM. Importantly, these studies highlight the benefits from changing from sedentary living to a more active lifestyle.

2.2.3 Hypertension

2.2.3.1 Epidemiology and clinical outcomes

The prevalence of hypertension worldwide in 2000 was estimated at 26.4% and it is predicted to rise to 29.2% by 2025 (Kearney et al., 2005). The number of people with hypertension is predicted to rise by 60% from 972 million worldwide in 2000 to 1.56 billion by 2025 (Kearney et al., 2005), a substantial rise even after accounting for population growth. It has been proposed that hypertension will be one of the most negative factors impacting on the global burden of disease over the next 2 decades (Reid and Thrift, 2005; Yach et al., 2004). In Australia, approximately 30% of the population is classified as hypertensive (Australia Heart Foundation, 2005; Briganti et al., 2003).

46% of people with hypertension in the absence of hyperlipidemia are classified as HiMF due to obesity and/or impaired glucose handling. Other diseases related to hypertension are the development of T2DM (Mancia, 2005; Okosun et al., 2001; Pette and Staron, 2000), and arterial stiffness and CVD (Franklin, 2004; Laurent and Boutouyrie, 2005; Schiffrin, 2004; Tomson and Lip, 2005). Hypertensive individuals have increased risk for peripheral arterial disease, myocardial infarction, stroke and heart failure (Almgren et al., 2005; Ayodele et al., 2005; Clement et al., 2004; Laurent

and Boutouyrie, 2005). Up to 75% of the CVD occurring in individuals with diabetes is attributed to hypertension (Sowers et al., 2001). Hypertension may cause, and alternatively be caused by, chronic renal disease (Andersen and Agarwal, 2005; Briganti et al., 2005; Hsu et al., 2005; Whitworth, 2005) and it is related to premature death (Bog-Hansen et al., 2004). Control of hypertension may lead to 28-44% and 20-35% reductions in the prevalence of stroke and ischemic heart disease, respectively (He and MacGregor, 2003).

2.2.3.2 Aetiology

Chronic increases in systolic blood pressure (SBP) above 140 mmHg and/or diastolic blood pressure (DBP) above 90 mmHg are defined as hypertension (Franklin, 2004; Ganong, 2003; Hajjar and Kotchen, 2003). Essential hypertension is a term used when the aetiology of the hypertension cannot be determined (almost 90% of hypertension cases are considered to be essential hypertension) (Ganong, 2003). There are substantial data to suggest that overweight and obesity are major contributors for the development of essential hypertension (Carroll et al., 1995; de Paula et al., 2004; Garrison et al., 1987; Hall, 2000; Hall et al., 2003; Rocchini, 1990; Rocchini et al., 1987). Several anthropometric variables predict hypertension. These include BMI (Garrison et al., 1987; Jones et al., 1994; Sung and Ryu, 2004), waist circumference (Sung and Ryu, 2004), waist/hip ratio (Sung and Ryu, 2004), body mass (Daniels et al., 1996; Garrison et al., 1987; Rocchini et al., 1987), adiposity (Daniels et al., 1996; Garrison et al., 1987), visceral fat (Faria et al., 2002) and LBM (Daniels et al., 1996).

Arterial blood pressure (BP) may be expressed as the product of cardiac output (Q) and peripheral vascular resistance (PVR), $BP=Q \times PVR$ (Ganong, 2003; Hanson, 1984). Although chronic elevation in Q may lead to hypertension, it is mostly chronic elevations in PVR that cause hypertension. Overweight and obese individuals are characterized by increases in plasma volume, pre-load and after-load and Q (Carroll et al., 1995; Crandall et al., 1986; Frohlich et al., 1983; Messerli et al., 1983; Redon, 2001; Rocchini, 1990; Schmieder and Messerli, 1987). The additional blood flow is diverted mainly to the non-adipose tissues (i.e. gastrointestinal tract, kidneys, heart and brain (Rocchini, 1990). It may also lead to abnormal hypertrophy in these organs (Carroll et al., 1995). Several factors have been shown to increase plasma volume and Q in obese

individuals, including increased sodium retention, increased sympathetic nervous system activity (Rocchini, 1990), and diets high in salt (Andersson et al., 1984; Lev-Ran and Porta, 2005).

Hypertension is also associated with PVR (Cooper, 2004; Frohlich et al., 1983; Hall, 2003). The increase in PVR is probably a consequence of increased arterial stiffness (Franklin, 2004) and increased sympathetic nervous activity (Hall, 2003; Lev-Ran and Porta, 2005). An important mechanism in the development of hypertension is increased activity of the renin-angiotensin-aldosterone system (Cooper, 2004; de Paula et al., 2004; Romero and Reckelhoff, 1999; Sowers et al., 2001). The renin-angiotensin-aldosterone system contributes to the regulation of BP, vascular tone and sodium and water balance (de Paula et al., 2004; Lev-Ran and Porta, 2005; Lingappa, 2003). Renin is secreted from the juxtaglomerular cells (in the kidney). In plasma, renin catabolises angiotensinogen to angiotensin I. In the lungs, angiotensin I is converted (by angiotensin converting enzyme-ACE) to angiotensin II, a powerful arterial and endothelial vasoconstrictor that in turn increases BP (Cowley and Roman, 1996; Lev-Ran and Porta, 2005; Lingappa, 2003). When angiotensin II reaches the adrenal cortex, it causes the secretion of aldosterone, which enhances retention of sodium and water by the kidney (Hall, 2003; Hall et al., 1999).

High levels of sodium (salt) intake are also associated with increase sympathetic nervous system as the kidney needs to maintain pressure natriuresis (excretion of sodium by kidneys) to maintain sodium balance that in turn leads to increase systemic BP (Hall et al., 2003; Lev-Ran and Porta, 2005). Other mechanisms that may affect the sympathetic and renin-angiotensin-aldosterone systems include hyperinsulinemia, fatty acids, increased leptin levels (hyperleptinemia) (Crandall et al., 1986; Hall et al., 1999; Haynes et al., 1997; Shek et al., 1998; Tack et al., 1996) and increased levels of endothelin-1 (Egan et al., 1987; Lembo et al., 1992) and norepinephrine (Baron, 1994).

Many individuals with hypertension demonstrate various combinations of increased blood glucose levels, triglycerides and hyperinsulinemia (Lembo et al., 1992). Hyperinsulinemia and hyperleptinemia can lead to increased secretion of norepinephrine and increased activity of the sympathetic nervous system (Haynes et al., 1997; Shek et al., 1998; Tack et al., 1996; ter Maaten et al., 1998). In addition, hyperinsulinemia may lead to hypertension as it alters the haemodynamic responses (i.e.

increases stroke volume, Q and PVR), that in turn may increase SBP, DBP and mean arterial pressure (Baron, 1994; Baron and Brechtel, 1993).

Rocchini (1990) offered a model (Figure 2.4) to explain the development of hypertension in obese individuals. Increased adipose tissue leads to hyperinsulinemia, over-activation of the sympathetic nervous system and aldosterone levels that in turn cause increased sodium retention. Increased sodium retention leads to increase in plasma volume and Q that in turn, may lead to hypertension.

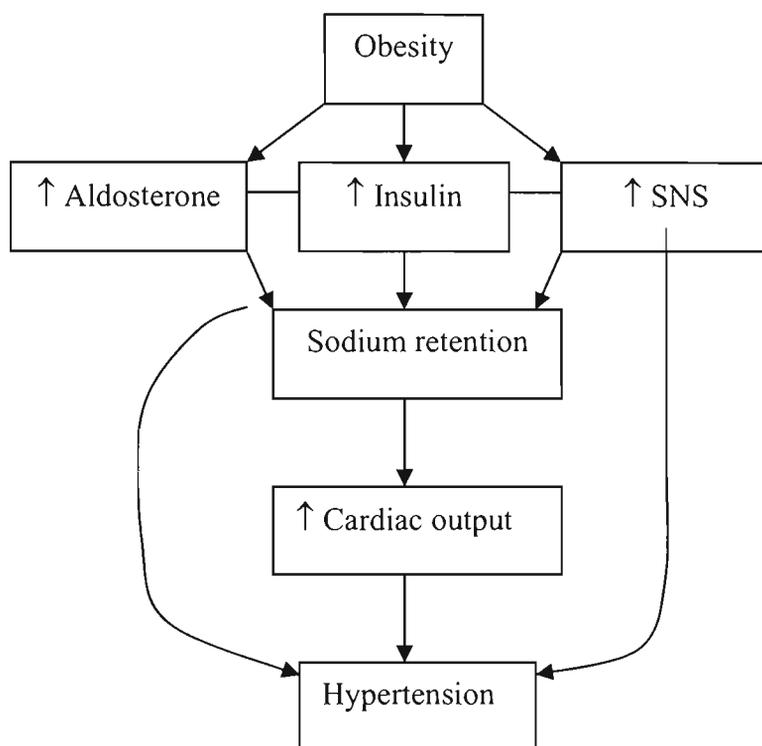


Figure 2.4. Mechanism of hypertension in obesity.

SNS (sympathetic nervous system). Based on Rocchini (1990).

2.2.4 Dyslipidemia

2.2.4.1 Epidemiology and clinical outcomes

In contrast to the other traditional metabolic risk factors, the number of people suffering from dyslipidemia has been in decline over the past five decades. In a recent survey from the US (Carroll et al., 2005), it was reported that between 1960 and 2002, the age-adjusted mean total cholesterol of individuals aged 20-74 years decreased from $5.75 \text{ mmol}\cdot\text{L}^{-1}$ to $5.26 \text{ mmol}\cdot\text{L}^{-1}$ and between the age of 60 to 74 years from $6.0 \text{ mmol}\cdot\text{L}^{-1}$ to $5.28 \text{ mmol}\cdot\text{L}^{-1}$ in men and $6.63 \text{ mmol}\cdot\text{L}^{-1}$ to $5.59 \text{ mmol}\cdot\text{L}^{-1}$ in women. These

reductions are all clinically significant. Similarly, the age-adjusted mean total for low-density lipoprotein (LDL) was reduced between 1976 and 2002 from $3.34 \text{ mmol}\cdot\text{L}^{-1}$ to $3.19 \text{ mmol}\cdot\text{L}^{-1}$ in all adults but also in men and women separately. High-density lipoprotein (HDL) levels did not change in men, but increased in women from $1.39 \text{ mmol}\cdot\text{L}^{-1}$ to $1.45 \text{ mmol}\cdot\text{L}^{-1}$ between 1976 and 2002. These improvements in lipid profiles may be partly explained by the counterbalancing influences of increased lipid levels due to poor diet and/or hyperinsulinemia, offset by increased prescription and use of lipid-lowering medications, particularly statins. It has been reported that in 1988-1994, 3.4% of adults (aged 20 years or older) were using lipid lowering medications, but by 1999-2002, this had increased to 9.3%. For the same time span, the percentages of individuals aged 60-74 who were prescribed lipid lowering medications jumped from 6.8% to 24.3% in men and 8.7% to 21.6% in women (Carroll et al., 2005).

It has been recognised that total cholesterol, HDL cholesterol and triglycerides are strongly associated with atherosclerosis and coronary artery disease (Farmer and Gotto, 1997). Currently, elevated levels of triglyceride ($>1.7 \text{ mmol}\cdot\text{L}^{-1}$) and/or low level HDL ($<0.9 \text{ mmol}\cdot\text{L}^{-1}$) are used as a cut-off level to identified individuals with high risk for T2DM and CVD (Zimmet et al., 2005). It has been shown that both triglyceride and HDL are strong predictors for future ischemic heart disease (Jeppesen et al., 1997). In addition, the Framingham Heart Study reported that individuals with $\text{HDL}<0.90 \text{ mmol}\cdot\text{L}^{-1}$ are at eight-fold increased risk for developing coronary artery disease, compared to individuals with $\text{HDL}>1.7$ (Gordon et al., 1977). The Veterans Affairs HDL Intervention Trial reported that for every 1% increase in HDL, there was a 3% reduction in death or myocardial infarction (Boden, 2000).

2.2.4.2 Aetiology

Dyslipidemias are characterised by abnormal levels of lipids in the blood (Farmer and Gotto, 1997) and are strongly associated with obesity. Markers of dyslipidemias include elevated total cholesterol (hypercholesterolemia), LDL, triglyceride and/or low levels of HDL (Farmer and Gotto, 1997; Grundy, 1998; Miranda et al., 2005). A major potential causative factor for hyper triglyceridaemia and/or low HDL is insulin resistance (although dyslipidemia can also lead to insulin resistance) (Miranda et al., 2005). Ginsberg (2000) offered a model to describe the connection between insulin resistance

and dyslipidemia (Figure 2.5). According to the model, under condition of insulin resistance, the capacity for uptake of free fatty acid (FFA) by fat cells is reduced while the release of FFA from fat cells and uptake by the liver is increased. However, as the liver has limited capacity to oxidise FFA, most FFA will be stored as triglyceride. An increased level of triglyceride in the liver leads to fatty liver (Ginsberg, 2000; Miranda et al., 2005). In addition, increased plasma glucose levels may also increase triglyceride synthesis in the liver that in turn increases very low-density lipoprotein (VLDL) and apolipoprotein B (apoB). Through the Cholesteryl ester transfer protein (CETP), VLDL exchanges triglyceride for cholesteryl ester (CE) from LDL and HDL. Lipoprotein lipase or hepatic lipase then changes triglyceride-rich LDL into small dense (SD) LDL. The reduction in HDL is partly explained by renal excretion of apolipoprotein A-1 (Ginsberg, 2000; Miranda et al., 2005).

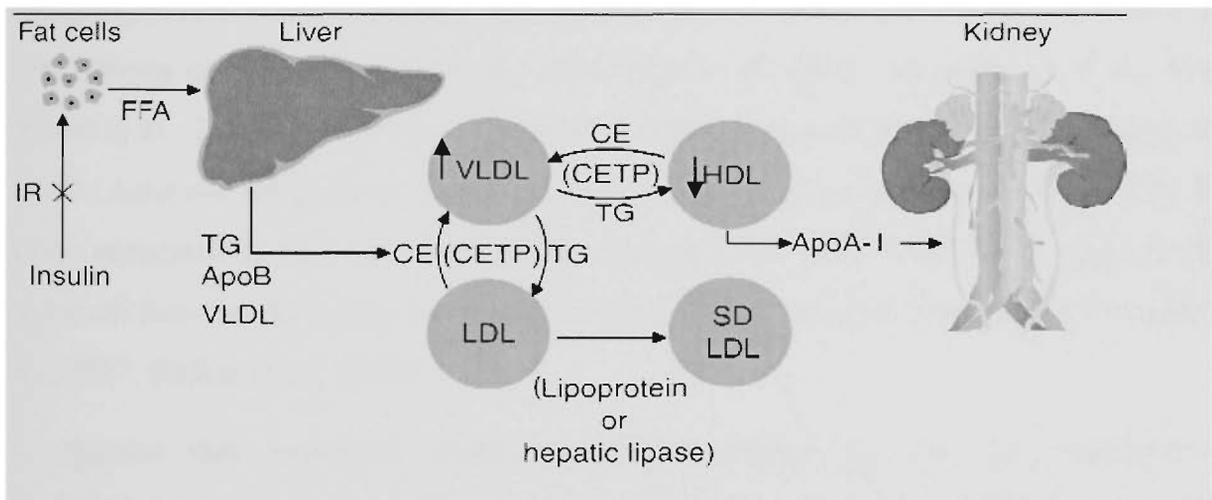


Figure 2.5. Insulin resistance and dyslipidemia.

IR (insulin resistance), FFA (free fatty acid), TG (triglyceride), ApoB (apolipoprotein B), VLDL (very low density lipoprotein), CE (cholesteryl ester), CETP (Cholesteryl ester transfer protein), ApoA-1 (apolipoprotein A-1), SD (small dense). Adapted from Ginsberg (2000).

2.3 Emerging metabolic risk factors

In recent years, other metabolic factors have been proposed as potential predictors of insulin resistance/T2DM and CVD. These include the inflammatory marker C reactive protein (CRP), and the proinflammatory cytokines, tumor necrosis factor (TNF)- α , interleukin (IL)-6, interleukin (IL)-1 β , interleukin (IL)-8, the hepatic enzyme gammaglutamyltransferase (GGT) and alanine aminotransferase (ALT) and brain-derived neurotrophic factor (BDNF).

2.3.1 Inflammatory markers

Increased levels of inflammatory markers are characteristic of individuals with HiMF and may also be a consequence of normal ageing (Das, 2002a; Grimble, 2003; Rutter et al., 2004; Sjöholm and Nystrom, 2005; Visser et al., 2002). It is now well accepted that increased levels of inflammatory markers may lead to HiMF and T2DM (Duncan et al., 2003; Festa et al., 2000; Hak et al., 2001; Han et al., 2002; Hotamisligil et al., 1993; Rutter et al., 2004). It has been suggested that they may also lead to atherosclerosis and CVD (Arroyo-Espliguero et al., 2004; Rutter et al., 2004; Verma and Yeh, 2003). The close associations between markers of inflammation, T2DM and CVD suggests that some of these markers may be useful for diagnosis in clinical practice (De Lorenzo et al., 2007; Ridker et al., 2004).

It appears that increased adiposity plays a crucial role in the regulation of proinflammatory cytokines (Bastard et al., 1999; Hak et al., 2001; Hofmann et al., 1994; Hotamisligil et al., 1993; Kennedy et al., 2004; Marcell et al., 2005). Increased levels of TNF- α have been associated with obesity (Hotamisligil et al., 1993; Miranda et al., 2005). It has been reported that TNF- α levels increase with BMI, body mass, percentage body fat, glycosylated hemoglobin (HbA1c) and waist to hip ratio (Rask-Madsen et al., 2003; Tsukui et al., 2000; Youd et al., 2000; Zahorska-Markiewicz et al., 2000). Furthermore, increase TNF- α is associated with increased levels of triglycerides and LDL and a reduction of HDL (Kume et al., 1998; Sherman et al., 1988; Szmitko et al., 2003).

There is a link between increased adiposity and increase levels of cytokines (Marcell et al., 2005; Miranda et al., 2005). The adipose cells secrete TNF- α and IL-6, it is possible

that an increased volume of adipose tissue may lead to increase level these cytokines (Das, 2002a). In addition, it has been revealed that in obesity and diabetes there is significant increase in TNF- α mRNA expression and TNF R2 receptors in adipose cells (Hofmann et al., 1994). TNF- α levels are also correlated with insulin resistance (Rask-Madsen et al., 2003; Tsukui et al., 2000). Some studies have demonstrated that infusion of insulin increases muscle glucose uptake by two-to-four fold (Rask-Madsen et al., 2003; Youd et al., 2000). Glucose uptake, however, was completely inhibited by the infusion of TNF- α (Hotamisligil et al., 1994; Hotamisligil et al., 1996; Hotamisligil et al., 1993; Rask-Madsen et al., 2003). TNF- α infusion inhibited also peripheral blood flow and capillary recruitment and prevented a reduction in vascular resistance (Youd et al., 2000). Finally, it has been reported that TNF- α may lead to insulin resistance as it increases serine phosphorylation (Kanety et al., 1995). This in turn, inhibits the insulin-stimulated tyrosine kinase phosphorylation of the insulin receptor and insulin receptor substrate (IRS)-1 (Hotamisligil et al., 1994; Hotamisligil et al., 1996; Kanety et al., 1995; Peraldi et al., 1996).

The production of CRP by the liver is stimulated by IL-6 (Bastard et al., 1999; Du Clos, 2000). It has been shown that elevated CRP is associated with higher BMI, body fat (Bastard et al., 1999; Marcell et al., 2005; Mendall et al., 1996; Visser et al., 1999) and dyslipidemia (Mendall et al., 1996). Furthermore, there is inverse correlation between CRP and exercise capacity (Marcell et al., 2005). It is important to note however, that although increased levels of CRP are associated with obesity, it has been suggested that these are increased independently of obesity (Festa et al., 2000; McLaughlin et al., 2002). It has been reported that increases in CRP is directly affected by the number of risk factors a person has rather than the degree of obesity per se (Festa et al., 2000).

The above data suggest that inflammatory markers play a major role in glucose metabolism, insulin resistance and T2DM (Koistinen et al., 2003; Mandarino, 1999; Perez-Martin et al., 2001). This raises the possibility of targeting them in intervention programs for individuals with HiMF. In addition it is important to study the association between the inflammatory markers, insulin resistance and glucose homeostasis in this population.

2.3.2 Hepatic enzymes

GGT and ALT are commonly used in clinical practice because they represent low-cost, sensitive and accurate markers to identify liver dysfunction (Emdin et al., 2005; Pompella et al., 2004). It has been reported that increased levels of GGT and ALT are positively associated with BMI, T2DM, lipids levels, BP, hypertensive medications, smoking, uric acid and negatively with physical activity levels and HDL (Brenner et al., 1997; Patel et al., 2007; Ruttman et al., 2005; Wannamethee et al., 1995; Wannamethee et al., 2005). Furthermore, these hepatic enzymes have a strong association with the development of CVD and may be used to indicate early metabolic abnormalities. (Lee et al., 2006; Lim et al., 2004; Onat et al., 2006). It has been reported that GGT plays a role in plaque formation during the atherosclerotic process by catalysing the oxidation of LDL (Paolicchi et al., 2004; Paolicchi et al., 2006). GGT and ALT are also believed to be an independent risk factor associated with CVD mortality (irrespective of alcohol consumption and liver disease) both in men and women (Conigrave et al., 1993; Ruttman et al., 2005; Wannamethee et al., 1995; Wannamethee et al., 2005). For instance, it has been reported that after hypertension and smoking, GGT ranks third as a risk factor for CVD mortality (Ruttman et al., 2005). In a study of 8,043 construction workers age 25-64, with 6 years follow-up, increases in GGT were associated with increases in relative risk for mortality (Brenner et al., 1997). The latter reported that compared to individuals with normal GGT levels ($<15 \text{ U}\cdot\text{L}^{-1}$), individuals with GGT of $15\text{-}19 \text{ U}\cdot\text{L}^{-1}$ had 1.46 relative risk for death, individuals with $20\text{-}29 \text{ U}\cdot\text{L}^{-1}$ had 1.78, individuals with $30\text{-}49 \text{ U}\cdot\text{L}^{-1}$ had 2.09 and individuals with $50 \text{ U}\cdot\text{L}^{-1}$ or more had 3.44 relative risk. Wannamethee et al. (1995) reported that GGT levels $>24 \text{ U}\cdot\text{L}^{-1}$ were associated with a significant increase in mortality from all causes (relative risk =1.22 or 818 deaths from 7613 middle-aged participants) during 11.5 years follow-up. Similarly, individuals with elevated ALT ($\geq 29 \text{ U}\cdot\text{L}^{-1}$) had 3.38 relative risk for T2DM, compared to individuals with ALT $<17 \text{ U}\cdot\text{L}^{-1}$ (Sattar et al., 2004). As GGT and ALT can add important treatment and prognostic information for individuals with metabolic and CVD, some investigators have suggested that these measurements should be added to the conventional risk factors list (Emdin et al., 2005; Perry et al., 1998).

2.3.3 Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is part of the neurotrophic factor family that is produced from the ventromedial hypothalamus (Fox and Byerly, 2004; Friedel et al., 2005; Kernie et al., 2000). BDNF contributes to the development of the brain by regulating synaptic plasticity, neurogenesis and neural survival (Mattson et al., 2004). It has been reported that BDNF assists in learning and memory (Tyler et al., 2002) and that low levels of BDNF are associated with the development of neuropsychiatric disorders such as depression and Alzheimer disease (Tsai, 2003). It has been hypothesised that BDNF (together with serotonin) regulates neural plasticity and survival through the activation of tyrosine kinase *trkB*, the insulin receptor substrate-proteins (IRS), phosphatidylinositol 3-kinase (PI3-K) and Akt (Mattson et al., 2004).

In the past decade, it has been revealed that BDNF influences the endocrine system. High levels of BDNF are thought to suppress appetite and may also be important in the control of blood glucose levels and insulin resistance (Lebrun et al., 2006; Nakagawa et al., 2000; Nonomura et al., 2001; Ono et al., 1997). BDNF may also enhance lipid metabolism (Tsuchida et al., 2002). It appears that the primary effect of BDNF hyposecretion is on food consumption (hyperphagia-overeating) that in turn may contribute to body weight gain and poor glycaemic control (Fox and Byerly, 2004; Kernie et al., 2000; Lebrun et al., 2006). BDNF infusion has been shown to suppress appetite and increase weight loss (Pelleymounter et al., 1995). Individuals with T2DM are reported to have lower levels of BDNF, compared to healthy individuals, and there is an inverse correlation between BDNF levels and fasting plasma glucose levels ($r=-0.3$, $p<0.01$) (Krabbe et al., 2007). In addition, it has been reported that high levels of glucose inhibit the output of BDNF from the brain (Krabbe et al., 2007). As discussed above, low levels of BDNF is associated with the development of neuropsychiatric disorders. This may help to explain how individuals with T2DM exhibit more neuropsychiatric diseases, compared to the general population (i.e. elevated blood glucose levels inhibits BDNF output that in turn, may lead to the development of neuropsychiatric diseases) (Allen et al., 2004; Krabbe et al., 2007). In contrast, others have reported increased BDNF levels with obesity, and decreased levels in individuals with anorexia nervosa (Monteleone et al., 2004). Suwa et al. (2006) reported that serum BDNF levels were elevated in newly diagnosed females with T2DM, compared to females with normal glucose tolerance. Moreover, they reported a positive correlation

between BDNF and BMI ($r=0.54$, $p<0.01$), percentage of body fat ($r=0.56$, $p<0.01$), triglyceride level ($r=0.47$, $p<0.05$), fasting glucose level ($r=0.44$, $p<0.05$) and insulin resistance ($r=0.51$, $p<0.05$). The authors suggested that BDNF levels are up regulated as a compensatory mechanism for the underlying pathological conditions. In addition, they hypothesised that the increased levels of BDNF are due to poor eating habits (Suwa et al., 2006). Further studies are needed in order to examine the association between BDNF level and other metabolic risk factors such as obesity, insulin resistance and dyslipidaemia in individuals with varying numbers of metabolic risk factors for T2DM and CVD. This was a focus of one of the studies in this PhD thesis.

2.4 Clusters of metabolic risk factors: pathophysiology

Elevated blood glucose and insulin resistance are major metabolic perturbations that characterise individuals with HiMF. Skeletal muscle is an important site for glucose disposal in the body (Shulman et al., 1990) and under normal conditions, more than 66% of the oral glucose ingested is disposed in skeletal muscle (Perez-Martin et al., 2001). The insulin resistance and metabolic alterations in this population appear to involve changes to skeletal muscle metabolism and structure. Several abnormal cellular insulin actions have been offered as sources of skeletal muscle insulin resistance. These include insulin receptor binding, alteration in insulin-signalling protein such as Akt and its 160 kDa (AS160) substrate, GLUT4, glucose oxidation and mitochondrial function. These cellular alterations may contribute to the reduction in glycogen synthesis, glycogen content and glucose disposal. (Mandarino, 1999; Perez-Martin et al., 2001). These metabolic abnormalities in individuals with HiMF may also be related to abnormal peripheral blood flow, alteration of endothelial function and secretion of proinflammatory cytokines.

2.4.1 Insulin-signalling and insulin resistance

2.4.1.1 Insulin receptor

The attachment of insulin to its receptor (insulin binding) is the first cellular action of insulin. It has been suggested that in most individuals with insulin resistance, the binding of insulin to its receptor within skeletal muscle is not compromised (Caro et al.,

1987; Mandarino, 1999), however, reductions in the number of insulin receptors have been reported in both obesity and T2DM (Caro et al., 1987; Lonroth et al., 1983; Pedersen et al., 1982). These data may explain the reduction in insulin sensitivity in some obese individuals (Caro et al., 1987; Mandarino, 1999; Perez-Martin et al., 2001). Overall, it appears that insulin receptor function is not compromised in diabetes. This suggests that the main reason for insulin resistance in obese individuals and patients with T2DM lies in down stream of the receptor (Kriketos et al., 1996; Wade et al., 1990).

2.4.1.2 Insulin pathways

Insulin has two major pathways of action, the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3-K) pathway. Both activated after the binding of insulin to the insulin receptor that in turn causes tyrosine autophosphorylation of the insulin receptor substrate-proteins (IRS) (Le Roith and Zick, 2001; Miranda et al., 2005; Myers and White, 2002; Saltiel, 1996; Virkamaki et al., 1999) (Figure 2.6). IRS proteins activate several downstream signalling proteins (protein-protein interaction) (Virkamaki et al., 1999). In the MAPK pathway (also known as Erk kinase pathway) the protein-protein signalling (interaction) include Shc, growth factor receptor binding protein-2 (Grb2), mammalian Son of Sevenless (mSOS) and Ras. The stimulation of Ras leads to a cascade of Raf to MEK and to the activation of MAPK (Le Roith and Zick, 2001; Miranda et al., 2005; Moodie et al., 2002; Virkamaki et al., 1999; Weng et al., 2001) (Figure 2.6).

The second pathway, The PI3-K pathway, is activated by tyrosine phosphorylation on the insulin receptor substrate protein (IRS 1-4) (Pratipanawatr et al., 2001). In turn, the phosphorylated IRS 1-4 engaged with P85, a regulatory subunit of the PI3-K. Activated PI3-K contains both P85 and P110 subunit that produce phosphatidylinositol 3,4,5-phosphate (PIP3). PIP3 triggers or activates Akt. It has been shown that Akt and AS160 (Cartee and Wojtaszewski, 2007) influencing protein synthesis, glucose transport, and glycogen synthesis, as well as having anti-lipolytic and anti-apoptotic effects (Figure 2.6 and also Figure 2.7) (Le Roith and Zick, 2001; Miranda et al., 2005).

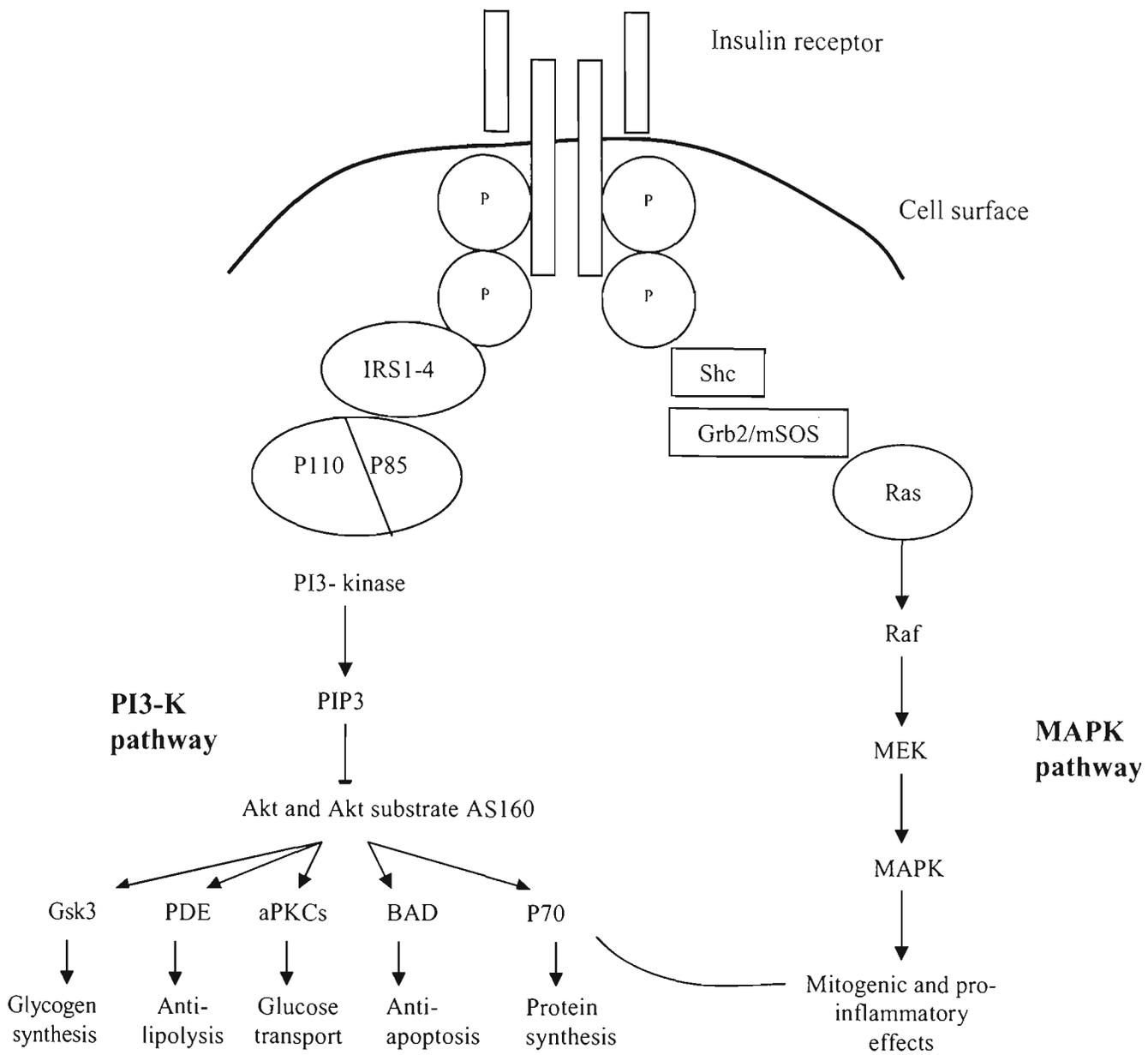


Figure 2.6. Insulin-signalling pathways.

MAPK (mitogen-activated protein kinase), PI3-K (phosphatidylinositol 3-kinase), P (phosphorylation), IRS 1-4 (insulin receptor substrate protein), Grb2 (growth factor receptor binding protein-2), mSOS (mammalian Son of Sevenless), Ras (a small G-protein), MEK (MAPK/ERK kinase) Gsk 3 (glycogen synthase kinase 3), PDE (phosphodiesterase), aPKCs (activated atypical protein kinase C), P70 (protein 70). Adapted from Le Roith and Zick (2001) and Miranda et al. (2005).

2.4.1.3 Changes in insulin-signalling in obesity and insulin resistance

Obesity and insulin resistance are characterised by a reduction of the ability of insulin to stimulate glucose uptake in skeletal muscle and adipose tissues (Dohm et al., 1988; Lockwood and Amatruda, 1983; Pratipanawatr et al., 2001). DeFronzo et al. (1985) reported 38% reduction in total body glucose uptake and 45% in leg glucose uptake in patients with T2DM, compared to healthy controls. In the past 15 years, evidence has accumulated to suggest that alterations in the insulin-signalling mechanism may be responsible for the reduction in glucose uptake that is associated with chronic

conditions such as obesity and T2DM (Cusi et al., 2000; Virkamaki et al., 1999). It has been demonstrated that in obese non-diabetic and normal weight hypertensive individuals, the insulin stimulation of the PI3-K pathway is abnormally reduced (Goodyear et al., 1995b) and sometimes almost absent in T2DM (Christ et al., 2002; Cusi et al., 2000; Krook et al., 2000; Krook et al., 2004; Lemieux et al., 2005). Similarly, Pratipanawatr et al. (2001) reported that insulin stimulation of IRS-1 tyrosine phosphorylation and insulin stimulation of the PI3-K is decreased in participants with a family history of T2DM. In contrast, the MAPK pathway is considered to be unaffected, suggesting that insulin resistance only affected the PI3-K pathway (Cusi et al., 2000).

As described previously, Akt and its substrate AS160 are important downstream proteins in the PI3-K pathway. They form an important link between the insulin-signalling cascade, glycogen and protein synthase and the translocation of GLUT4 from the cytoplasm to the membrane (Figure 2.6) (Krook et al., 2004; Le Roith and Zick, 2001; Miranda et al., 2005). It has been reported that both Akt (Krook et al., 1998) and AS160 phosphorylation (Jager et al., 2007; Karlsson et al., 2005) are reduced in individuals with T2DM and those who also have elevated levels of inflammatory markers. As such, it has been hypothesised that increased inflammation may reduce insulin-signalling in the PI3-K pathway and might also be a link between overweight and insulin resistance/T2DM (Hotamisligil et al., 1994; Hotamisligil et al., 1993; Hotamisligil and Spiegelman, 1994). Virkamake et al. (1999) have offered several possible explanations for the alteration in the insulin-signalling mechanism. These include mutation of the insulin receptor and IRS-1, and increases in plasma cell differentiation factor-1 (PC-1), rad (type of Ras protein that associated with T2DM) and hyperinsulinemia. Other factors that can lead to alterations in insulin-signalling include accumulation of FFA (Hawkins et al., 2003) leading to reduced tyrosine phosphorylation of IRS-1, PI3-K and P85/IRS-1 signalling (Miranda et al., 2005) and increased levels of leptin and proinflammatory cytokines (Myers and White, 2002; Virkamaki et al., 1999). Cytokines may reduce tyrosine phosphorylation from insulin-signalling (Hotamisligil et al., 1996; Peraldi et al., 1996). However, further studies are needed in order to examine the effect of inflammation and other metabolic risk factors associated with HiMF (such as body fat and dyslipidemia) on insulin-signalling proteins such as Akt and AS160. This is a focus of one of the studies in this thesis (Study Four).

2.4.1.4 Insulin stimulates glucose influx

A major facilitator of glucose influx is the glucose transport (GLUT) family (Douen et al., 1990; Gould and Seatter, 1997). An important GLUT within skeletal muscle and adipose tissues is GLUT4 (Douen et al., 1990; Klip and Paquet, 1990; Palfreyman et al., 1992). Insulin stimulation and muscle contraction (exercise) are the two main mechanisms that lead to translocation of GLUT4 to the plasma membrane (Douen et al., 1990; Hirshman et al., 1990; Klip and Paquet, 1990; Ploug et al., 1993) and as such, controlling blood glucose level (Klip and Paquet, 1990).

GLUT4 is sensitive to insulin (Douen et al., 1990; Gould and Seatter, 1997; Palfreyman et al., 1992) and with insulin stimulation the number of GLUT4 transporters in the plasma membrane increases by up to 1.5-fold (Douen et al., 1990) and glucose uptake in the muscles by almost two-fold (Dohm et al., 1988). As GLUT4 plays a crucial role in glucose metabolism, it has been hypothesised that GLUT4 is altered in obese individuals and individuals with insulin resistance (Garvey et al., 1991). Garvey et al. (1991) reported that compared to lean individuals, obese people have a reduction in the adipose cell membrane GLUT4 content and GLUT4 mRNA (by 40% and 36% respectively). Furthermore, they showed that the reduction in membrane GLUT4 content and GLUT4 mRNA is even more severe in patients with T2DM (by 85% and 86% respectively). Similar results have been reported in skeletal muscle. Dohm et al. (1991) and Kennedy et al. (1999) reported that GLUT4 protein was reduced by 18-32% in skeletal muscle of obese and individuals with T2DM compared to lean individuals. Pedersen et al. (1990) however, reported no change in GLUT4 protein concentration or in GLUT4 mRNA in obese individuals and patients with T2DM compared to lean individuals. This inconsistency may indicate that the skeletal muscle insulin resistance state is largely due to alterations in the insulin-signalling cascade (such as Akt), rather than in GLUT4 *per se* (Zorzano and Camps, 1997).

2.4.1.5 Muscle contraction stimulate glucose influx

Muscle contraction (similar to insulin stimulation) increases glucose influx to the muscle by increasing the number of GLUT4 in the plasma membrane (Christ et al., 2002; Douen et al., 1990; Garthwaite and Holloszy, 1982; Goodyear et al., 1990b; Lemieux et al., 2005; Ploug et al., 1984; Ploug et al., 1993). The correlation between GLUT4 and contraction stimulated glucose uptake is between 0.48 to 0.95 (Brozinick Jr et al., 1993; Henriksen et al., 1990). An important factor is that the increase in membrane permeability (more GLUT4) to glucose by muscle contraction occurs even in the absence of insulin (Douen et al., 1990; Garthwaite and Holloszy, 1982; Goodyear et al., 1990a; Goodyear et al., 1990b; Horton et al., 1995; Ploug et al., 1984; Ploug et al., 1993; Sternlicht et al., 1989).

It is well accepted that muscle contraction-stimulated GLUT4 translocation and insulin-stimulated GLUT4 translocation occurs via two different pathways (Christ et al., 2002; Douen et al., 1990; Goodyear et al., 1990b; Horton et al., 1995; Idstrom et al., 1986; Jessen and Goodyear, 2005; Ploug et al., 1987; Ploug et al., 1993; Sternlicht et al., 1989). Although it has been shown that insulin and contraction stimulated GLUT4 translocation pathways are separate, it has been suggested that at some stage the pathways converge (Goodyear et al., 1995a; Tomas et al., 2002). Studies reported that in young non-obese individuals (Houmard et al., 1999; Youngren et al., 2001) and in healthy rats (Chibalin et al., 2000; Peres et al., 2005), short-term aerobic training (muscle contraction) increases phosphorylation of the insulin receptor and IRS1 suggesting that the convergence occurs at the insulin receptor. Most studies however, including studies involving healthy young people, middle-aged individuals, obese individuals and those with hypertension, have indicated that the convergence between the two pathways is in downstream signalling at the level of Akt or AS160 (Cartee and Wojtaszewski, 2007; Goodyear et al., 1995a; Kramer et al., 2006; Lemieux et al., 2005; Tanner et al., 2002b; Treadway et al., 1989).

The pathway through which exercise stimulates GLUT4 is not fully understood (Horton et al., 1995; Jessen and Goodyear, 2005; Tomas et al., 2002). Several mechanisms have been offered as possible explanations for GLUT4 translocation during contraction. These include activation of AMP-activated protein kinase (AMPK), bradykinin and/or Akt and AS160, (Figure 2.7) (Cartee and Wojtaszewski, 2007; Christ-Roberts et al., 2004; Jessen and Goodyear, 2005).

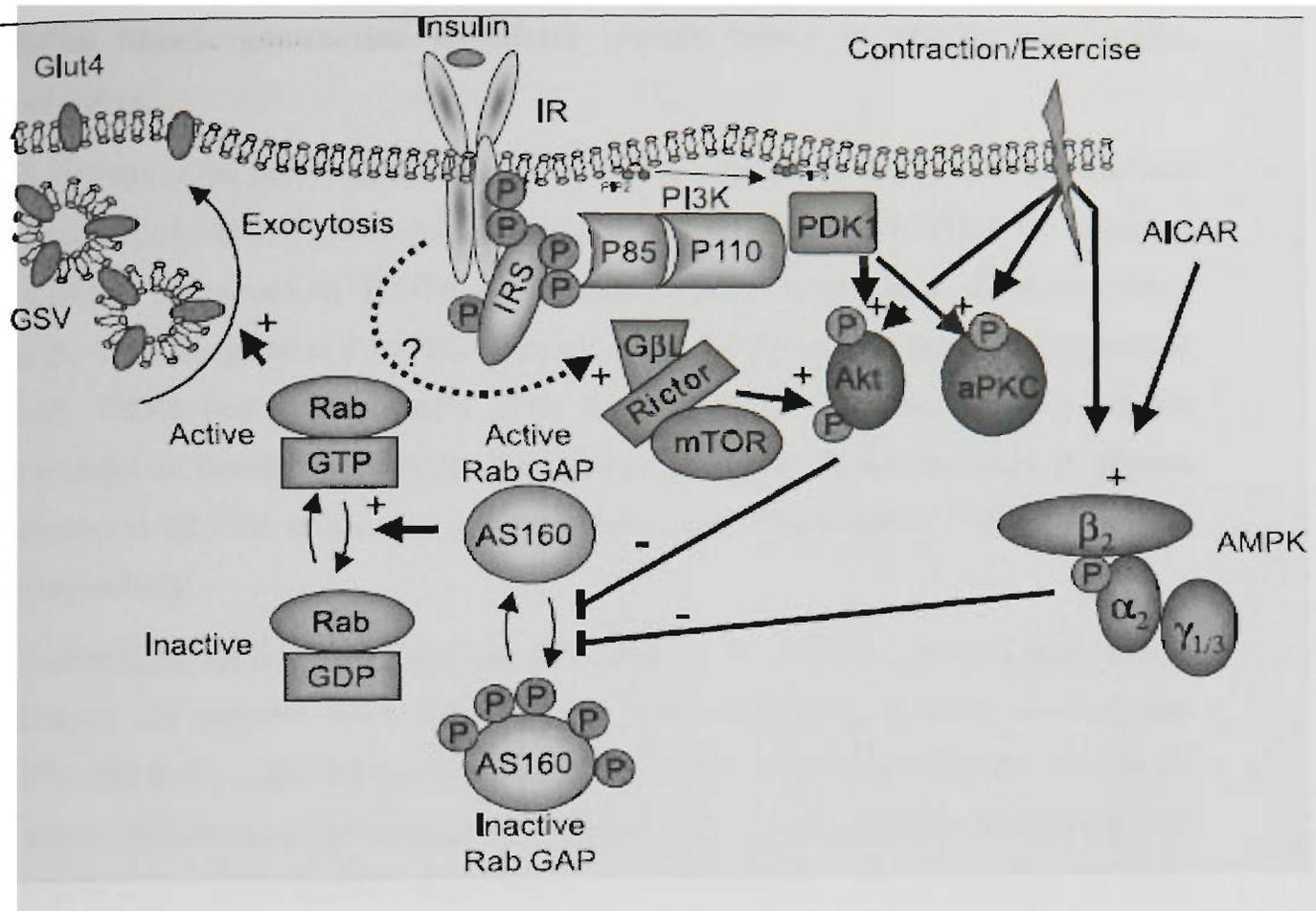


Figure 2.7. The role of AS160 in muscle contraction and GLUT4 translocation.

IR (insulin receptor), AICAR (5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside), IRS (insulin receptor substrate), P85/P110 (regulatory/catalytic subunits of phosphatidylinositol 3-kinase, PI3K), PDK1 (phosphatidylinositol dependant kinase 1), aPKC (atypical protein kinase C), AMPK (AMP-activated protein kinase), AS160 (Akt substrate), GSV (GLUT4 glucose transporter storage vesicles). Adapted from Cartee and Wojtaszewski (2007).

2.4.1.6 Muscle contraction stimulates glucose influx in obesity and insulin resistance

In contrast to the pathological changes to insulin-stimulated GLUT4 translocation and glucose uptake (PI3-K pathway) in obesity, insulin resistance and T2DM, the influence of muscle contraction on GLUT4 remains intact (Christ-Roberts et al., 2004; Henriksen et al., 1990; Megeney et al., 1993). Kennedy et al. (1999) reported that although patients with T2DM had approximately 32% lower plasma membrane GLUT4 content compared to healthy individuals, both groups exhibited similar increases in plasma membrane GLUT4 levels after an acute bout of aerobic exercise (71% versus 74% respectively).

Furthermore, some studies, but not all (Christ et al., 2002), reported that aerobic training can improve some defects in the insulin-signalling proteins in obese rats (Hevener et al., 2000; Saengsirisuwan et al., 2004). It has been reported that even in the absence of changes in tyrosine phosphorylation of the insulin receptor, IRS, PI3-K, Akt and in some cases GLUT4 (Lemieux et al., 2005) after aerobic training, glycogen synthesis and glucose disposal increased (Christ-Roberts et al., 2004; Goodyear et al., 1995a; Lemieux et al., 2005). These data emphasise that exercise can improve insulin sensitivity and glucose metabolism even in the absence of changes in the PI3-K pathway (Christ et al., 2002) and GLUT4 (Lemieux et al., 2005). Furthermore, it indicates that GLUT4 translocation is not an essential mechanism for training-induced improvements in insulin action and glucose metabolism (Lemieux et al., 2005). Moreover, it highlights the importance of exercise for glucose metabolism and glucose homeostasis in healthy individuals, and importantly in obese people and those with insulin resistance and T2DM (Hughes et al., 1993; Kennedy et al., 1999). It may also demonstrate the importance of including exercise in therapeutic / preventive regimens for individuals with HiMF.

2.4.2 Skeletal muscle structure and insulin resistance

2.4.2.1 Muscle morphology

Skeletal muscle contains different types of fibres (Merrifield and Atkinson, 2000; Pette and Staron, 2000). Muscle fibres can be characterized according to their structure and function. Muscle fibres may be categorized according to structure and function as

follows: (i) slow, fatigue-resistant, aerobically active (containing a high number of mitochondria) fibres, known as type I fibres (Goldspink, 1983, 1999; Mancini et al., 1989; Pette and Staron, 2000; Schiaffino and Reggiani, 1994), and (ii) type II fibres that may further be categorized into two subgroups including type IIa, and type IIb (Essen et al., 1975; Peter et al., 1972). Type IIb fibres are fast, develop high tension, and are easily fatigued (Peter et al., 1972; Schiaffino and Reggiani, 1994).

Neuromuscular activity is essential for building specific muscle fibre phenotypes and to maintain their properties (Pette and Staron, 2000). When the neuromuscular activity is insufficient (i.e. inactivity, immobilization, bed rest, ageing) this will induce atrophy of both slow and fast fibres (Ansved, 1995; Danieli-Betto et al., 1995; Hickey et al., 1995; Klueber et al., 1989; Kriketos et al., 1996; Lillioja et al., 1987; Marin et al., 1994; Marin et al., 1992; Tanner et al., 2002a; Wade et al., 1990).

There is substantial evidence to indicate that alterations in skeletal muscle fibre types, mainly a reduction in percentage of type I fibres and an increase in percentage of type II fibres, are associated with obesity, glucose intolerance and T2DM (Hickey et al., 1995; Kriketos et al., 1996; Marin et al., 1994; Tanner et al., 2002a). Studies have revealed that fatter individuals have higher percentages of fast fibre types (r between 0.40 to 0.49) (Hickey et al., 1995; Kriketos et al., 1996; Lillioja et al., 1987; Staron et al., 1984; Wade et al., 1990) and lower percentages of type I fibres (r between -0.39 to -0.68) (Hickey et al., 1995; Kriketos et al., 1996; Marin et al., 1994; Tanner et al., 2002a).

As type I fibres are characterised by high capillary density (Essen et al., 1975; Saltin and Gollnick, 1983), lipid storage capacity (Bonen et al., 1981), insulin binding (Essen et al., 1975; James et al., 1985), insulin-stimulated glucose uptake (Henriksen et al., 1990; Megeney et al., 1993; Ploug et al., 1987), high GLUT4 content (Essen et al., 1975; Horton et al., 1995; Zorzano and Camps, 1997) and high oxidative enzymes activities (Castillo et al., 1994; Hickey et al., 1995; Horton et al., 1995). This may support the hypothesis that alteration of fibre types may contribute to obesity and insulin resistance (Hickey et al., 1995; Marin et al., 1994). Additionally, it suggests that the pathology in obesity and HiMF is within the skeletal muscle rather than limitation in insulin delivery (Castillo et al., 1994; Hickey et al., 1995; Marin et al., 1994).

Some studies, however, have reported no differences in skeletal muscle fibre types between lean and obese individuals (Kelley and Simoneau, 1994). He et al. (2001) reported no significant differences in muscle fibre types I, IIa and IIb among obese

people, patients with T2DM and lean people. It appears that other factors (such as, increase muscle lipid content and a reduction in oxidative enzyme activity) rather than muscle fibre type alteration *per se* may contribute to the development of obesity and insulin resistance. This may indicate that the alteration in fibre types that was described previously as a cause for obesity and abnormal glucose metabolism is not aetiological, rather, both phenomena happen simultaneously due to other factors (i.e physical inactivity and poor diet).

2.4.2.2 Mitochondria and oxidative enzymes

Obese individuals and patients with T2DM exhibit reductions in oxidative enzyme activity and oxidative capacity of skeletal muscle (He et al., 2001; Kriketos et al., 1996). A reduction in oxidative enzyme activity may be an important contributor to the development of obesity and T2DM (Kelley et al., 2002). Reductions in oxidative capacity of skeletal muscle in obese individuals and people with T2DM may be related to mitochondrial dysfunction or reduced mitochondrial numbers. Kelley et al. (2002) reported that the mitochondria of obese people and patients with T2DM are smaller by up to 35%, compared to lean people of similar age. Moreover, in 30% of the obese people and 40% of the patients with T2DM, mitochondrial membrane structure was thicker, compared to lean controls. They also reported positive correlations between mitochondrial size and glucose disposal rate ($r=0.72$). Reductions in mitochondrial size accompanied by increases in membrane thickness may explain the reduction in muscle oxidative capacity in obese people and in patients with T2DM. The authors suggested that the reduction in mitochondrial size of these populations is probably due to sedentary lifestyle or/and excess exposure to long-chain fatty acid CoA (Kelley and Simoneau, 1994) that in turn may lead to a reduction of muscle capacity to utilise fat as a source of energy (Yki-Jarvinen et al., 1987). Also, it is possible that reductions in FFA metabolism may be related to reductions in type I fibres and capillary density as well reductions in oxidative metabolism as discussed previously. These data emphasise the important role that skeletal muscles play in glucose metabolism and glycaemic control (Eriksson et al., 1997; Kelley et al., 2002). It may also demonstrate the importance of targeting skeletal muscle in any intervention program (Baron, 1994; Clark et al., 2003).

2.4.2.3 Glycogen synthesis

It has been long believed that intrinsic skeletal muscle abnormalities, including reductions in glycogen synthesis and oxidative capacity, are important mechanisms that may lead to obesity (DeFronzo et al., 1985; Kriketos et al., 1996; Lillioja et al., 1987; Shulman et al., 1990), insulin resistance and T2DM (DeFronzo et al., 1985; Katz et al., 1983; Shulman et al., 1990).

Skeletal muscle is an important site for glucose disposal in the body (Shulman et al., 1990). The main pathway of glucose disposal within muscle, both in healthy and diabetic individuals, is glycogen synthesis (Cline et al., 1999; Katz et al., 1983; Shulman et al., 1990).

Individuals with HiMF are characterised by a reduction in glucose metabolism. It is possible that the reduction in glucose uptake in muscle is related to impaired glycogen synthesis within skeletal muscle (Shulman et al., 1990). The latter reported up to 60% reduction in the rate of glycogen synthesis in patients with T2DM, compared to healthy controls, suggesting that the primary intracellular metabolic defect responsible for the decrease in glucose metabolism in patients with T2DM is impaired glycogen synthesis (Marin et al., 1992). Similarly, Cline et al. (1999) reported that patients with T2DM demonstrated lower whole body glucose metabolism and muscle glycogen synthesis (by up to 80%) compared to healthy individuals. The authors also reported a reduction in GLUT4, and concluded that in patients with T2DM, the main cause for impaired glycogen synthesis was a reduction in insulin-stimulated GLUT4 translocation (Cline et al., 1999).

However, impaired glycogen synthesis *per se* may not be the cause of abnormal glucose uptake in skeletal muscle. The positive correlation between type I fibres and glycogen synthesis and negative correlation between type II fibres and glycogen synthesis (Essen et al., 1975; Lowry et al., 1978) suggests that the initial problem may be a reduction in slow twitch fibres that in turn decreases oxidative metabolism (He et al., 2001; Henriksen et al., 1990; Kelley et al., 2002; Kriketos et al., 1996; Megeney et al., 1993; Ploug et al., 1987).

2.4.2.4 Muscle capillarisation.

The intrinsic skeletal changes in obese individuals and individuals with insulin resistance include not only abnormal muscle fibre types but also alterations to skeletal muscle capillarisation (Honig et al., 1982; Lillioja et al., 1987; Murrant and Sarelius, 2000; Sarelius et al., 2000). Muscle capillary content is one of the main factors that determine muscle blood flow and oxidative and metabolic capacities (Lillioja et al., 1987; Marin et al., 1994). It has been demonstrated that there are negative correlations between capillary density and obesity level, and capillary density and fasting glucose and insulin concentrations (for all $r = \sim -0.46$) (Lillioja et al., 1987). Lillioja et al. (1978) also reported positive correlation between muscle capillary density and insulin action ($r = 0.63$). These findings may suggest that an abnormal reduction in muscle capillary content may be an important factor associated with insulin resistance due to at least two factors: 1) a reduction in the amount of insulin available to muscle via circulating blood, and/or 2) an increase in diffusion distance from the capillary to the muscle fibres that may compromise insulin diffusion and availability (Kriketos et al., 1996).

On the other hand, Saltin et al. (1979) and Eriksson et al. (1994) reported the opposite phenomena in a 15-year longitudinal study of 29 individuals with impaired glucose tolerance. During the follow up period, 13 patients developed T2DM. Surprisingly, these patients had higher numbers of capillaries around all muscle fibre types compared to the patients with impaired glucose tolerance, and there were strong positive correlations between capillaries per muscle fibre and insulin levels ($r = 0.82$) in response to a glucose load (OGTT). It is possible that the increases in capillaries served as a compensatory mechanism for the reduction in capillary insulin diffusion and metabolic capacity (Baron et al., 1991; Baron et al., 1990; Ciaraldi, 2002; Eriksson et al., 1994).

2.4.3 Blood flow and metabolic abnormalities

Peripheral blood flow is a major factor determining substrate availability to skeletal muscle (Baron, 1994; Dawson et al., 2002; Eringa et al., 2004; Nuutila et al., 1996; Raitakari et al., 1996; Rattigan et al., 1997; Scott et al., 2002). Under normal conditions, a number of hormones, including insulin, act as blood flow mediators (Anderson et al., 1991; Bonadonna et al., 1998; Clark et al., 2003; Coggins et al., 2001; Dawson et al., 2002; Raitakari et al., 1996; Rattigan et al., 1997). It has been suggested that in

individuals with HiMF, insulin-mediated vasodilatation and blood flow are impaired, thereby contributing to insulin resistance and glucose intolerance (Baron et al., 2000; Laakso et al., 1992; Zierler, 1961). Insulin-mediated glucose uptake (IMGU) depends on both arteriovenous glucose difference (A-VG diff, represents glucose extraction that in turn represents tissue permeability) and blood flow (F) (represents the rate glucose and insulin are delivered). $IMGU=(A-VG \text{ diff})\times F$ (Laakso et al., 1992), and any reduction in tissue permeability and/or blood flow (delivery) may lead to a reduction in IMGU (Baron et al., 2000). It has been reported that following a bolus dose of insulin, leg blood flow increased two-fold in lean and obese people, but did not change in individuals with T2DM and it was concluded that changes in both muscle permeability to glucose and blood flow were responsible (Laakso et al., 1992). Others reported that even apparently-healthy obese individuals have lower vasodilatory responses to insulin, compared to lean individuals (Dela et al., 1995a; Tack et al., 1996; Utriainen et al., 1997). It appears that in some people with HiMF, there is a reduction in the ability of insulin to stimulate an increase in blood flow to skeletal muscle.

2.4.4 Endothelial function and vascular resistance

The endothelium is the innermost layer of blood vessels and is very important for vascular homeostasis (Guerci et al., 2001b; Masaki et al., 1991). The endothelium also controls vasoconstriction and vasodilatation of blood vessels, and helps to maintain blood flow, systemic BP and fluid balance (Guerci et al., 2001b; Li and Forstermann, 2000). There is a close association between the presence of metabolic risk factors and endothelial dysfunction (Caballero, 2003).

It has been shown that endothelial structure and function are altered by risk factors such as obesity, hypertension, hypercholesterolemia, inflammation, smoking and ageing. (Caballero et al., 1999; Ganz and Vita, 2003; Luscher et al., 1991; Unger, 2002). As previously discussed (see Hypertension: Aetiology), increased insulin resistance, hypertension and obesity are associated with elevated levels of catecholamines (Caballero et al., 1999) and endothelin-1 (Caballero et al., 1999; Hickey et al., 1985; Yanagisawa et al., 1988). Both catecholamines and endothelin-1 are very powerful arterial vasoconstrictors (McAuley et al., 2000) that increase PVR. These risk factors and the increased levels of vasoconstrictor hormones, may expose the endothelium to

increased mechanical forces that impair the endothelium-dependent control mechanisms including the vasodilatation responses to insulin, acetylcholine and nitric oxide (NO)(Ganz and Vita, 2003; Li and Forstermann, 2000; Noris et al., 1995; Verma et al., 2003; Werns et al., 1989; Yanagisawa et al., 1988).

Caballero (2003) offered a model (Figure 2.8) to describe the contribution of obesity and insulin resistance to endothelial dysfunction. The mechanisms involved in the development of endothelial dysfunction include: fat-derived metabolic products, hormone secretion (such as leptin), and proinflammatory agents. In turn, insulin resistance and endothelial dysfunction increases as obesity increases. Also, the endothelial function is affected by conditions such as hyperglycemia, hypertension and dyslipidemia (Grassi et al., 2004) .

Increased levels of vasoconstrictor hormones, and an increase in blood vessel water content (a hallmark of obesity), may also decrease elastic properties of the blood vessels and increase collagen content leading to blood vessel stiffness. It has been suggested that “vascular stiffness” limits peripheral (particularly to the skeletal muscle) blood flow (Maxwell et al., 1998). It may also cause a reduction in oxidative perfusion and increased afterload (the resistance/pressure against which the left ventricle ejects blood). It has been suggested that conditions that cause a disruption of vasodilator agents activity will lead to a reduction in exercise capacity (Tooke, 1999; Tooke and Hannemann, 2000). Furthermore, arterial stiffness and endothelial dysfunction are affected by, and also contribute to the development of insulin resistance, T2DM, hypertension and CVD (Cooper, 2004; Fishman, 1979; Ganz and Vita, 2003; Guerci et al., 2001a; Nakamura et al., 2004; Pinkney et al., 1997; Schieffer et al., 1995; Shimokawa, 1999; Verma et al., 2003; Zelis and Flaim, 1982).

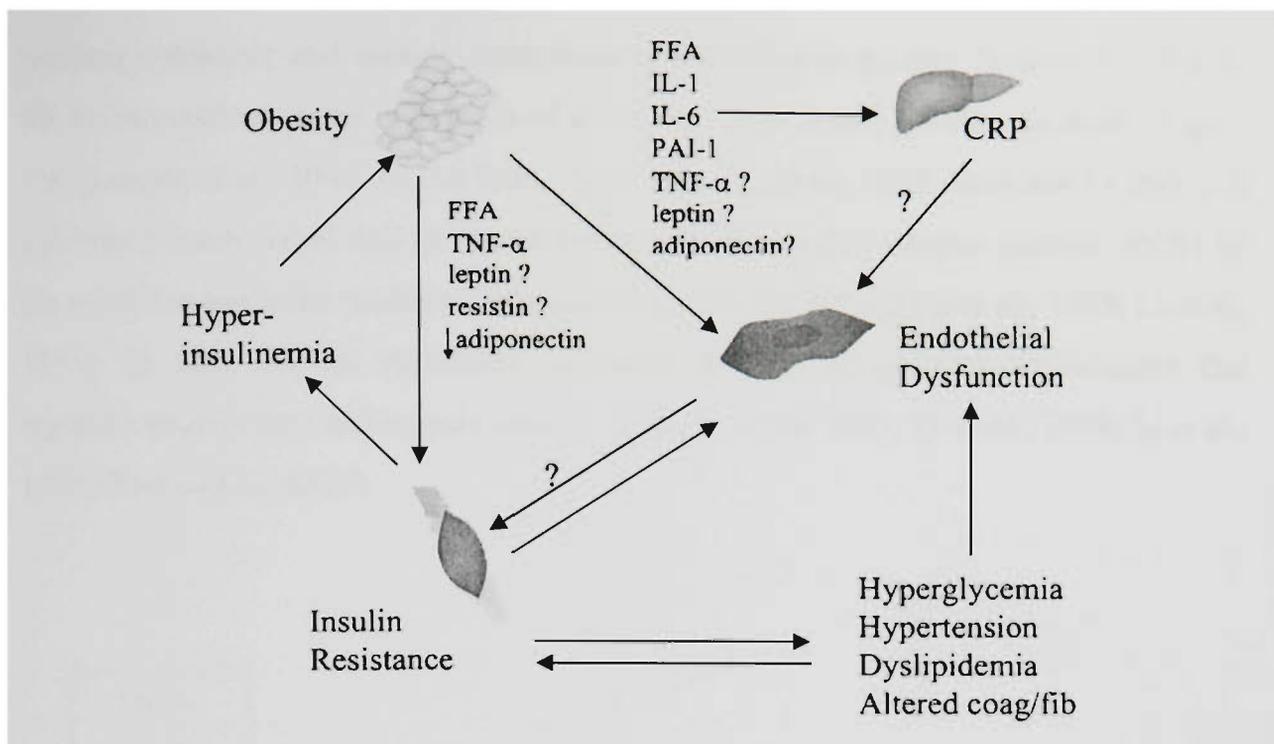


Figure 2.8. Mechanisms through which obesity, insulin resistance and endothelial dysfunction are closely associated.

Adapted from Caballero (2003).

2.4.5 Inflammatory markers and skeletal muscle abnormalities

Increased levels of proinflammatory markers are characteristic of individuals with HiMF and may also be a consequences of normal ageing (Das, 2002a; Grimble, 2003; Rutter et al., 2004; Sjöholm and Nystrom, 2005; Visser et al., 2002). Both inflammation and ageing, are associated with catabolic/cachectic effects on skeletal muscle (Alloatti et al., 2000; Espat et al., 1994; Farber and Mannix, 2000; Grimble, 2003; Tisdale, 1999; Visser et al., 2002). Increased levels of cytokines are associated with loss of muscle strength (Alloatti et al., 2000; Visser et al., 2002). It has been showed that TNF- α infusion can reduce total skeletal muscle amino acid concentration by 20% over six hours (in rats) (Tayek, 1996). Similarly, Lang et al. (2002) reported that following 24 h infusion of TNF- α , global protein synthesis in skeletal muscle (myofibrillar and sarcoplasmic proteins) was reduced by 39% and in the heart by 25%. Several links between cytokines and protein loss have been demonstrated. These include a reduction in mRNA translation efficiency (the first stage in the translation of mRNA into protein) due to alteration in cap-binding protein complex eIF-4E availability (Lang et al., 2002), platelet-activating factor (PAF) and NO (Alloatti et al., 2000). Another proposed link

between cytokines and muscle catabolism is alteration in nuclear factor-kB (NF-kB). NF-kB is involved in the regulation of genes involved in cell growth and death (Figure 2.9) (Langen et al., 2001; Li and Reid, 2000, 2001; Li et al., 1998; Reid and Li, 2001). It has been demonstrated that increased production of reactive oxygen species (ROS) by the mitochondria is the mediator between cytokines and NF-kB (Li et al., 1999; Li et al., 1998). In turn, NF-kB stimulates increased activity of ubiquitin/proteasome that regulates protein loss and muscle atrophy (Langen et al., 2001; Li et al., 1999; Li et al., 1998; Reid and Li, 2001).

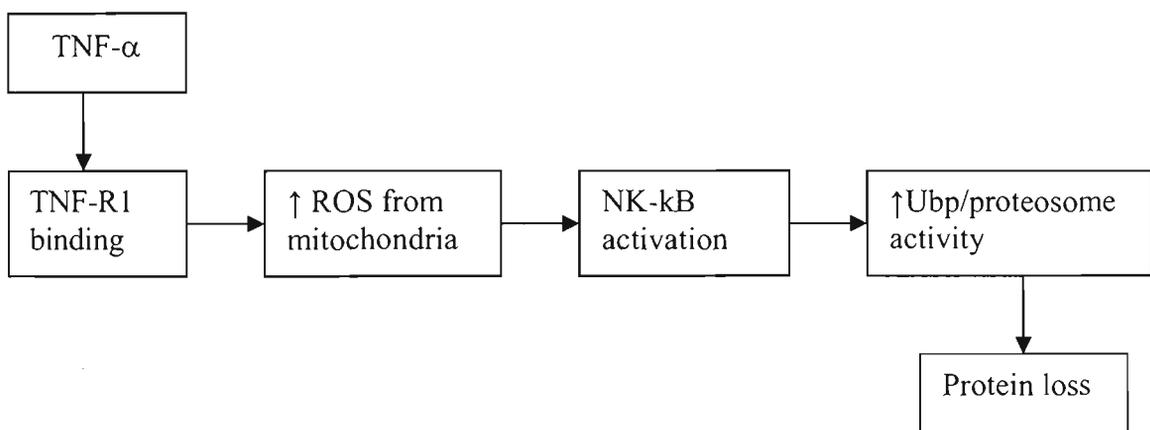


Figure 2.9. *TNF-α and muscle catabolism.*

TNF (tumor necrosis factor), TNF-R1 (type 1 TNF-α receptor), ROS (reactive oxygen species), NK-kB (nuclear factor kB), Ubq (ubiquitin). Adapted from Reid and Li (2001).

In summary, increase levels of proinflammatory cytokines contribute to the development of insulin resistance and HiMF. They are also associated with loss of muscle mass and strength. As such, any intervention in individuals with HiMF should target the reduction in proinflammatory markers and promote increase of muscle mass and strength.

2.5 Associations between metabolic risk factors and functional capacities and quality of life

Muscle atrophy and strength loss, and changes in muscle structure and metabolism are common characteristics of individuals with HiMF and T2DM (Nyholm et al., 1997; Vaag et al., 1992; Willey and Fiatarone-Singh, 2003; Yki-Jarvinen and Koivisto, 1983). It has been reported that muscle strength and aerobic fitness are inversely associated with HiMF (Jurca et al., 2004; LaMonte et al., 2005). Impaired capacity to perform activities of daily living (ADL's) and lower self-perceived physical, emotional and social quality of life (QoL) are also associated with increased cardiovascular risk profiles (Chambers et al., 2002; Doll et al., 2000; Katz et al., 2000; Ko, 2006; Rejeski et al., 2006). However, these studies included patients who had already developed overt cardiac disease, including coronary artery disease and heart failure. It is possible that these reductions in the capacity to perform ADL's and QoL were skewed by the influence of symptomatic cardiac disease. It remains unclear if individuals with HiMF, in the absence of symptomatic heart disease also have impaired capacities to perform ADL's and lower self-perceived QoL.

There is controversy in regard to the effect of overweight *per se* on QoL of obese individuals. Some reviews have suggested impaired capacity to perform ADL's and lower self-perceived physical, emotional and social QoL in obese individuals (Fontaine and Barofsky, 2001; Kushner and Foster, 2000). It has been reported that an increase in body mass is associated with self-perceived reduction in the capacity to perform some ADL's (such as walking and climbing stairs) (Stewart and Brook, 1983). It has also been reported that obese individuals have lower positive mood states, and increased incidence of anxiety and depression (Sullivan et al., 1993), body-image dissatisfaction and binge-eating (Kushner and Foster, 2000). Fontaine et al. (1996) and Fine et al. (1999) reported that obese individuals have lower scores in all eight scales of the SF-36 questionnaire (including physical functioning, role physical, bodily pain, general health vitality, social functioning, role emotional and mental health) compared to the general population. Moreover, Fontaine et al. (1996) reported that the main effect of obesity was on bodily pain (indicates increase in pain) and vitality. An increase in bodily pain is a common finding in obese individuals and it may be used as an independent predictor for self-perceived QoL (Barofsky et al., 1997). These findings are similar to

other reports indicating that obesity impacts on self-perceived physical and mental health indicators (Han et al., 1998; Mannucci et al., 1999; Marchesini et al., 2000).

In contrast, some studies have reported inverse relationships between overweight and mental health (as measured by depression), known as the “jolly fat” hypothesis (Crisp and McGuiness, 1976). The inverse relationship between overweight and lower depression and anxiety is particularly observed in working class men, aged 40 yr or older (Crisp and McGuiness, 1976; Crisp et al., 1980). More recently studies have reported that being overweight is associated with lower risk of depression (Li et al., 2004; Palinkas et al., 1996). In their study, Palinkas et al. (1996) reported that middle-aged and elderly individuals with BMI<25 had significantly higher levels of depression (as measured by the Beck Depression Inventory) compared to middle-aged and elderly individuals with BMI>30. The odds ratio for depression in overweight (BMI 25-29.9) compared to normal weight (BMI<25) individuals was 0.34 and the odds rate between obese (BMI>30) and normal weight individuals (BMI<25) was 0.28. This indicates that at least in some individuals the “jolly fat” hypothesis is supported by the evidence.

2.6 Influences of ageing on skeletal muscle, functional capacities and quality of life

2.6.1 The effect of ageing on skeletal muscle

Muscle atrophy and strength loss, and changes to muscle fibre types are common characteristics of individuals with HiMF (Nyholm et al., 1997; Vaag et al., 1992; Willey and Fiatarone-Singh, 2003; Yki-Jarvinen and Koivisto, 1983). As most individuals with HiMF are middle-aged or older (Ford et al., 2002), these characteristics may not be related solely to the development of the condition but may also be consequences of normal ageing. There is a similarity between the deteriorations of skeletal muscle and the cardiovascular system due to ageing and that caused by poor lifestyle, inactivity, bed rest and muscle disuse (Bloomfield, 1997; Convertino, 1997; Convertino et al., 1997; Danieli-Betto et al., 1995; Grimby et al., 1982; Hagerman et al., 2000; Hunter et al., 2000; MacDougall et al., 1980; Tanaka et al., 2004).

Sarcopenia, from Greek “poverty of flesh” (Roubenoff and Hughes, 2000), and reduction in aerobic capacity are part of normal ageing (Evans, 1997; Fleg and Lakatta,

1988; Grimby and Saltin, 1983; Iannuzzi-Sucich et al., 2002; Mishra and Misra, 2003; Roubenoff and Hughes, 2000). Sarcopenia may be accelerated by poor nutrition, increased proinflammatory cytokines, mitochondrial dysfunction, hormonal alteration and physical inactivity (Castaneda et al., 1995; De Los Reyes et al., 2003; Fiatarone-Singh, 1998; Lamberts et al., 1997; Mishra and Misra, 2003; Poehlman, 1999; Roubenoff and Hughes, 2000).

It has been suggested that muscle mass, muscle cross-sectional area and muscle strength are reduced by 18-40% between the second and ninth decades of life (Bemben, 1999; Grimby et al., 1982; Larsson, 1983; Larsson et al., 1979; Lexell et al., 1986; Proctor et al., 1995; Rogers and Evans, 1993; Runnels et al., 2005; Thompson, 1994). In addition there is a reduction in the transcription and synthesis of myosin heavy chains (Balagopal et al., 1997; Balagopal et al., 2001). The high correlation between lean muscle mass and muscle strength ($r=0.75$ to 0.9) suggests that reduction in muscle strength with ageing is probably a result of reductions in muscle mass and cross-sectional areas (Balagopal et al., 1997; Grimby et al., 1982). Although there is a significant reduction in muscle mass and muscle cross-sectional areas with ageing, some studies have reported that ageing has limited effect on muscle fibre composition (Essen-Gustavsson and Borges, 1986; Grimby et al., 1984; Grimby and Saltin, 1983; Houmard et al., 1998; Proctor et al., 1995; Thompson, 1994). Essen-Gustavsson and Borges (1986) reported no significant difference in muscle fibre type I, IIA and IIB between healthy individuals aged 20, 30, 40, 50, 60 and 70 yr, despite a lower muscle area in the elderly individuals.

It appears that muscle enzyme activities are less affected by ageing than muscle structure (Grimby, 1995; Grimby et al., 1982; Larsson, 1983; Rogers and Evans, 1993; Thompson, 1994). Some investigators reported no change in the muscle oxidative enzymes citrate synthase (CS) (Borges and Essen-Gustavsson, 1989; Proctor et al., 1995), Succinate dehydrogenase (SDH) (Proctor et al., 1995) and 3-hydroxyacyl-CoA-dehydrogenase (HAD) (Borges and Essen-Gustavsson, 1989; Essen-Gustavsson and Borges, 1986) or the glycolytic enzymes lactate dehydrogenase (LDH) (Borges and Essen-Gustavsson, 1989; Essen-Gustavsson and Borges, 1986) and creatine phosphokinase (CPK) (Borges and Essen-Gustavsson, 1989; Essen-Gustavsson and Borges, 1986) with ageing.

In contrast, other investigators reported significant reductions in muscle enzymes activity with healthy elderly populations (Coggan et al., 1993; Larsson, 1978; Larsson et

al., 1978; Orlander et al., 1978) including 20-24% reduction in CS (Coggan et al., 1993; Coggan et al., 1992; Essen-Gustavsson and Borges, 1986; Houmard et al., 1998) and ~25% reduction in SDH and HAD (Coggan et al., 1992). These changes, to some extent, may be related to alterations in mitochondrial structure and function with ageing (Pesce et al., 2001). These discordant findings maybe the result of differences in populations studied, differences in physical activity habits between the participants, and malnutrition / anorexia and disuse associated with ageing (Larsson, 1983; Thompson, 1994).

Between the second and eighth decades there is a significant alteration in the LBM quantity and quality (Hunter et al., 2000; Roubenoff and Hughes, 2000). There is a negative correlation between age and LBM ($r=-0.39$) (Hunter et al., 2000). In the second decade, muscle mass represents 59% of the LBM, mostly made up of myocytes, (the other major components being water and connective tissue(Bemben et al., 1995)), but this has declined to 46% by the eighth decade (Ellis, 1990; Roubenoff and Hughes, 2000). Furthermore, with ageing, there are overall reductions in LBM and increases in body fat (Bemben et al., 1995; Ellis, 1990).

In addition to the changes in skeletal muscle, it has been reported that there are many cardiovascular alterations associated with normal ageing, but affected by an overhang of CVD processes. These include increases to one or more of arterial stiffness, BP, cardiac mass, left ventricular remodelling and alterations to diastolic filling patterns and reductions in stroke volume and Q (Benetos et al., 2002; Cheitlin, 2003; Geokas et al., 1990; Isoyama and Nitta-Komatsubara, 2002; Lewis and Maron, 1992; Oxenham and Sharpe, 2003). These cardiovascular changes may accrue independently of cardiovascular risk factor (Benetos et al., 2002; Lewis and Maron, 1992) and together with the alteration in muscle mass and muscle respiratory capacity may lead to reductions in aerobic capacity with ageing (Figure 2.10) (Cheitlin, 2003; Coggan et al., 1993; Fleg and Lakatta, 1988; Fletcher et al., 2001; Geokas et al., 1990; Houmard et al., 1998; Oxenham and Sharpe, 2003; Proctor and Joyner, 1997).

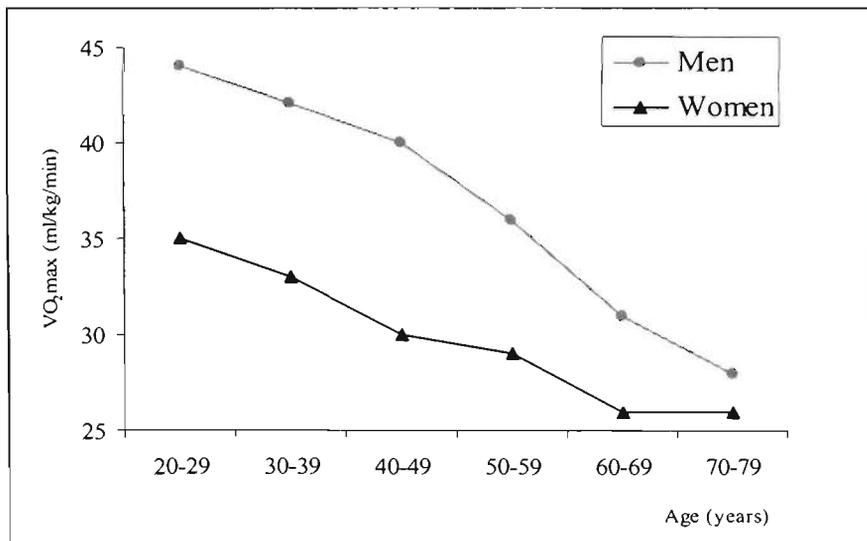


Figure 2.10. Maximum aerobic capacity declines with advancing age

Adapted from Oxenham and Sharpe (2003).

2.6.2 The effect of ageing on functional capacity and quality of life

Alterations to muscle and reductions in muscle strength may lead to increase disability and impaired capacities for ADL's in the elderly (Evans, 1997; Foldvari et al., 2000; Guralnik et al., 1995; Guralnik et al., 1994; Hausdorff et al., 2001; Poehlman, 1999; Rantanen et al., 1999). This include a reduction in self-selected walking speed (Bassey et al., 1988; Bassey et al., 1992; Fiatarone et al., 1990; Kwon et al., 2001; Wolfson et al., 1995) and walking distance (Bassey et al., 1988), chair rise and stair climbing (Bassey et al., 1992) and poor balance and coordination (Duncan et al., 1992; Hausdorff et al., 2001; Wolfson et al., 1995). Furthermore, a reduction in muscle strength is associated with a reduction in immune function (Castaneda et al., 1995) and increased risk for respiratory abnormality (Arora and Rochester, 1982).

Muscle strength is an important factor that contributes to falls in the elderly (Wolfson et al., 1995). The significant fear of falling is not only in the physical aspect (i.e. injuries related to falls include hip fractures, bruising and soft tissue injury) (Nevitt et al., 1989), but also from the psychological aspect. Fear of falling may limit ADL's in the elderly that in turn may reduce the QoL (Cummings and Nevitt, 1994). In addition, it has been reported that psychological factors such as depression are important predictors of falls. As such, interventions that improve muscle strength and psychological well-being may

in turn lead to a reduction in falls which may translate to an improvement in QoL (Cesari et al., 2002)

2.7 Pharmacotherapy for individuals with clusters of metabolic risk factors

As discussed previously, HiMF represents metabolic risk factors for T2DM and CVD and as such, it should be targeted vigorously in order to keep the risk factors within a desirable target (Hanefeld and Schaper, 2005). It appears that the treatment for the HiMF encompasses two main parts, lifestyle modifications including improvements to diet and exercise / physical activity (will be discussed later) and pharmacological interventions (Hanefeld and Schaper, 2005; Pi-Sunyer, 2006). It has been suggested that each one of the risk factors present should be targeted in a specific manner (Reaven, 2006).

2.7.1 Pharmacotherapy for obesity

The range of pharmacological options for obesity include three main modes of action: modification of appetite (less food intake), increased thermogenesis (increase energy expenditure), and inhibition of nutrient absorption from the gastrointestinal tract (Alemany et al., 2003; Bray, 2001; Das and Chakrabarti, 2006; Fernandez-Lopez et al., 2002; Pi-Sunyer, 2006). Currently, there are many classes of drugs that are prescribed to treat obesity (Bray, 2001; Spanswick and Lee, 2003), but the three most commonly prescribed drugs are sibutramine, orlistat, and phentermine (Alemany et al., 2003; Das and Chakrabarti, 2006; Pi-Sunyer, 2006).

Sibutramine is a tertiary amine that originally was developed as an antidepressant (James et al., 2000). It may assist in appetite control as it acts as an inhibitor of adrenaline and serotonin reuptake (Fernandez-Lopez et al., 2002; James et al., 2000; Pi-Sunyer, 2006). Randomised clinical trials (sibutramine versus placebo) have shown that the weight loss with the active compound persists for up to 2 years, with associated reductions in hunger and anticipation of food consumption (Hansen et al., 1998, 1999; James et al., 2000; Walsh et al., 1999). The average weight loss with sibutramine in comparison to placebo was 4.5 kg over 12 months (Li et al., 2005). Some studies

however, but not all (Finer et al., 2000), reported that thermogenic effect of sibutramine is accompanied by significant increases in adrenaline secretion, heart rate (HR), BP and plasma glucose level (Hansen et al., 1998). As such, people with known overt CVD were excluded from studies that examined the effect of the drug (Li et al., 2005). In addition, sibutramine has other side effects that include nausea and dry mouth (Hanotin et al., 1998; James et al., 2000). Finally, there is no scientific evidence that the treatment with sibutramine reduces morbidity or mortality from obesity associated disease (Li et al., 2005).

Orlistat is a gastrointestinal lipase inhibitor that reduces fat absorption by 30% (Davidson et al., 1999; Drent et al., 1995; Halford, 2004). It acts on the stomach duodenum wall by covering it with a hydrophobic surface-active layer that inhibits the action of pancreatic and gastric lipase (reduces the breakdown of ingested fat) (Comai and Sullivan, 1980; Halford, 2004; Yamamoto et al., 2000). It has been shown that lipase inhibitors can lead to a significant weight loss of 5 kg initially (but only ~3 kg compared to placebo) and less regain of weight over 2 years, compared to placebo (Davidson et al., 1999; Li et al., 2005; Sjostrom et al., 1998; Yamamoto et al., 2000). Furthermore, treatment with orlistat may lead to a reduction in plasma triglycerides, (Davidson et al., 1999; Yamamoto et al., 2000), total cholesterol, LDL and glucose and insulin concentration and BP (Davidson et al., 1999; Drent et al., 1995; Halford, 2004; Sjostrom et al., 1998). However, treatment with orlistat can cause fatty/oily stools, increased defaecation, oily spotting, liquid stools, flatus with discharge, abdominal pain and a reduction in the levels of vitamin D and E (Davidson et al., 1999; Drent et al., 1995; Li et al., 2005; Sjostrom et al., 1998).

Phentermine, similar to sibutramine, is an appetite suppressor which is thought to act by blocking serotonin reuptake in the brain. Treatment with phentermine can lead to a greater weight loss than placebo by ~3kg (Li et al., 2005; Maggio and Pi-Sunyer, 1997). Phentermine is usually prescribed short-term as the patient can develop tolerance (Bray, 2001; Li et al., 2005). Side effects from phentermine may include palpitation, tachycardia, hypertension and gastro-intestinal effects (Li et al., 2005)

It appears that the anti-obesity medications may enhance short term weight loss. However, they may have limited long-term benefits (Alemany et al., 2003; Astrup and Lundsgaard, 1998; Fernandez-Lopez et al., 2002). To date, most drug therapy for obesity has led to poor long term outcomes and in some cases even to addiction (drugs

based on amphetamine) (Bray, 2001). The overall weight loss (in comparison to placebo control) is less than 5 kg and there is lack of evidence for the effect of these drugs for changing long term prognosis from obesity related disease and QoL (Li et al., 2005). In addition, these drugs have some severe side effects that in turn may lower QoL and may lead patients to stop using them.

It the primary intervention for individuals with risk factors for CVD and T2DM should be lifestyle modification (diet and exercise). If lifestyle modification fails then specific pharmacotherapy can be used (Alemany et al., 2003; Maggio and Pi-Sunyer, 1997; Pi-Sunyer, 2006).

2.7.2 Pharmacotherapy for dyslipidaemias

Maintaining normal lipid levels is an important goal in clinical practice in order to prevent the development of coronary artery disease (Deedwania et al., 2006; Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol In Adults, 2001; Schuster et al., 2004; Wood, 1998). An important group of drugs for the treatment of dyslipidaemia are statins (Knopp and Paramsothy, 2006; Scheen, 2006; Stender et al., 2005). Statins prevent the formation of cholesterol by inhibiting the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate (Endres and Laufs, 2004). In addition, statins improve endothelial function (endothelium-dependent vasodilatation), probably by reducing oxidative stress (reduction of ROS) and promoting NO bioavailability (Endres and Laufs, 2004; John et al., 2001; John et al., 2005; O'Driscoll et al., 1997). Also, statins up-regulate the action of Akt, the protein that regulates many processes involved in body metabolism (see Figure 2.6) (Endres and Laufs, 2004), lower inflammation (CRP) and improve arterial stiffness (Albert et al., 2001; Matsuo et al., 2005).

Treatment with statins has anti-atherosclerotic effects (Matsuo et al., 2005) and can modify lipid profiles in individuals with dyslipidaemia (Deedwania et al., 2006; Hanefeld and Schaper, 2005). Statin treatment may also reduce LDL cholesterol, in 58-88% of the cases, to levels recommended by the European Second Joint Task Force (Stender et al., 2005). The latter also reported that triglycerides were reduced and HDL increased after treatment with statins. Similar results were reported in other studies that examined the effect of statins on blood lipid profile (Caslake et al., 2003; Deedwania et

al., 2006; Hunninghake et al., 2003). Ballantyne et al. (2003) and Schuster et al. (2004) for instance, reported that statin treatment reduced LDL by $\sim 40\%$, non-HDL cholesterol by $\sim 45\%$ and triglyceride by $\sim 20\%$ and increased HDL by $\sim 9\%$. In addition, it has been reported that statins (such as atorvastatin) can improve insulin sensitivity in insulin-resistant individuals (Huptas et al., 2006). Clinical benefits of statins include reduced mortality, and acute coronary events and the need for revascularisation in patients with coronary artery disease, with or without other risk factors (Pyorala et al., 2004). A prospective meta-analysis study of more than 90,000 participants reported that statin intervention may reduce the occurrence of coronary events and stroke by approximately 20% and all cause of mortality by 12% for each $\text{mmol}\cdot\text{L}^{-1}$ reduction in LDL cholesterol (Baigent et al., 2005).

2.7.3 Pharmacotherapy for type 2 diabetes

Lifestyle modification is the first treatment for T2DM. However, if it fails to maintain fasting blood glucose levels $< 7 \text{ mmol/L}$ and $\text{HbA1c} < 7\%$, it has been recommended to start with drug therapy with either sulfonylureas or metformin. If after 4-8 weeks of monotherapy blood glucose level is still $> 7 \text{ mmol/L}$ and $\text{HbA1c} > 7\%$, it has been recommended that a second oral hypoglycaemic agent should be added. If oral treatments fail, daily insulin injection may be recommended (DeFronzo, 1999; Goodarzi and Bryer-Ash, 2005; Tripathi and Srivastava, 2006). The effects of five T2DM medications: sulfonylureas, repaglinide, metformin, troglitazone and acarbose are presented in Table 2.4. From the five medications listed in the table, the two most frequently prescribed medications for patients with T2DM are sulfonylureas and metformin (DeFronzo and Goodman, 1995; Goodarzi and Bryer-Ash, 2005; Tripathi and Srivastava, 2006).

The main action of sulfonylureas is to increase insulin secretion by stimulating the beta cells in the pancreas (Davies, 2002; Siconolfi-Baez et al., 1990). Sulfonylureas have the best absolute effect on patients with T2DM with fasting plasma glucose level of $\geq 13.9 \text{ mmol}\cdot\text{L}^{-1}$ (Simonson et al., 1997). In addition, it has been suggested that patients with high levels of plasma C-peptide after a meal respond better to this treatment. In contrast, people who have lived with longstanding diabetes, and also those with a poor diet will be less affected by the treatment (Blaum et al., 1997). Approximately 75% of patients

treated with this drug will not achieve long term normalisation of glucose levels (DeFronzo, 1999).

Metformin is a biguanide type of medication and is the preferred medication for overweight patients with T2DM, as it can lead to weight loss and improve lipid profiles (Campbell and Howlett, 1995; DeFronzo, 1999; Fontbonne et al., 1996; Goodarzi and Bryer-Ash, 2005; Tripathi and Srivastava, 2006). Metformin reduces blood glucose levels by two main actions: inhibition of hepatic gluconeogenesis (glucose production by the liver) (Johnson et al., 1993; Matthaei et al., 2000; Reaven et al., 1992; Stumvoll et al., 1995; Tripathi and Srivastava, 2006; Wollen and Bailey, 1988), and increased tissue (mainly skeletal muscle) sensitivity to insulin (Johnson et al., 1993; Matthaei et al., 2000; Reaven et al., 1992; Stith et al., 1996). The increase in insulin sensitivity is related to up-regulation of the tyrosine kinase receptor (Goodarzi and Bryer-Ash, 2005; Stith et al., 1996), GLUT4 number and activity and glycogen synthesis (DeFronzo, 1999; Klip and Leiter, 1990). Similar to sulfonylureas, only ~25% of the patients on metformin are effectively managed with this drug. However, combination therapy of metformin and sulfonylureas is effective (DeFronzo, 1999; Reaven et al., 1992). Metformin has a positive effect on blood lipids profiles (Matthaei et al., 2000), including decreased levels of triglyceride and LDL cholesterol (Jeppesen et al., 1994; Reaven et al., 1992) and no change (Fontbonne et al., 1996) or small improvements in HDL cholesterol (Reaven et al., 1992). Treatment with metformin however, may lead to adverse reactions such as gastrointestinal disturbance (diarrhoea, abdominal discomfort and anorexia), lactic acidosis and a reduction in serum B12 levels (Goodarzi and Bryer-Ash, 2005).

In summary, drug therapies such as sulfonylurea or metformin, in addition to glycaemic control with diet have been shown to be an effective method of reducing plasma glucose levels in patients with T2DM. The effectiveness of these drugs as a mono-therapy however, is relatively short-lived and combination therapies are needed in order to achieve long term glucose control (Turner et al., 1999). However, even combination therapy fail to exert adequate glycaemic control when assessed over intervals of 5-10 years. This is most likely related to a progressive decline in insulin secretion as shown in the UKPDS study (Turner et al., 1999).

Table 2.4. Comparison of sulfonylureas, repaglinide, metformin, troglitazone and acarbose when used as monotherapy.

Drug	Sulfonylureas and Repaglinide	Metformin	Troglitazone	Acarbose
Mechanism of action	↑ insulin secretion	↓ hepatic glucose production, ↑ muscle insulin sensitivity	↓ hepatic glucose production, ↑ muscle insulin sensitivity	↓ GI absorption
Decrease in FPG level (mmol/L)	3.3-3.9	3.3-3.9	1.9-2.2	1.1-1.67
Decrease in HbA1c (% points)	1.5-2.0	1.5-2.0	1.0-1.2	0.7-1.0
Trig level	↔	↓	↓	↔
HDL cholesterol level	↔	↔↑	↑	↔
LDL cholesterol	↔	↓	↑	↔
Body mass	↑	↓	↑	↔
Plasma insulin	↑	↓	↓	↔
Adverse events	Hypoglycemia	GI disturbance, lactic acidosis (very rare)	Anemia, hepatic toxicity (sometime irreversible hepatic failure)	GI disturbances

FPG (fasting plasma glucose), GI (gastrointestinal), Trig (triglyceride), HDL (high-density lipoprotein), LDL (low-density lipoprotein). Adapted from DeFronzo (1999).

2.7.4 Pharmacotherapy for hypertension

There are many classes of anti-hypertensive drugs including beta-blockers, alpha-blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II antagonists, calcium channel blockers, diuretics, and aldosterone receptor blockers. The two major systems that these drugs aim to target are the sympathetic nervous system and the renin-angiotensin-aldosterone system (Ernsberger and Koletsky, 2006). Approximately two-thirds of hypertensive patients will be treated with two or more anti-hypertensive medications (Chobanian et al., 2003). Reductions in BP are essential as each 10 mmHg reduction in SBP may reduce mortality (by 15%), and the risk for myocardial infarction

(11%) and microvascular complications (retinopathy or nephropathy) (13%) (Adler et al., 2000). It appears that the most prescribed classes of drugs for the treatment of hypertension are ACE-inhibitors and beta-blockers (Sarafidis and Bakris, 2006).

ACE-inhibitors are vasodilators. The main action of this class of drug is to reduce BP and afterload by inhibiting angiotensin-mediated vasoconstriction (Cohn, 1973; Gersh, 2000). ACE-inhibitors cause direct smooth muscle relaxation and dilatation of arteries by preventing the conversion from angiotensin I to angiotensin II in the lungs (Gheorghide et al., 2000). ACE-inhibitors are widely used in the treatment of hypertensive individuals who also have T2DM as they reduce BP with no effect or even small benefits on insulin sensitivity and lipid metabolism (Giordano et al., 1995; Hauf-Zachariou et al., 1993; Lithell, 1991). In addition, ACE-inhibitors enhance endothelial function in patients with T2DM (O'Driscoll et al., 1999).

Beta-blockers inhibit the effects of over-activation of the sympathetic nervous system and reduce cardiovascular morbidity and mortality (Gersh, 2000; Packer et al., 2001; Poole-Wilson et al., 2003; Sharpe and Doughty, 1998; UK Prospective Diabetes Study Group, 1998). In the past, beta-blockers were not recommended as first choice for hypertensive individuals who also had insulin resistance or T2DM, as they had adverse effects on glycaemic control, insulin resistance and lipoprotein metabolism (Bell, 2004; Giugliano et al., 1997; Jacob et al., 1998; Jacob et al., 1996; Lithell, 1991; Sarafidis and Bakris, 2006). Some of the more recent beta-blockers also block alpha-1 receptors (e.g carvedilol and labetalol). This promotes vasodilatation and also may have favourable metabolic effects on insulin resistance and lipid metabolism (Jacob et al., 1998; Sarafidis and Bakris, 2006). It has been reported that treatment with carvedilol (a non-selective beta-blockers with alpha-1 blocking properties) has no adverse effect on metabolic parameters (Uzunlulu et al., 2006) and may even improve insulin resistance (Bakris et al., 2004; Jacob et al., 1996) and glucose (Bakris et al., 2004; Giugliano et al., 1997; Jacob et al., 1996) and lipid metabolism (increase HDL and decrease total cholesterol, LDL and triglycerides) in hypertensive individuals with and without T2DM (Giugliano et al., 1997; Hauf-Zachariou et al., 1993; Jacob et al., 1996; Seguchi et al., 1990).

Despite the pharmacological treatment for individuals with HiMF, it has been reported that 36% of individuals with hypertension and 77% of patients with hypercholesterolemia have not received optimal drug treatments (Wong et al., 2006). In

addition despite the drug therapy, the number of obese patients with T2DM has increased in recent years. It is likely that this has been caused by long term exposure to poor behavioural lifestyle (Blaum et al., 1997; Hu et al., 2001a). It is now well accepted that non-pharmacological interventions including lifestyle modifications should be the first line of intervention for individuals with HiMF and T2DM.

2.8 Non-pharmacological interventions for individuals with clusters of metabolic risk factors

Lifestyle modifications that include improvements to both diet and exercise are considered the cornerstone in the treatment of HiMF and should be the first intervention for preventing and managing metabolic risk (Hu, 2006; Maggio and Pi-Sunyer, 1997; Pi-Sunyer, 2006; Schulze and Hu, 2005; Stone and Saxon, 2005). Up to 60% of patients who adopt a healthy lifestyle can achieve clinically significant improvements in metabolic risk profiles, independent of drug treatments (Hu, 2006; Knowler et al., 2002; Tuomilehto et al., 2001).

2.8.1 Diet and weight loss

There is substantial evidence to demonstrate the benefits from diet and weight loss to reduce risk factors for CVD. There are many types of nutritional plans, most involving caloric restriction (Malik and Hu, 2007). It is not the focus of the work reported in this thesis to compare different dietary interventions in terms of metabolic effects. The following section briefly describes the benefits associated with diets (including caloric restriction) and weight loss in preventing and managing HiMF.

It is clear that diet modification and weight loss can lead to improvements in:

- Plasma glucose level HbA1c and the development of T2DM (Amatruda et al., 1988; Anderson et al., 1994; Henry et al., 1986a; Henry et al., 1986b; Kelley et al., 1993; Moreno et al., 2006; Pan et al., 1997).
- Hepatic glucose production (Kelley et al., 1993).
- Fasting plasma cholesterol, triglyceride and LDL levels (Anderson et al., 1994; Ebbeling et al., 2005; Kelley et al., 1993; Liu et al., 1985; Moreno et al., 2006).

- FFA (Henry et al., 1986a).
- HDL (Uusitupa et al., 1990; Wing et al., 1994).
- Insulin resistance and increases in insulin sensitivity and insulin secretion (Ebbeling et al., 2005; Gumbiner et al., 1990; Kelley et al., 1993; Moreno et al., 2006; Pittas et al., 2006).
- Inflammatory markers (e.g. CRP level) (Pittas et al., 2006).
- BP (Amatruda et al., 1988; Anderson et al., 1994; Moreno et al., 2006; Uusitupa et al., 1990).
- Medication use and costs for patients with T2DM (Maggio and Pi-Sunyer, 1997).

Despite the wide range of benefits from diet and weight loss, most diets fail (Ball et al., 2002). It has been reported that almost half of people who follow a weight loss diet regain all of the lost weight within a year, 3 in 4 (75%) regain weight within 3 years and only 1 in 20 (4.6%) successfully maintains the weight loss at 5 years (Crawford et al., 2000).

2.8.2 Exercise training interventions

2.8.2.1 Introduction

The mechanisation and computerisation of home and work environments has led to many people adopting sedentary lifestyles (Martinez-Gonzalez et al., 1999; Martinez, 2000; Pi-Sunyer, 2002). It has been reported that physical inactivity is a major risk factor threatening global health (Murray and Lopez, 1996). This is probably due to the direct association between physical inactivity and obesity (Cameron et al., 2003; Grundy et al., 1999; Martinez-Gonzalez et al., 1999; Martinez et al., 1999), T2DM (Helmrich et al., 1991; Hu et al., 2004a; Hu et al., 1999) and heart disease (Fletcher et al., 1996; Haskel, 1984; Smith et al., 1995) and negative associations with insulin sensitivity and glucose tolerance. In contrast, increases in exercise capacity may protect people from premature death (Erikssen et al., 1998). The latter reported that even a small improvement in physical fitness is associated with significantly lower mortality. Hawley (2004) suggested a model (Figure 2.11) to describe the relationship between

reductions in physical activity and the development of obesity, insulin resistance and T2DM. According to the model, reductions in physical activity lead to a reduction in aerobic power and alterations to skeletal muscle structure and metabolism, in turn leading to reductions in lipid oxidation and glucose uptake and increased muscle triglyceride and FFA content. These muscle alteration may increase insulin resistance and cause T2DM (Hawley, 2004).

It is now accepted that exercise training should be included as an integral part of the treatment / intervention for people who live with HiMF and T2DM (ACSM, 2000b; American Diabetes Association, 1999; Creviston and Quinn, 2001; Eriksson, 1999; Hagberg et al., 2000; Hu et al., 1999). The two most commonly used forms of exercise in people with chronic conditions, such as HiMF and T2DM, are aerobic and resistance trainings (ACSM, 2000b; Creviston and Quinn, 2001).

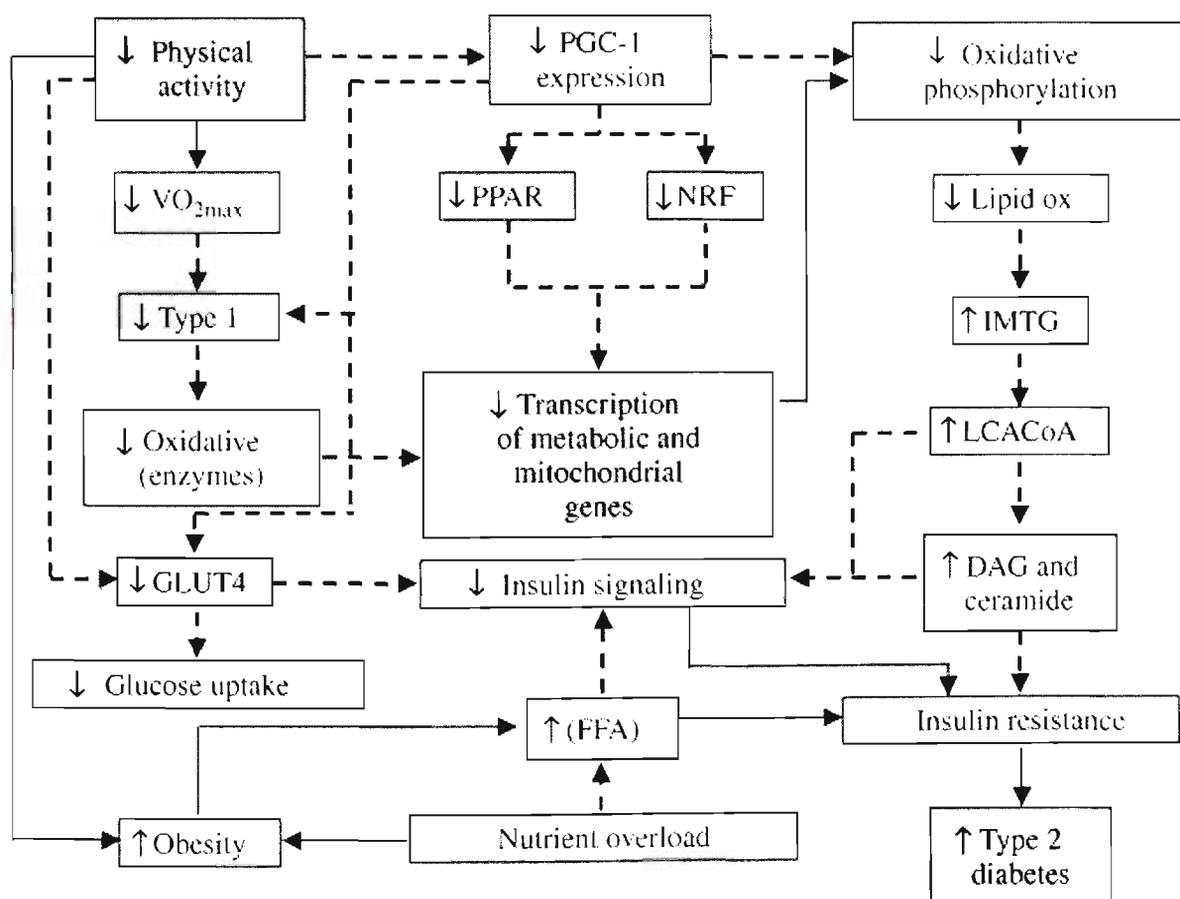


Figure 2.11. Relationship between physical inactivity and the development of obesity, insulin resistance and T2DM.

VO_{2max} (maximal oxygen uptake), PGC-1 (peroxisomal proliferator activator receptor coactivator), NRF (nuclear respiratory factor), FAT/CD36 (fatty acid transporters), FFA (free fatty acid), IMTG (muscle triacylglycerol), LCACoA (long-chain acyl CoA), DAG (diacylglycerol). Adapted from Hawley (2004).

2.8.2.2 Aerobic exercise training

Aerobic exercise training is the conventional and most frequently recommended exercise mode for obese people and/or those with hypertension and/or insulin resistance/T2DM (Buemann and Tremblay, 1996; Eriksson, 1999; Hagberg et al., 2000; Pescatello et al., 2004; Rissanen and Fogelholm, 1999). The metabolic benefits from aerobic exercise training are well established (ACSM, 2000b; Buemann and Tremblay, 1996; Koivisto and DeFronzo, 1984). Aerobic exercise, such as walking, running, cycling and swimming, involves large muscle groups and as such, they require large amounts of substrates (oxidation of glucose and fat). It has been reported that muscle glucose uptake can increase up to 20-fold during exercise (Eriksson, 1999).

Regular physical activity may assist by inhibiting the progression of HiMF and may lead to restoration of euglycemia and glucose homeostasis, and improve insulin sensitivity and lipid profiles (Borghouts and Keizer, 2000; Christ-Roberts et al., 2004; Christ et al., 2002; Colwell, 2003; Couillard et al., 2001; Dela et al., 1995b; Houmard et al., 2004; Koivisto and DeFronzo, 1984; Kraus et al., 2002; Marcell et al., 2005; Rinder et al., 2004; Sciacqua et al., 2003). The improvement in glucose metabolism may be related to increased GLUT4 level and activity in skeletal muscles (Christ-Roberts et al., 2004; Christ et al., 2002; Dela et al., 1994; Ferrier et al., 2004; Lemieux et al., 2005; Tomas et al., 2002) and the increased activation of glycogen synthase (Bak et al., 1989; Christ-Roberts et al., 2004; Lemieux et al., 2005) and glycogen storage (Borst and Snellen, 2001; Chibalin et al., 2000; Dela et al., 1995b).

Aerobic training increases VO_{2peak} (Christ-Roberts et al., 2004; Lee et al., 2005; Ligtenberg et al., 1997; Marcell et al., 2005; Trovati et al., 1984; Watkins et al., 2003), and an increase in VO_{2peak} is a strong predictor of all-cause mortality in both clinical and non-clinical populations (Blair et al., 1996). Other benefits from aerobic training include increases in oxidative enzyme activity (Dela et al., 1995b), weight loss (Alam et al., 2004; Buemann and Tremblay, 1996; Dumortier et al., 2003; Gwinup, 1975; Lee et al., 1994; Okura et al., 2005; Vanninen et al., 1992), a reduction in total and abdominal fat (Alam et al., 2004; Dumortier et al., 2003; Giannopoulou et al., 2005; Lee et al., 2005; Marcell et al., 2005; Savage et al., 2003) and a reduction of proinflammatory markers (Straczkowski et al., 2001). In addition, aerobic training inhibits and reduces the incidence of hypertension (Pescatello et al., 2004) by lowering SBP and DBP (Hagberg et al., 2000; Schneider et al., 1992; Sciacqua et al., 2003). Aerobic training

also lowers resting and submaximal heart rate (HR) (Krotkiewski et al., 1985; Schneider et al., 1984; Schneider et al., 1992) increases stroke volume and Q (ACSM, 2000b) and improves endothelial function (Sciacqua et al., 2003).

2.8.2.3 Aerobic exercise training: limitations

Despite the wide range of benefits from aerobic training, this form of exercise has some major limitations that should be addressed. The effect of aerobic exercise as a single intervention on weight loss is relatively limited (Bruce et al., 2004; Ferrier et al., 2004; Fiatarone-Singh, 1998; Giannopoulou et al., 2005; Krotkiewski et al., 1985; Watkins et al., 2003). Buemann and Tremblay (1996) in their review concluded that changes in body mass after aerobic training occur mainly when training was combined with weight loss diets. However, it is important to acknowledge that aerobic training can improve the lipoprotein profile of individuals with HiMF even without weight loss (Kraus et al., 2002).

The ability of some individuals to perform aerobic exercise may be limited, due to increased oxygen cost and mechanical work of breathing during exercise (Skinner, 1987). Other important factors that may lead to difficulties in adopting aerobic exercise training include significant comorbidity related to musculoskeletal pain (e.g. osteoarthritis) and/or low motivation (Focht et al., 2002; Focht et al., 2004; Willey and Fiatarone-Singh, 2003). Furthermore, some obese individuals with bad experiences in previous attempts to exercise may have negative feelings toward entering future exercise programs (ACSM, 2000a).

In addition, aerobic training is relatively ineffective for the preservation of muscle mass and strength or reversal of muscle wasting (Ballor et al., 1996; Dumortier et al., 2003; Fleg and Lakatta, 1988; Rinder et al., 2004; Segal et al., 1991; Straczkowski et al., 2001). It has been hypothesised that a training regimen that does not alter skeletal muscle mass, metabolism and strength, such as aerobic training, has a limited effect on age-related alteration in body composition and sarcopenia (Fiatarone-Singh, 1998), glycaemic control (Dumortier et al., 2003; Eriksson et al., 1997; Ferrier et al., 2004; Houmard et al., 2004; Ligtenberg et al., 1997; Watkins et al., 2003) and lipid profile (Dumortier et al., 2003; Ferrier et al., 2004; Rinder et al., 2004; Watkins et al., 2003).

Similarly, not all investigators have reported improvements in the inflammatory state of obese individuals after aerobic training (Marcell et al., 2005).

Some individuals with HiMF, particularly those with complications from diabetes, suffer from peripheral neuropathies that may diminish sensation of pain and lead to injury of their feet. As such, it has been recommended that these patients avoid exercises that demand weight bearing (such as treadmill walking, prolonged walking, jogging or step exercises) (American Diabetes Association, 1999). On the other hand, these individuals should be encouraged to perform exercise such as chair exercises, arm exercises or any other exercises that do not require weight bearing (American Diabetes Association, 1999). Increased levels of physical activity are thought to be very important for the long-term management for people with HiMF. Based on the limitations of aerobic training for these patients, alternative training modes including resistance exercise training should be explored, and this is one of the main foci of this thesis.

2.8.3 Resistance (strength) exercise training

2.8.3.1 Introduction

Resistance training (RT) is the preferred training regimen to increase muscle strength and mass both of which are important for the performance of ADL's in many populations including the young, elderly and those who suffer from chronic diseases (such as CVD and T2DM) (Abe et al., 2003; Abernethy et al., 1994; Castaneda et al., 2002; King, 2001; Kraemer et al., 2001; Levinger et al., 2005b; Maiorana et al., 2002; Pollock et al., 2000).

RT and aerobic training have different effects on health and fitness (Table 2.5). Resistance exercise is primarily an anaerobic activity, depending predominantly on muscle capacity to generate energy from adenosine-triphosphate (ATP) and phosphocreatine (Fleck and Kraemer, 1997). Although RT is primarily an anaerobic activity the stimulus for either muscle strength gain or muscle endurance gain is dependent mostly on the number of repetitions used. Usually up to 12 repetitions will target muscle strength where 20 or more repetitions will increase muscle endurance capacity

(Hoffman, 2002). Since resistance exercise do not require a high level of aerobic capacity, it can be performed by individuals with very low aerobic power.

Increases in skeletal muscle strength following RT occur via to two distinct pathways. These are firstly, neural adaptation (mainly in the first 6 weeks of training) (Lillegard and Terrio, 1994) that results in increased firing rate and synchronisation of motor units, and secondly, an increase in muscle cross-sectional area (hypertrophy) (Aagaard, 2003; Astrand and Rodahl, 1986; Fleck and Kraemer, 1988; Goldspink, 1999; Lillegard and Terrio, 1994; Staron et al., 1994). The relative increases in muscle strength after RT is similar in males and females (Tracy et al., 1999).

Table 2.5. The effects of aerobic and strength training on selected functional and clinical variables.

<u>Exercise</u>	<u>Aerobic</u>	<u>Resistance</u>	
Bone mineral density	↑	↑↑↑	
Body composition:			
Fat mass	↓↓	↓	
Muscle mass	↔	↑↑	
Strength	↔	↑↑↑↑	
Glucose metabolism:			
Insulin response to	↓↓	↓↓	glucose challenge
Basal insulin levels	↓	↓	
Insulin sensitivity	↑↑	↑↑	
Serum lipids			
TC	↓↔	↓↔	
HDL	↑↔	↑↔	
LDL	↓↔	↓↔	
Resting heart rate	↓↓	↔	
Blood pressure at rest			
Systolic	↓↓	↓↔	
Diastolic	↓↓	↓↔	
VO ₂ max	↑↑↑	↑	
Endurance time	↑↑↑	↑↑	
Anaerobic power	↓↔	↑↑	
Anaerobic capacity	↔	↑↑	
Physical function	↑↑	↑↑↑	
Basal metabolism	↑	↑↑	

LBM- lean body mass, HDL- high-density lipoprotein, LDL- low-density lipoprotein. ↓↔ refers to reduction or no change. ↑↔ refers to increase or no change. This table integrate the data from Braith and Stewart (2006), Pollock and Vincent (1996) and Stone et al. (1991).

2.8.3.2 Resistance training for healthy middle-aged and elderly individuals

RT appears to be an effective method to combat age-related sarcopenia (Fiatarone-Singh, 1998; Hurley and Roth, 2000) in otherwise healthy individuals. An increase in muscle strength is the most common finding as a result of RT. Increased skeletal muscle strength may improve the functional capacity and reduce disability of elderly people (Bemben and McCalip, 1999; Brandon et al., 2000; Fiatarone et al., 1994; McCartney et al., 1995; Miszko et al., 2003; Nichols et al., 1995; Pennix et al., 2001). Improvement in the capacity to perform ADL's is important as it was thought to be a surrogate for QoL in the elderly (Pennix et al., 2001; Thomas, 2001). As such, an improvement in the capacity to perform ADL's may improve self-reported QoL (Poehlman, 1999). The inverse correlation between muscle strength and the time taken to complete ADL's such as walking 6 m ($r=-0.75$) and rising from a chair ($r=-0.63$) (Fiatarone et al., 1990) indicates that physical training that increases muscle strength may lead to improvements in the capacity to perform ADL's. Nichols et al. (1995) reported that 12 weeks of RT significantly increased the strength of lower and upper body segments that in turn, improved the capacity to climb stairs and perform a balance task. Ten weeks of RT increased knee extensor strength of elderly participants by 54% (Westhoff et al., 2000). An improvement in knee extensor strength coincided with an improvement in the time to complete the functional test up-and-go (rise from a chair, walking three meters and then returning to the chair and sitting down). Other investigators reported increases in the distance covered for a six-minute walk test (Ettinger et al., 1997; Hughes et al., 2004; Rubenstein et al., 2000), an increased gait velocity (Fiatarone et al., 1994; Hunter et al., 1995; Judge et al., 1993) and a reduction in time to complete tasks such as lifting and carrying (Ettinger et al., 1997), stair descent (LaStayo et al., 2003) and stairs climbing (Fiatarone et al., 1994) after RT.

RT also offers some protection against lost of bone mineral density and osteoporosis (Menkes et al., 1993; Nelson et al., 1994; Pruitt et al., 1992) and reduces the risk of falls in the elderly (Chang et al., 2004; Gardner et al., 2000; MacRae et al., 1996; Rubenstein et al., 2000). It has been reported that an intervention comprising behaviour therapy, attention to medication compliance, gait and balance re-education and RT may reduce the risk of falling in the elderly by 25% (Tinetti et al., 1994). In addition, the patients in

the intervention group reported fewer injuries associated with falls and increased confidence to perform ADL's (Tinetti et al., 1994).

2.8.3.2.1 The effects of resistance training on metabolic variables in healthy elderly populations

In this section, several of the outcome measures (e.g. BP, lipid profile and glycaemic control) that are discussed for studies in apparently healthy middle-aged and elderly participants, were not the primary focus of these studies, and were included in background data in the participant sections of the articles. In other words, it was not the intention of these researchers to “improve” metabolic risk factors in already healthy individuals. This post hoc analysis may limit the conclusions drawn from these studies.

2.8.3.2.1.1 The effect of resistance training on body composition

RT has a limited effect on weight loss in healthy populations. Many studies have reported that body mass did not change significantly after RT in populations such as healthy young (Ivey et al., 2000), and middle-aged and elderly individuals (Ivey et al., 2000; Treuth et al., 1995a). However, lack of change of body mass may mask increases in muscle mass accompanied by decreases in fat mass (Lemmer et al., 2001; Pratley et al., 1994). It has been shown that there is a small, but significant, reduction in body fat (~1-2%, $p < 0.05$) and an increase LBM (~1.5 kg, $p < 0.01$) after RT (Campbell et al., 1994; Campbell et al., 1999; Nichols et al., 1993; Pratley et al., 1994). However, even small increases in LBM may yield positive outcomes in terms of resting metabolic rate (RMR) (r range 0.51-0.56) (Lemmer et al., 2001; Ryan et al., 1995). An increase in RMR (by ~7%) appears to be an important outcome of RT (Campbell et al., 1994; Pratley et al., 1994; Ryan et al., 1995; Treuth et al., 1995b) that in turn, may assist in maintaining body mass (Ryan et al., 1995).

2.8.3.2.1.2 The effect of resistance training on blood pressure and heart rates

Currently, there are conflicting data in regard to the capacity of RT to reduce BP (systolic or diastolic, or both) at rest and during submaximal exercise in young, middle-

aged and elderly persons (Cornelissen and Fagard, 2005). In a small study of 15 elderly participants engaging in submaximal resistance exercise (double leg press at 80% of one repetition maximum, 1RM), HR, SBP and DBP were all lower during the actual exercise after 12 weeks of RT (HR by 14%, SBP by 20% and DBP by 34%) (McCartney et al., 1993). Stone and colleagues (1983) examined the adaptation of resting HR to six weeks of RT in previously untrained young men. They observed a significant reduction in resting HR after the first three weeks of training (85 ± 10 bpm to 78 ± 14 bpm). In addition, they reported that resting HR continued to drop in the last three weeks of training (from 78 ± 14 to 74 ± 12). The authors surmised that the reduction in resting HR following RT was due to either a shift towards parasympathetic dominance and/or an increase in stroke volume as a result of increased venous return (Stone et al., 1983), but neither of these mechanisms was directly measured in this study.

In contrast, several studies have reported that RT did not alter the hemodynamic response at rest or during submaximal effort (Cononie et al., 1991; Copeland et al., 1996; Haykowsky et al., 2000a; Parker et al., 1996). For instance, Cononie et al. (1991) and Haykowsky et al. (2000) reported that 26 weeks and 16 weeks of RT, respectively, did not affect resting or submaximal HR, SBP and DBP of elderly. However, it is possible that both protocols were not of sufficient intensity and/or volume to provoke improvement in BP and heart rates. The training study of Copeland et al. (1996) included 3-4 sets of 8-12 repetitions at 65-80% of one repetition maximum (1RM). However, it was of relatively short duration study (6 weeks), and the training was unsupervised. In addition the authors did not report the compliance rate of participants. These data may indicate that supervised training of longer duration, and higher numbers of sets and repetitions may be required in order to elicit improvements in resting hemodynamics. It has been concluded that further studies are needed in order to assess the effect of RT to reduce resting BP and HR (Cornelissen and Fagard, 2005), and this was one of the foci of this thesis (Study Three).

2.8.3.2.1.3 The effect of resistance training on lipids, glucose and markers of inflammation

Currently there are limited data on the effect of RT as a single intervention on blood lipids and proinflammatory markers of healthy individuals. It appears that RT has a limited effect on lipid profiles (Hurley, 1989), probably because both are within the normal range in a healthy population. It has been reported that 16 weeks of RT (3 days a week) did not affect total cholesterol, LDL, HDL, triglyceride or fasting glucose levels of elderly individuals (Treuth et al., 1995a). Bruunsgaard (2004) reported no change in plasma TNF- α or IL6 levels after 12 weeks of RT in 10 elderly individuals. Nevertheless, there are limited randomised controlled data on the effects of RT as a single intervention on risk factors such as lipids and proinflammatory markers and as such further studies are need in order to examine the effect of RT on these variables.

2.8.3.2.1.4 The effect of resistance training on muscle mass and muscle structure

RT is an effective training regimen to attenuate age-related alterations to muscle structure, function and muscle mass (Abernethy et al., 1994; Adams et al., 1993; Frontera et al., 1988; Hagerman et al., 2000; Hepple et al., 1997b; Izquierdo et al., 2003; Ryan et al., 1995). It has been suggested that both ageing and muscle strength have effects on the ability to synthesise myosin heavy chain (MHC) (Balagopal et al., 1997). RT has positive effects on the major muscle fibre types (I, IIa and IIb) (Balagopal et al., 2001; Frontera et al., 1990; Hagerman et al., 2000; Hikida et al., 2000) and may increase the expression and synthesis rate of MHC and myofibrils (Balagopal et al., 2001; Hasten et al., 2000; Welle et al., 1999). 12 weeks of progressive RT increased muscle strength in men (Trappe et al., 2000) and women (Trappe et al., 2001) by 50-56%. The increases in muscle strength were partly attributed to increases in fibre cross-sectional areas (45% and 28% in men and women, respectively). Similar increases in muscle fibre cross-sectional area (LaStayo et al., 2003) were reported for type I fibre (by up to 46%) (Frontera et al., 1988; Hather et al., 1991; Hikida et al., 2000), type IIa (by up to 46%), and type IIb fibres (by up to 52%) after RT (Charette et al., 1991; Fiatarone-Singh et al., 1999; Frontera et al., 1988; Hather et al., 1991). In addition, significant hypertrophy was observed in total mid-thigh muscle area (Fiatarone et al., 1990) and total quadriceps area (9.3%-13%) of middle age and elderly people, as

measured by CT scan (Frontera et al., 1988; Izquierdo et al., 2003), by MRI (Tracy et al., 1999) and by whole body muscle mass (Yarasheski et al., 1999). It appears that in conjunction with the changes in muscle morphology oxidative enzymes activity is also positively affected by RT (Frontera et al., 1990).

Reductions in capillary supply and capillary density have been reported within skeletal muscle with ageing (Coggan et al., 1992). Alterations in the capillarisation network may lead to an increase in diffusion distance and limit work capacity (Roca et al., 1989). Some investigators reported that RT may improve perfusion to muscle by increasing skeletal muscle capillary supply (capillary contacts) (Hepple et al., 1997a; Hepple et al., 1997b), capillary density and capillaries per fibre ratio (Frontera et al., 1990). Hagerman et al. (2000) and Luthi et al. (1986) however, reported no significant change in muscle capillary supply and capillary density after RT in young and older people. Similarly Hepple et al. (1997a and 1997b) reported no change in capillary density or capillary-to-fibre ratio after RT. This lack of change maybe related to the hypertrophy that was observed in the muscle fibre types and as such, the growth of the capillary may have been masked by the increased cross sectional area of the fibres (Hagerman et al., 2000).

2.8.3.2.2 The effect of resistance training on peak aerobic power

It is widely accepted that aerobic training is the most effective training mode to improve aerobic fitness (Belman and Gaesser, 1991; Kohrt et al., 1991; Makrides et al., 1990). There is also a body of evidence supporting the application of RT to improve $VO_{2\text{ peak}}$. The mechanism may include favourable alterations to muscle morphology in response to RT. RT may have the effect of shifting skeletal muscle phenotype towards a higher proportion of slow, oxidative muscle fibre types, improve oxidative enzyme activity and increase capillary density. These changes may increase the potential for oxygen delivery to, and consumption by, muscle (Frontera et al., 1990; Hepple et al., 1997a), and offer an explanation for improvements in $VO_{2\text{ peak}}$ and exercise duration following RT (Ades et al., 1996; Hagerman et al., 2000; Staron et al., 1989). Hepple et al. (1997b) and Hagerman et al. (2000) reported that RT protocols that consisted of 3 sets, relatively high intensity (6-12 repetitions), 2 to 3 days a week, elicited ~7% increase of $VO_{2\text{ peak}}$ and ~8% increase in exercise time. Furthermore, Ades and colleagues (1996) reported that 12 weeks of RT increased mean walking time to fatigue (treadmill) by 38%.

Although the data support the hypothesis that RT has the potential to improve VO_2 peak in the elderly, other studies reported no change in aerobic power following RT (Pollock et al., 1991; Sagiv et al., 1989). Hagberg et al. (1989) and Pollock et al. (1991) reported that VO_2 peak did not change after 6 months of RT, despite significant improvements in muscle strength. These conflicting data suggest that low intensity RT programs that include a single set, moderate loads and 10-12 repetitions, as was applied in the studies of Hagberg et al. (1989) and Pollock et al. (1991), do not provide enough stimulus to provoke increases in aerobic power in healthy elderly individuals.

2.8.3.3 Resistance training for individuals with clusters of metabolic risk factors

Compared to aerobic training, there is little evidence (particularly from randomized controlled studies) regarding the effect of RT in people with HiMF and T2DM (Eriksson, 1999; Willey and Fiatarone-Singh, 2003). However, there has been recent interest and speculation concerning the potential benefits of RT for individuals with HiMF. The following sections will describe the effect of RT on muscle strength and its application for the capacity to perform ADL's and QoL. In addition, the effect of RT on metabolic risk factors will be examined. The possible benefits of RT for individuals with HiMF are the core focus of this thesis.

2.8.3.3.1 The effect of resistance training on strength/endurance and quality of life

Individuals with HiMF are usually characterised by higher body mass and body fat (both fat percentage and fat mass), compared to their healthy age-matched peers (Lee et al., 2005; Segal et al., 1991; Straczkowski et al., 2001). It has been shown that there is a negative association between body mass and fat mass and the capacity to perform ADL's. There is also a negative association between body mass and fat mass and increased risk for disability for individuals with HiMF (Hausdorff et al., 2001). In addition, individuals with HiMF may have reduced exercise and functional capacities (Jurca et al., 2004; Lee et al., 2005).

The increases in strength and muscle mass after RT in individuals with HiMF is similar to the adaptation in healthy middle-aged and elderly individuals (Herriott et al., 2004). RT may help to counteract both ageing and disease-related sarcopenia. The range of muscle strength gains reported in response to RT for people with HiMF and T2DM is between 11% and 75% (Dela et al., 2004; Dunstan et al., 2002; Dunstan et al., 1998; Maiorana et al., 2002; Rice et al., 1999; Shaibi et al., 2006; Stewart et al., 2005), accompanied by a ~1-2 kg increase in LBM (Castaneda et al., 2002; Dunstan et al., 2002; Maiorana et al., 2002). These studies ranged from 8 to 26 weeks duration. As for healthy individuals, it has been reported that increases in muscle strength in populations with HiMF and T2DM may lead to improvements in the capacity to perform ADL's (Dela and Kjaer, 2006; Grant et al., 2004; Hurley and Roth, 2000; Winett and Carpinelli, 2001).

In contrast to improvements in muscle strength and the capacity to perform ADL's following RT, not all investigators have reported improvements in well-being and QoL. Perrig-Chiello et al. (1998) reported that although muscle strength significantly increased after 8 weeks of RT, participants did not report improvements to their own health ratings or sense of well-being. The authors suggested that well-being is a trait, not a state, and so longer periods of training may be required to elicit these benefits (Perrig-Chiello et al., 1998).

It is now generally accepted that RT has positive effects on muscle strength, muscle mass and the capacity to perform ADL's in individuals with HiMF. However, there is a controversy in the literature in regard to the ability of RT to improve the risk profiles of these individuals. The effects of RT on metabolic risk factors (both conventional and emerging metabolic) are an important outcome of the work presented in this thesis.

2.8.3.3.2 The effect of resistance exercise training on conventional metabolic risk factors

2.8.3.3.2.1 Blood pressure during resistance exercise: acute effects

Some clinicians and health professionals have raised concerns about the appropriateness of RT for elderly individuals, particularly those with CVD and hypertension (Mitchell and Wildenthal, 1974; Painter and Hanson, 1984). Resistance exercise invokes a

“pressure load” on the heart, characterised by reductions in Q and ejection fraction, and elevations in end-systolic volume, PVR, afterload and systemic BP (Bezucha et al., 1982; Huonker and Keul, 1996; Lentini et al., 1993; McCartney, 1999; Sagiv et al., 2000; Sagiv et al., 1988; Sullivan et al., 1992). In the past, these physiological changes (particularly the increases in afterload) were thought to be problematic for people with CVD due to both acute (e.g. increase in BP that may lead to ischaemia and arrhythmias) and chronic (e.g. left ventricular hypertrophy and remodelling) maladaptations. Similar outcomes have been observed for people engaged in long term weight lifting (Effron, 1989; George et al., 1998; Pearson et al., 1986; Salke et al., 1985). It is important to note that there are particular concerns regarding isometric (static) resistance exercise (Bezucha et al., 1982; Dubach et al., 1997; Elkayam et al., 1985; Koch and Broustet, 1992; Mitchell and Wildenthal, 1974) and high intensity dynamic resistance exercises that may lead to Valsalva manoeuvre (sharp increases in intrathoracic pressure causing central haemodynamic perturbations) (MacDougall et al., 1985; McCartney, 1999; Sale et al., 1994).

It is well documented that moderate (up to 85% of 1RM) RT has no adverse effect on left ventricular structure and function of healthy young and elderly individuals (Haykowsky et al., 2000a; Haykowsky et al., 2000b; Haykowsky et al., 2000c; Kanakis and Hickson, 1980; Ricci et al., 1982; Sagiv et al., 1989), and even for people with overt cardiac disease, including chronic heart failure (Levinger et al., 2005a; Pu et al., 2001). In addition, moderate intensity resistance exercise has less detrimental haemodynamic effects, compared to aerobic exercise (Cheetham et al., 2002). According to the American Heart Association (Pollock et al., 2000) and the American College of Sport Medicine (ACSM, 2000a), the following guidelines should be considered when prescribing RT to healthy and clinical populations. Resistance exercise should be dynamic, with 10-15 repetitions at moderate intensity (40-85% of 1RM). In addition, participants should practice correct breathing and lifting techniques in order to prevent undesirable increases in intrathoracic pressure (Valsalva Manouever).

2.8.3.3.2 Resistance training and resting blood pressure

Hypertension is a common element for many people with HiMF, and has also been recognised as a contributor to the development of CVD (see 2.2.3.1. Hypertension:

epidemiology and clinical outcomes). As such, a reduction in resting BP should be an important goal of any intervention for this population. Meta-analyses by Fagard (1999) (meta-analysis of 68 randomised-controlled studies) and Kelley and Kelley (2000) (meta-analysis of 12 randomised controlled studies) calculated that the average reduction of resting SBP after RT is ~3.2 mmHg and DBP by ~2.5 mmHg. Although these changes appear to be small, it has been reported that even small reductions in BP of the order of 5-6 mmHg may reduce the risk for CVD, including stroke by up to 40% and coronary artery disease by up to 14% (Collins et al., 1990). Nevertheless, it is important to note that the meta-analyses cited above yielded average BP decreases of only about half of that of the study by Collins et al. (1990). With respect to the two meta-analyses, both healthy and hypertensive individuals were included and this may have had the effect of diluting the possible benefits for those with hypertension.

There is currently a lack of consensus on the possible benefits of RT for BP for people with hypertension (Cornelissen and Fagard, 2005; Fagard, 1999, 2006). The lack of agreement may be related to the limited randomised controlled data that used RT as a single intervention for this population (Braith and Stewart, 2006; Cornelissen and Fagard, 2005), and also due to varying training protocols. Nevertheless, the current state of knowledge is that RT has limited benefits for reducing DBP or SBP for hypertensive individuals (Fagard, 2006). Although Blumenthal et al. (1991) reported that 16 weeks of circuit weight training reduced SBP by a clinically significant 7 mmHg and DBP by 6 mmHg in middle-aged participants with mild hypertension, most studies have reported only minor changes or no change at all following RT. Stewart et al. (2005) reported that a combined aerobic and RT program had no effect on SBP for hypertensive elderly people, compared to the control group, DBP however, was reduced by ~4 mmHg. Similarly, Harris and Holly (1987) reported that 9 weeks of low intensity RT (3 sets of 20-25 repetitions at 40% of 1RM) as a single intervention reduced DBP (by 4.5 mmHg) but not SBP in hypertensive participants. Cononie et al. (1991) reported no significant change to BP of hypertensive elderly after 26 weeks of RT. The latter used a protocol that consisted of 1 set of 12 repetitions. The data may suggest that RT has a limited effect on resting BP, however it also demonstrates that RT does not often cause adverse events, including increases in BP as was feared by many health professionals (Blumenthal et al., 1991; Cononie et al., 1991; Cornelissen and Fagard, 2005; Harris and Holly, 1987). Further studies with different training protocols (i.e. higher number of

sets, repetitions and intensity) should be conducted in order to evaluate the effect of RT on resting BP of individuals with HiMF and is a focus of this thesis.

2.8.3.3.2.3 The effects of resistance training on body composition and lipids profile

Increase in body mass, BMI and waist circumference (abdominal obesity) have been identified as important risk factors for the development of metabolic disorders and CVD (Dalton et al., 2003; Despres, 1991; Friedman and Fanning, 2004; Lemieux et al., 2000; Pi-Sunyer, 2002; Sowers, 1998) and increased risk of mobility disability (Launer et al., 1994). Most studies reported no change in body mass or BMI following RT (Table 2.6). Most of the studies that did find reductions in body mass also included dietary interventions (Dunstan et al., 2002; Joseph et al., 2001; Rice et al., 1999) and/or aerobic exercise (Balducci et al., 2004; Cuff et al., 2003; Stewart et al., 2005). Measuring absolute body weight and/or BMI however, may not be the most appropriate method to assess positive (or negative) alterations in body composition following RT. It has been described that regular RT increases muscle mass with or without a reduction in body fat in many populations including overweight individuals (Olson et al., 2007), these with HiMF, and those with diabetes (Castaneda et al., 2002; Harris and Holly, 1987; Hurley et al., 1988; Stone et al., 1991). As body mass measurement includes both lean and fat mass, fat loss may be accompanied by muscle gain. Favourable changes to body composition after RT may lead to improved glucose homeostasis, and this is probably related to increased muscle mass (Eriksson et al., 1997; Sanchez and Leon, 2001). As skeletal muscle is an important tissue for glucose disposal, an increase in muscle mass should, in theory, lead to improved glucose homeostasis (Sanchez and Leon, 2001).

It appears that RT may improve blood lipid profiles, but the full benefits may be delayed (Table 2.6). Reductions in total cholesterol, LDL and/or triglyceride have been reported in studies of at least 16 weeks duration (Cauza et al., 2005b; Honkola et al., 1997; Hurley et al., 1988; Rice et al., 1999). HDL levels however, may be elevated with shorter training durations (10 weeks) (Eriksson et al., 1998). Recently however, Sigal et al. (2007) reported that 26 weeks of RT did not reduce total cholesterol, LDL and/or triglyceride and/or increase HDL for patients with T2DM. It is important to acknowledge that in the study by Sigal et al. (2007) the lipid profile also did not improve with aerobic training or combined training interventions (aerobic and resistance together). Similarly, Olson et al. (2007) reported that 1 year of moderate RT did not change the lipids profile of overweight women. As there are relatively small numbers of

randomised controlled studies that have examined the effect of RT as a single intervention on the blood lipid profile, further studies are needed in order to establish whether RT can alter lipid profiles in individuals with HiMF, and this is a focus of this thesis.

Table 2.6. The effects of resistance training on body mass, BMI and lipids profile

Key: CT (clinical trial, but with no inactive control group, or a trial that compared the effect of training between clinical and healthy populations), RCT (randomised controlled trial), CCT (clinical controlled trial, participants were matched to groups), T2DM (type 2 diabetes mellitus), IGT (impaired glucose tolerance), RT (resistance training), AeT (aerobic training), Ex (exercise), CWT (circuit weight training), Chol (total cholesterol), LDL (low density lipoprotein), Trig (triglycerides), HDL (high density lipoprotein).

Reference	Trial type	Participants	Exercise	Duration	LBM	Fat	BMI	Lipids	Comments
Smutok et al. (1994)	CCT	T2DM, IGT and/or hyperinsulinemia	11 Ex; 2 sets; 12-15 reps; 3 times/wk	20 wk	↔	-----	↔	-----	Did not monitor diet
Ryan et al. (1996)	CT	Obese	RT alone 14 Ex; 5-15 reps; high intensity; 3 times/wk	16 wk	↔	↔ both % and mass	↔	-----	No inactive control group
			RT + diet	16 WK	↔	↓ both % and mass	↓		
Eriksson et al. (1997)	CT	T2DM	11 Ex; 1 set; 15-20 reps at 50% 1RM; twice/wk	12 wk	-----	-----	↔	↔ Chol ↔ HDL ↔ Trig	No control group
Honkola et al. (1997)	CCT	T2DM	CWT; 8-9 Ex; 2 sets; 12-15 reps; 2 times/wk	22 wk	-----	-----	↓	↓ Cho ↓ LDL ↓ Trg	Non-randomised

Reference	Trial type	Participants	Exercise	Duration	LBM	Fat	BMI	Lipids	Comments
Ishii et al. (1998)	CCT	T2DM	9 Ex; 2 sets; 10-20 reps at 50-55% 1RM; 5 times/wk	4-6 wk	↔	↔	↔	-----	Participants enrolled to groups
Dunstan et al. (1998)	RCT	T2DM	CWT; 6 Ex; 3 sets; 10-15 reps at 50-55% 1RM	8 wk	-----	-----	↔	-----	-----
Eriksson et al. (1998)	CCT	IGT	CWT; 8 Ex; 3 sets; 8-10 reps at 50-60% 1RM	10 wk	-----	↔ %	↔	↔ Chol ↔ Trig ↑ HDL	No inactive control group
Rice et al. (1999)	RCT	Obese	7 Ex; 1 set; 8-12 reps	16 wk	-----	↓ ↓ Also waist circumference	↓	-----	Double intervention: including diet
Joseph et al. (2001)	RCT	Obese	5 Ex; 2 sets; 8 reps at 80% 1RM and 1 set to fatigue	4 wk	↔ but ↓ diet alone	↓ ↓ Also waist circumference	↓	-----	Double intervention: including diet Changes in body weight are similar to diet alone

Reference	Trial type	Participants	Exercise	Duration	LBM	Fat	BMI	Lipids	Comments
Maiorana et al. (2001; 2002)	Randomised crossover design	T2DM	CWT 45 s in each station: RT: 7 Ex at 55-65% 1RM. AeT: 70-85% HRpeak	8 wk	-----	-----	-----	↔ Chol ↔ LDL ↔ HDL ↔ Trig	Double intervention Also ↑ endothelial function
Dunstan et al. (2002)	RCT	Obese + T2DM	9 Ex; 3 sets; 8-10 reps at 50-85% 1RM; 3 times/wk	26 wk	↑	↓ ↓ waist circumference	↓	↔ Chol ↔ LDL ↔ HDL ↔ Trig	Double intervention: including weight loss diet
Castaneda et al. (2002)	RCT	T2DM	5 Ex; 3 sets; 8 reps at 60-80% 1RM; 3 times/wk	16 wk	↑	↔	↔	↔ Chol ↔ LDL ↔ HDL ↔ Trig	-----
Banz et al. (2003)	RCT (aerobic or resistance trainings)	HiMF	8 Ex; 3 sets; 10 reps 3 times/wk	10wk	↑	↓	↔	↔ Chol ↔ LDL ↔ HDL ↔ Trig	No inactive control group
Cuff et al. (2003)	RCT	Obese + T2DM	RT: 5 Ex; 2 sets; 12 reps + AeT: (60-75% HRR	16 wk	↔	↓	↓	↔ Chol ↔ LDL ↔ HDL ↔ Trig	Double intervention No- inactive control group

Reference	Trial type	Participants	Exercise	Duration	LBM	Fat	BMI	Lipids	Comments
Balducci et al. (2004)	RCT	T2DM	RT: 6 Ex; 3 sets; 12 reps at 40-60% 1RM + AeT: 30 min; 40-80% HRR	52 wk	↑	↓	↓	↔ Chol ↔ LDL ↔ Trig ↑ HDL	Double intervention
Fenicchia et al. (2004)	CT	Obese +T2DM	9 Ex; 3 sets; 8-12 reps at 80% 3RM; 3 times/wk	6 wk	↔	↓	↔	-----	No clinical control group.
Tokmakidis et al. (2004)	CT	Overweight + T2DM	RT: 6 Ex; 3 sets; 12 reps at 60% 1RM; twice a week AeT: 45 min walking at 60-70% Hrmax; twice a week	16 wk	-----	-----	↔	-----	Double intervention No control group
Reynolds et al. (2004)	CT	Overweight + hypertension	8 Ex; 2 sets; 10-12 reps to failure; 3 times/wk	16 wk	↑	↔	↔	-----	No control group
Cauza et al. (2005b)	RCT	T2DM	11 Ex; 3-6 sets; 10-15 reps	16 wk	↑	↓	↔	↓ Cho ↓ LDL ↓ Trig ↑ HDL	Comparison between RT and AeT. No inactive control group
Ibanez et al. (2005)	CT	T2DM	7-8 Ex; first 8 weeks; 3-4 sets; 10-15 reps at 50-70% 1RM. Last 8 weeks 3-5 sets; 5-6 reps at 70-80% 1RM	16 wk	↓	↔	-----	-----	No control group
Polak et al. (2005)	CT	Obese	RT: 13 Ex; 1-2 sets; 12-15 reps at 60-70% 1RM; 3 times/wk	12 wk	↔%	↔	↔	↔ Chol ↔ Trig ↔ HDL	No control group

Reference	Trial type	Participants	Exercise	Duration	LBM	Fat	BMI	Lipids	Comments
Stewart et al. (2005)	RCT	Overweight + hypertension	RT: 7 Ex; 10-15 reps at 50% 1RM; 3 times/wk AeT: 45 min at 60-90% HRmax	26 wk	↑	↓ waist circumference	↓	↔ Chol ↔ LDL ↔ Trig ↑ HDL	Double intervention RT + AeT
Sigal et al. (2007)	RCT	T2DM	RT (alone): 7 Ex; 7-9 reps; 3 times/wk AeT (alone): 15-45 min at 60-75% HRmax Combined RT+AeT (compared to RT and AeT alone)	26 wk	↔	↔	↔	↔ Chol ↔ LDL ↔ Trig ↔ HDL	-----
								↔ Chol ↔ LDL ↔ Trig ↔ HDL	
								↔ Chol ↔ LDL ↔ Trig ↔ HDL	
Olson et al. (2007)	RCT	Overweight	RT: 9 Ex; 8-12 reps; 2-3 times/wk	52 wk	↑	↔	↔	↔ Chol ↔ LDL ↔ Trig ↔ HDL	-----

2.8.3.3.2.4 The effects of resistance training on insulin levels and glucose homeostasis

Most studies that have examined the effect of RT on insulin levels have reported no change to fasting plasma insulin and glucose levels (Table 2.7). However, it seems that RT may have the potential to improve insulin sensitivity, insulin resistance and glucose homeostasis in healthy people (Dela and Kjaer, 2006; Hurley et al., 1988; Poehlman et al., 2000), and also people who are overweight with and without HiMF and T2DM (Albright et al., 2000; Dela and Kjaer, 2006; Shaibi et al., 2006).

It has been previously reported that even relatively short periods of training (8 weeks) that included both aerobic and resistance modes of exercise can reduce fasting blood glucose and HbA1c by 22.4% and 7.6%, respectively (Maiorana et al., 2001; Maiorana et al., 2002). Other investigators reported similar findings for combinations of resistance and aerobic exercise (Balducci et al., 2004; Tokmakidis et al., 2004), or resistance exercise and diet (Dunstan et al., 2002; Ibanez et al., 2005). Only a few studies have examined the effect of RT as a single intervention on insulin resistance and glucose control and even fewer randomised controlled studies have been performed (Table 2.7). Smutok et al. (1994) used a clinical controlled trial (CCT) design (Table 2.7) and reported reductions in plasma insulin and glucose levels following 20 weeks of RT. Eriksson et al. (1997) and Cauza et al. (2005a) both reported reductions in HbA1c after RT, but neither of these groups included non-exercise control participants. Two randomised controlled studies have reported that RT as a single intervention reduced HbA1c in patients with T2DM (Castaneda et al., 2002; Sigal et al., 2007). It is important to note that not all studies reporting an improvement in HbA1c also found reductions in fasting glucose levels (Brooks et al., 2007). HbA1c is generally accepted as a better indicator of long-term glycaemic control, compared to fasting blood glucose (Castaneda et al., 2002; Dunstan et al., 2002; Eriksson et al., 1997). As such, it is important to reduce the HbA1c levels for individuals with elevated levels of HbA1c (i.e. HiMF and T2DM).

It is difficult however to discriminate between studies that did or did not report improvements in metabolic risk factors after exercise training, as they tested different training modes, durations (4 to 52 weeks), numbers of exercises (5 to 11), types of exercises, training intensities (50-85% of 1RM), numbers of sets (1-3) and different populations (Table 2.7). Furthermore, other studies with similar training characteristics

reported no change to fasting glucose levels (Dunstan et al., 2002; Dunstan et al., 1998; Eriksson et al., 1997; Eriksson et al., 1998; Rice et al., 1999), fasting insulin (Dunstan et al., 2002; Dunstan et al., 1998; Eriksson et al., 1998) and HbA1c (Dunstan et al., 1998). The protocols of the above studies and the discordant findings make it difficult to identify the specific contributions of RT for improving insulin resistance and glycaemic control in individuals with HiMF and T2DM. If RT is to be adopted as a mainstream exercise intervention for people with HiMF, then further studies are needed in order to examine the specific benefits of RT as a single intervention for this population.

Table 2.7. The effect of resistance training on glucose, insulin and HbA1c levels

Key: CT (clinical trial, but with no inactive control group, or a trial that compared the effect of training between clinical and healthy populations), RCT (randomised controlled trial), CCT (clinical controlled trial, participants were matched to groups), T2DM (type 2 diabetes mellitus), IGT (impaired glucose tolerance), RT (resistance training), AeT (aerobic training), Ex (exercise), CWT (Circuit weight training).

Reference	Trial type	Participants	Exercise	Duration	Glucose	HbA1c	Fasting Insulin	Insulin Sensitivity	Comments
Smutok et al. (1994)	CCT	T2DM, IGT and/or hyperinsulinemia	11 Ex; 2 sets; 12-15 reps; 3 times/wk	20 wk	↓ after OGTT	-----	↓	-----	Non-randomised
Ryan et al. (1996)	CT	Obese	RT alone 14 Ex; 5-15 reps; high intensity; 3 times/wk	16 wk	↔	-----	↔	↑ ↑	No non-training control group
			RT + diet	16 wk	↔	-----	↔	-----	No control group
Eriksson et al. (1997)	CT	T2DM	11 Ex; 1 set; 15-20 reps at 50% 1RM; twice/wk	12 wk	↔ fasting	↓	-----	-----	Non-randomised
Honkola et al. (1997)	CCT	T2DM	CWT; 8-9 Ex; 2 sets; 12-15 reps; 2 times/wk	22 wk	-----	↔ But ↑ in control	-----	-----	Low intensity
Ishii et al. (1998)	CCT	T2DM	9 Ex; 2 sets; 10-20 reps at 50-50% 1RM; 5 times/wk	4-6 wk	↑ glucose disposal rate	↔	-----	↑	Non-randomised
Dunstan et al. (1998)	RCT	T2DM	CWT; 6 Ex; 3 sets; 10-15 reps at 50-55% 1RM	8 wk	↔ fasting	↔	↔	-----	Randomised

Reference	Trial type	Participants	Exercise	Duration	Glucose	HbA1c	Fasting Insulin	Insulin Sensitivity	Comments
Eriksson et al. (1998)	CCT	IGT	CWT: 8 Ex; 3 sets; 8-10 reps at 50-60% 1RM	10 wk	↔ fasting But ↑ glucose disposal	----	↔	↑	No non-active control group
Rice et al. (1999)	RCT	Obese	7 Ex; 1 set; 8-12 reps	16 wk	↔ fasting	----	↓	-----	Double intervention : including diet
Joseph et al. (2001)	RCT	Obese	5 Ex; 2 sets; 8 reps at 80% 1RM and 1 set to fatigue	4 wk	↔ During Hyperinsulinemia-euglycemic clamp	----	↔	-----	Double intervention : including diet Changes in body weight are similar to diet alone
Maiorana et al. (2001; 2002)	Randomised cross-over design	T2DM	CWT 45 s in each station: RT: 7 Ex at 55-65% 1RM. AeT: 70-85% HRpeak	8 wk	↓ fasting	↓	-----	-----	Double intervention CWT Also ↑ endothelial function
Dunstan et al. (2002)	RCT	Obese +T2DM	9 Ex; 3 sets; 8-10 reps at 50-85% 1RM; 3 times/wk	26 wk	↔ fasting	↓	↔	-----	Double intervention : including weight loss diet

Reference	Trial type	Participants	Exercise	Duration	Glucose	HbA1c	Fasting Insulin	Insulin Sensitivity	Comments
Castaneda et al. (2002)	RCT	T2DM	5 Ex; 3 sets; 8 reps at 60-80% 1RM; 3 times/wk	16 wk	↔ fasting	↓	-----	-----	↓ in prescribe medications Randomised No non-Ex control group
Banz et al. (2003)	RCT (aerobic or resistance trainings)	HiMF	8 Ex; 3 sets; 10 reps 3 times/wk	10wk	↔ fasting	-----	↔	-----	
Cuff et al. (2003)	RCT	Obese + T2DM	RT: 5 Ex; 2 sets; 12 reps + AeT: (60-75% HRR	16 wk	↔ fasting	↔	↔	-----	Double intervention No-nonEx control group
Balducci et al. (2004)	RCT	T2DM	RT: 6 Ex; 3 sets; 12 reps at 40-60% 1RM + AeT: 30 min; 40-80% HRR	52 wk	↓ fasting	↓	-----	-----	Double intervention
Fenicchia et al. (2004)	CT	Obese +T2DM	9 Ex; 3 sets; 8-12 reps at 80% 3RM; 3 times/wk	6 wk	↔ OGTT after training but ↓ with acute Ex	-----	↔	-----	No clinical control group.

Reference	Trial type	Participants	Exercise	Duration	Glucose	HbA1c	Fasting Insulin	Insulin Sensitivity	Comments
Tokmakidis et al. (2004)	CT	Overweight + T2DM	RT: 6 Ex; 3 sets; 12 reps at 60% 1RM; twice a week AeT: 45 min walking at 60-70% Hrmax; twice a week	16 wk	↓ fasting	↓	↓	↑	Double intervention No control group
Holten et al. (2004)	CT	T2DM	3 sets; 8-12 reps at 50-90% 1RM; 3 times/wk	6 wk	↔	↔	↔	↑	Single leg training No control group
Reynolds et al. (2004)	CT	Overweight + hypertension	8 Ex; 2 sets; 10-12 reps to failure; 3 times/wk	16 wk	↑ fasting but also ↑ disposal rate	-----	↔	-----	No control group
Cauza et al. (2005)	RCT	T2DM	11 Ex; 3-6 sets; 10-15 reps	16 wk	↓ fasting	↓	↔	↑	Comparison between RT and AeT. No non-Ex control group
Ibanez et al. (2005)	CT	T2DM	7-8 Ex; first 8 weeks; 3-4 sets; 10-15 reps at 50-70% 1RM. Last 8 weeks 3-5 sets; 5-6 reps at 70-80% 1RM	16 wk	↓ fasting	↔	-----	↑	No control group
Stewart et al. (2005)	RCT	Overweight + hypertension	RT: 7 Ex; 10-15 reps at 50% 1RM; 3 times/wk AeT: 45 min at 60-90% HRmax	26 wk	↔ fasting	-----	↔	-----	Double intervention RT + AeT

Reference	Trial type	Participants	Exercise	Duration	Glucose	HbA1c	Fasting Insulin	Insulin Sensitivity	Comments
Polak et al. (2005)	CT	Obese	RT: 13 Ex; 1-2 sets; 12-15 reps at 60-70% 1RM; 3 times/wk	12 wk	↔ fasting	-----	↔	↑	No control group
Shaibi et al. (2006)	RCT	Obese	RT: 10 Ex; 1-3 sets; 10-15 reps; moderate resistance	16 wk	↔ fasting	-----	↔	↑	Overweight adolescents
Brooks et al. (2007)	RCT	Elderly with T2DM	5 Ex; 3 sets; 8 reps at 60%-80% 1RM	16 WK	↔ fasting	↓	↔	↑	Double intervention RT+ standard care vs standard care
Sigal et al (2007)	RCT	T2DM	RT alone: 7 Ex; 7-9 reps; 3 times/wk AeT alone: 15-45 min at 60-75% HRmax Combined RT+AeT (compared to RT and AeT alone)	26 wk	-----	↓	-----	-----	-----
					-----	↓	-----	-----	-----
					-----	↓ more than RT or AeT alone	-----	-----	-----
Olson et al. (2007)	RCT	Overweight	RT: 9 Ex; 8-12 reps; 2-3 times/wk	52 wk	↔ fasting	-----	↔	↔	-----
Bell et al. (2007)	CT	Obese children with insulin resistance	CWT 1 min in each station: RT: 10 Ex; 12 reps at 55-65% 1RM. AeT: 65-85% HRpeak	8 wk	-----	-----	-----	↑	No control group

2.8.3.3.2.5 The effects of resistance training on insulin-signalling proteins

Only a limited number of studies have examined the effects of RT on insulin-signalling proteins and no study has examined the effect of RT on AS160. Some studies have suggested that RT may modulate insulin-signalling proteins (Krisan et al., 2004; Yaspelkis, 2006). It has been reported that RT increases the expression of AMPK subunit isoforms (Wojtaszewski et al., 2005) and may also increase GLUT4 protein density and mRNA after brief RT (Dela et al., 1994; Holten et al., 2004; Krisan et al., 2004). RT increases the activity of some insulin-signalling molecules such as IRS-1 associated with PI3-kinase (Krisan et al., 2004), Akt and glycogen synthase protein and total activity (Holten et al., 2004). This in turn may lead to greater flux of glucose to muscle cells and increase muscle capacity to store muscle glycogen (glycogen content) (Holten et al., 2004). It is important to note that the muscle samples for the studies by both Holten et al. (2004) and Dela et al. (1994) were taken approximately 16 hours after the last training sessions. It is possible that the increase in insulin-signalling proteins was due to the persisting effects of the most recent training sessions prior to biopsy, rather than a reflection of muscle adaptation to the training.

Some investigators have reported an increase in Akt phosphorylation up to 72 h after an acute bout of resistance exercise (Creer et al., 2005; Leger et al., 2006), while others have reported no change (up to 40 h) (Coffey et al., 2006; Deshmukh et al., 2006; Eliasson et al., 2006; Krisan et al., 2004). Recently, one study has reported a significant reduction in phosphorylated Akt after acute resistance exercise (Terzis et al., 2008). No change in AS160 phosphorylation was also reported after acute resistance exercise (Deshmukh et al., 2006). This finding is in contrast to the effects of acute aerobic exercise, which has been reported to increase Akt and AS160 phosphorylation (Deshmukh et al., 2006; Treebak et al., 2007). Furthermore, some investigators (Howlett et al., 2007), but not all (Koopman et al., 2005), have reported that AS160 phosphorylation decreases (up to 40%) and that there was a trend for a decrease in phosphorylated Akt (value was not reported) immediately after an acute bout of resistance exercise. Despite this reduction in AS160 phosphorylation, insulin stimulation was still able to elicit an increase in AS160 phosphorylation by two-to-three fold, suggesting that the reduction in phosphorylated AS160 and phosphorylated Akt does not necessarily translate into a reduced ability to respond to insulin stimulation (Howlett et al., 2007). Other studies have reported that acute resistance exercise reduces

insulin sensitivity for up to 48 h (Asp et al., 1996; Asp and Richter, 1996; Asp et al., 1997) while other have reported an increase in insulin sensitivity 24 h after resistance exercise (Fenicchia et al., 2004; Koopman et al., 2005). Taken together, these data suggest that RT may have the potential to improve some insulin-signalling proteins, however longer duration (several days) between the last training session and the muscle biopsy may be needed in order to examine the effect of RT to basal Akt and AS160 phosphorylation.

2.8.3.3.3 The effects of resistance exercise training on emerging metabolic risk factors

2.8.3.3.3.1 The effects of resistance training on markers of inflammation

To date, a very limited number of studies have examined the effect of RT alone on inflammatory markers in individuals with HiMF. As such, it is difficult to assess if RT can reduce the levels of some pro-inflammatory markers. Reynolds et al. (2004) reported that 16 weeks of moderate RT (2 sets of 10-12 reps 3 days/wk) improved insulin sensitivity without altering inflammatory markers (e.g. TNF- α) in elderly with hypertension. Kohut et al. (2006) examined the effect of aerobic training versus strength, flexibility and balance training in elderly individuals with and without other medical problems such as hypertension and T2DM. They reported that serum levels of IL-18, IL-6 and CRP were reduced with aerobic training but not with strength, flexibility and balance training. However, TNF- α was reduced with both training modes. In addition, Brooks et al. (2007) reported that 16 weeks of RT plus standard care in the treatment of elderly with T2DM reduced CRP levels by 20% (from 3.5 mg·L⁻¹ to 2.8 mg·L⁻¹), compared to standard care alone. Similarly, Olson et al. (2007) reported that 1 year of RT significantly reduced CRP levels (by mean of 3.0 mg·dl⁻¹), compared to baseline levels in overweight women, with no change in IL-6 levels. It is important to note however, that the reduction in CRP was not statistically significant when compared to the non-active control group (Olson et al., 2007). The findings of the above studies may suggest the RT has some potential to improve the inflammation status associated with ageing and metabolic. However, further studies are needed in order to examine the effect of RT alone on the inflammation status of individuals with HiMF.

2.8.3.3.3.2 The effects of resistance training on hepatic enzymes and BDNF

It appears that exercise may lower GGT and ALT concentrations. Epidemiological studies have reported inverse association between reported physical activity level and GGT (Wannamethee et al., 1995) and aerobic fitness and GGT (Borodulin et al., 2005). In addition, it has been reported that aerobic training reduced ALT concentration (as well as proinflammatory markers) in overweight individuals (Okita et al., 2004). These data suggest that interventions targeting increases in physical activity and/or aerobic fitness can lead to reductions in hepatic enzymes levels. To date, only one study has reported the effect of RT on GGT and no previous study has reported the effect of RT on ALT or BDNF. Holten et al. (2004) reported that 6 weeks of single leg RT (3 days/wk, 12-15 repetitions at 50-80% 1RM) did not change GGT levels in healthy middle-aged individuals and patients with T2DM.

BDNF plays a role in learning and memory processes and is also involved in energy homeostasis, obesity, insulin resistance and T2DM (Vaynman and Gomez-Pinilla, 2006). An increase in physical activity level is associated with a lower risk for neurological diseases such as dementia (Abbott et al., 2004). It has been described that moderate intensity aerobic exercise is an effective non-pharmacological intervention for depression, and aerobic exercise increases BDNF levels (Cotman and Engesser-Cesar, 2002; Garoflos et al., 2005; Kiraly and Kiraly, 2005; Sarbadhikari and Saha, 2006). Furthermore, it has been reported that aerobic training increases BDNF levels and was correlated with the improvement in learning in humans (Winter et al., 2007) and animals (Radak et al., 2006). However, most studies assessing the effect of exercise on BDNF levels have examined the benefits from the “brain” point of view (learning and memory) and not the metabolic consequences of the changes in BDNF. No previous study has examined the effect of RT on BDNF levels, or the metabolic consequences of these changes. As such, it is not known if RT can elicit metabolic improvements through changes to BDNF levels in people with HiMF. Further studies are needed in order to determine the effect of exercise on both GGT and BDNF levels, and these were foci of one of the studies in this thesis.

2.9 Conclusions

Both genetic and environmental factors contribute to the development of metabolic risk factors that in turn may lead to T2DM and CVD. However, the substantial increases in the prevalence of these risk factors, and the consequential morbidity and mortality outcomes, over the past two decades suggests that environmental factors such as poor lifestyle may be significant contributors to this epidemic. There is sound evidence to support the notion that interventions for individuals with HiMF should include lifestyle improvements, comprising increased levels of physical activity and/or improvement in diet.

It is generally accepted that symptomatic diseases (including cardiac) have adverse effects on the patient's capacity to perform ADL's and QoL. However, it is not known if the capacity to perform ADL's and self-perceived QoL are affected by metabolic risk factors in the absence of symptomatic disease, and if the capacity to perform ADL's and/or self-perceived QoL may be used separately or together as early warning signs for increased metabolic morbidity (T2DM and CVD).

Compared to other non-pharmacological interventions for individuals with HiMF (i.e. aerobic exercise training and diet), the benefits from RT are not well understood. It appears that RT may improve muscle strength and body composition that in turn should lead to increases in the capacity to perform ADL's and improvements in QoL. However, it is not clear if individuals with HiMF will benefit more, less or similarly to their healthy age peers with respect to ADL's and QoL. In addition, it is not clear if RT as a single intervention is sufficient to inhibit or improve metabolic risk factors (both traditional and emerging risk factors) for individuals with HiMF and individuals with low number of metabolic risk factors (LoMF).

The studies in this thesis are designed to explore the effects and the relationships between metabolic risk factors and the capacity to perform ADL's and QoL for individuals with HiMF and LoMF, and also to examine the potential benefits from RT in these two populations. The randomised controlled studies of RT as a single intervention for individuals with HiMF will add important, novel information regarding the benefits of this mode of exercise for this population, both in terms of important functional and clinical outcomes.

Chapter 3

3.0 General methodology

3.1 Study design

The main aim of this thesis was to examine the effect of RT for individuals with 2 or more metabolic risk factors (HiMF) associated with the MetS, T2DM and CVD with the experimental foci being on muscle strength and endurance, the capacity to perform ADL's, QoL and clinical outcomes. In addition, this thesis compared the effects of RT for individuals with HiMF and those with low numbers of metabolic risk factors (LoMF).

Study One examined the clinical (risk factor) and functional characteristics, and QoL for middle-aged individuals with HiMF and LoMF. Study Two was an examination of the effects of RT on body composition, functional capacities, strength and QoL for individuals with HiMF and LoMF. Study Three examined the effect of RT on conventional and emerging metabolic risk factors for these individuals. Study Four focused on the effect of RT for two insulin-signalling proteins (Akt and AS160) and skeletal muscle glycogen content for these populations. All post-training tests were conducted 3-5 days after the last training session in order to examine the chronic effects of training and to minimise the acute effect of the last training session. This chapter outlines the methods that are common to at least two studies. Methodologies specific to just one study are described separately in the relevant chapter.

3.2 Participants

Fifty-five middle-aged (50.8 ± 6.1 yr) men ($n=28$) and women ($n=27$) volunteered to participate in the study. The recruitment process and the thesis design are presented in Figure 3.1. At the end of the initial tests, each participant was allocated to one of two groups according to the number of metabolic risk factors associated with the MetS as defined by the International Diabetes Federation (IDF) (Table 2.1) (Zimmet et al., 2005). Participants with two or more metabolic risk factors were classified as HiMF and participants with one or no factors were classified as LoMF (The data collected at this

phase of the thesis have been used for Study One). The number of males and female volunteers recruited to the study was almost identical (men n=28, women n=27). However once the objective criteria for allocation to either HiMF or LoMF were applied, there were more men than women in HiMF, whilst the reverse was true for LoMF (Figure 3.1). Following the allocation for HiMF or LoMF, participants were randomly allocated to one of four groups: HiMF training (HiMFT), HiMF non-exercise control (HiMFC), LoMF training (LoMFT) and LoMF non-exercise control (LoMFC). The method of randomisation for the groups was stratified according to sex in order to ensure similar numbers of males and females within each group (i.e. HiMFT verses HiMFC and LoMFT versus LoMFC) (Figure 3.1). The data collected at this phase were used for Studies Two-Four. Participants were on a range of prescribed medications including beta-blockers (n=2), calcium channel blockers (n=2), ACE inhibitors (n=4), diuretics (n=1), statins (n=2), metformin (n=1), sulfonylurea (n=1) and hormone replacement therapy (n=6). Participants were included if they had not been involved in regular aerobic exercise training during the previous six months, or RT in the previous five years. Volunteers were excluded if they had a history of heart disease including heart failure or coronary artery disease. Each participant received written and verbal explanations about the nature of the study and those who chose to participate signed an informed consent document.

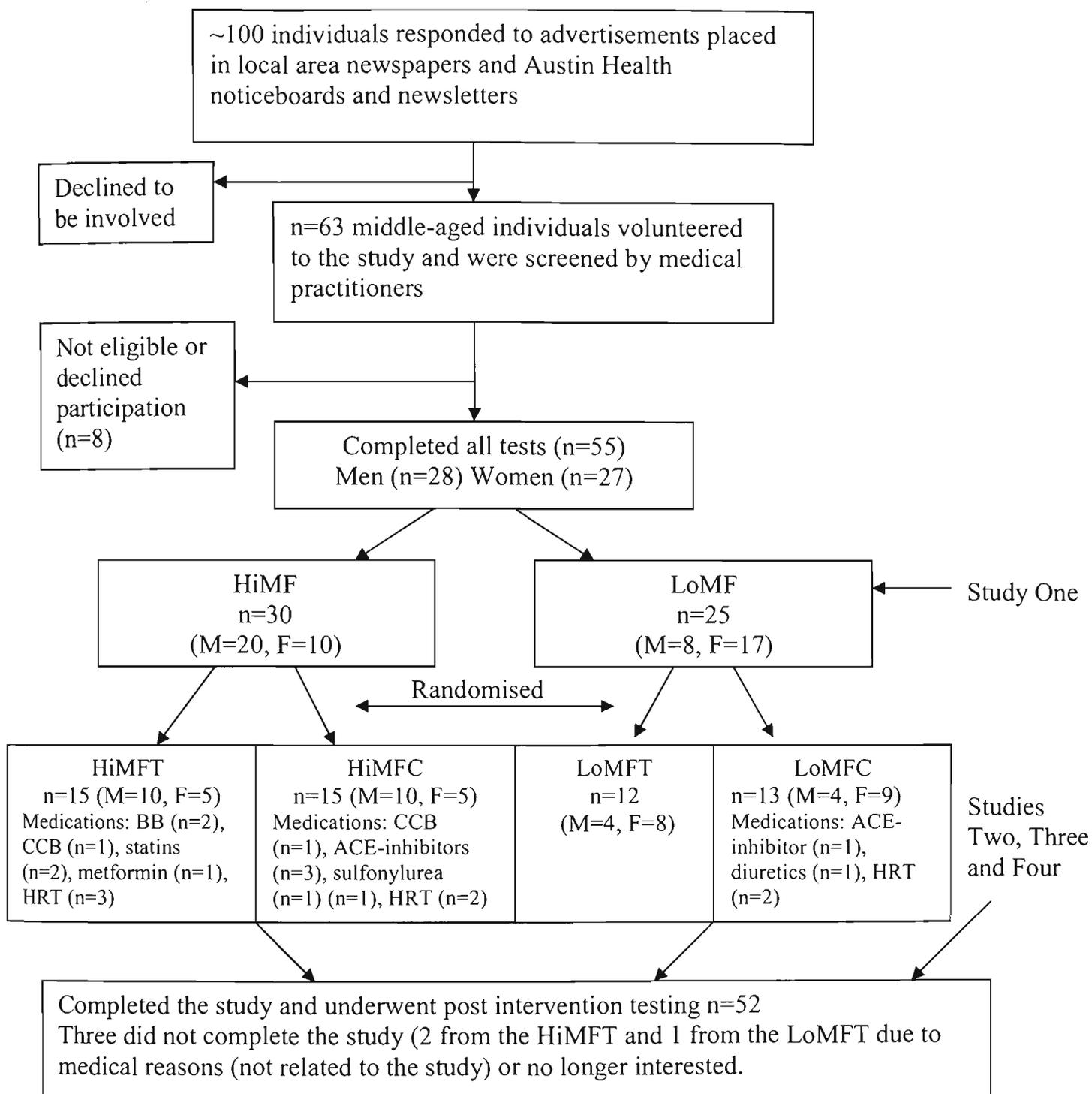


Figure 3.1. Illustrates the flow chart for group's allocation studies design..

3.3 Three-day dietary logs

Participants were issued with a kitchen scale (Kitchen Scale Model: KCHC-009, China) to measure serving weights, and recorded their diets in detail for two consecutive week days and a weekend day, preferably consecutive with the 2 week days (Appendix A). The logs were analysed by FoodWorks Professional Edition (Version 3.02.581, Xyris Software, Australia). The dietary logs were analysed by Ms. Ka Yan Tse, School of Human Movement, Recreation and Performance, Victoria University. Study participants

were encouraged not to alter their diets throughout their participation in the study (approx 3 months).

3.4 Anthropometric measurements

Height was measured with the participants standing barefoot on a stadiometer ($\pm 0.5\text{cm}$). Weight was measured with participants wearing just underwear whilst standing on a calibrated scale (August Sauter GmbH, Germany) ($\pm 0.05\text{kg}$). Waist circumference was measured with a steel tape and taken as the smallest circumference between the iliac crest and the lower border of the ribs. Three measurements were taken and the mean of the two closest measures was recorded.

Dual-energy X-ray absorptiometry (DXA) (GE Lunar Pxdigy, Software version 9.1, Madison, USA) was used to assess total body fat percentages, total body fat and lean body mass (LBM). In addition, the DXA and GE Lunar Pxdigy software were used to assess fat mass in the abdominal region, the latter defined as the lower boundary at pelvis cut and upper boundary as above pelvis cut by 20% of the distance between pelvis and neck cut (Figure 3.2). All DXA measurements were conducted by staff at the Bone Density Unit, Austin Health, Repatriation Campus. DXA is a fast, simple and safe technique to evaluate body composition (Laskey, 1996). Although DXA was initially designed as a tool for the diagnosis of osteoporosis, it has been recognised also as a precise tool to evaluate fat and LBM (Albanese et al., 2003; Van Loan, 1998).

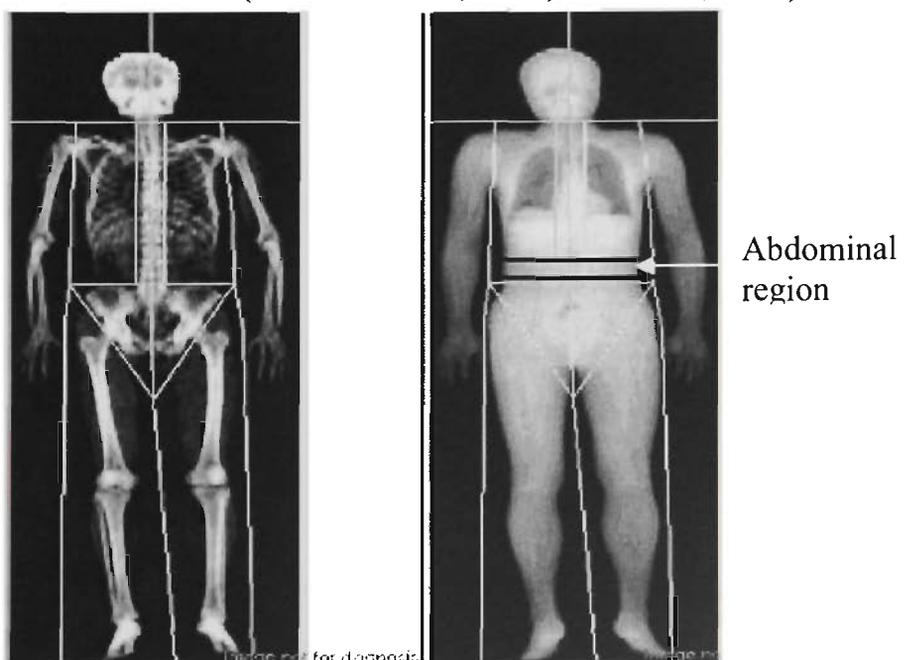


Figure 3.2. Whole body DXA measurements including the abdominal area.

3.5 Blood sample

3.5.1 Standard overnight fasting blood sample

A blood sample was collected after an overnight fast of at least 12 h. Blood was centrifuged and analysed (SYNCHRON LX ® System/Lxi725, Beckman, USA) for total cholesterol, triglyceride, high-density lipoprotein (HDL), glucose, and C-reactive protein (CRP) and the hepatic enzymes gammaglutamyltransferase (GGT) and alanine aminotransferase (ALT). Low-density lipoprotein (LDL) was calculated as:

$LDL = [\text{Total cholesterol} - (\text{HDL} + \text{triglyceride})] / 2.24$ (formula provided by the pathology laboratory, Austin Health).

HbA1c was analysed using a Primus CLC 330 analyser (Kansas City, Missouri, USA) and insulin was analysed with an automated Immulite 2000 immunoassay system (Immulite 2000, DPC, USA). Insulin resistance was assessed by the homeostasis model assessment (HOMA-IR). This model has been validated against the hyperinsulinemic-euglycemic clamp for insulin resistance (Matthews et al., 1985). HOMA-IR is calculated from fasting glucose and insulin, as follows:

$\text{Insulin resistance} = \text{fasting glucose (mmol}\cdot\text{L}^{-1}) \times \text{fasting insulin (}\mu\text{U}\cdot\text{ml}^{-1}) / 22.5$ (Haffner et al., 1996).

All of the above tests were conducted in the Austin Health pathology laboratory by staff of the laboratory.

3.5.2 Blood samples for BDNF and proinflammatory cytokines

On a different day, a 20 ml blood sample was taken following a fast of at least 3 h. The sample was centrifuged and the plasma immediately stored at -20°C until all samples were assayed together at the end of the data collection phase. BDNF was analysed with a standard Human BDNF enzyme-linked immunosorbent assay (ELISA) method (Catalog number: DY248 Minneapolis, MN, USA), according to the manufacturer's protocol. This assay was conducted at the Baker Heart Institute, Melbourne by Dr. Vance Matthews.

Proinflammatory cytokines, IL-1 β , IL-6, IL-8 and TNF- α were analysed using high sensitivity multiplex assays (Human High Sensitivity Cytokine assay, LincoPlex, Millipore, Billerica, MA, USA), according to the manufacturer's protocol. Cytokines were analysed at the University of Queensland, School of Human Movement Studies by Dr. Jonathan Peake.

3.6 Blood pressure

All blood pressure recordings were conducted by the PhD candidate on the brachial artery using a standard mercury sphygmomanometer after the participant had rested in a seated position for 15 minutes. Both systolic and diastolic (Korotkoff V) BP were recorded to the nearest 2 mmHg.

3.7 Aerobic power (VO_{2peak})

Aerobic power (VO_{2peak}) was assessed during a symptom-limited graded exercise test on a Cybex MET 100 cycle (Cybex Metabolic Systems, Ronkonkoma, NY, USA). The test started after a 5-minute period at rest. The protocol consisted of an initial intensity of 25W, then an increase to 40W after 1 min, and then followed by increments of 20W.min⁻¹ for males and 10W.min⁻¹ for females. The test was terminated when a participant's rating of perceived exertion had reached "very hard" [Borg scale = 17; (Borg, 1982)], or before that if clinical signs or symptoms of metabolic or cardiorespiratory abnormalities appeared. Expired respiratory gases were collected through a breath-by-breath (BxB) pneumotach system connected to gas analysers (Medgraphics, cardio2 and CPX/D System – Utilizing Breezeex Software, 142090-001, Revia, MN). The BxB data were integrated for each 15 sec interval, and the mean values for VO_2 , VCO_2 and ventilation (V_E) were used for that interval. The gas analyser was calibrated immediately before each test using gases that had been calibrated at alpha standard. HR was measured at rest and during the incremental test by 12-lead electrocardiography (Mortara, X-Scribe II, Milwaukee, WI, USA). Participants were asked not to consume caffeine or alcohol for a minimum of two hours before the exercise test.

3.8 Physical Performance Test

The Physical Performance Test (PPT) was based on the methods of Reuben and Siu (1990), with modifications by Brandon et al (2000) and Nichols et al (1995). The PPT was used to assess capacity for ADL's. The protocol included four functional mobility tasks consisting of a 15-meter rapid walking test, an up-and-go test, and stair climbing and stair descending. All tests were scored as time (sec). In the 15-meter rapid walking test, participants were instructed to walk at a fast but safe pace over a 15-meter distance. In the up-and-go test, participants were asked to rise from a standard chair (44 cm), walk 3 m, and return to a seated position on the chair. The stair tests consisted of a rapid ascent and descent of 22 stairs, whilst wearing a vest with weights evenly distributed around the torso corresponding to 15% of body mass (to mimic ADL's such as carrying a bag-pack or groceries). Participants rested between the ascent and descent for 45-60 sec. Participants underwent four-five attempts at each task with 40-60 sec rest intervals, and the best time for each test was reported. The ADL score was the sum of the best times for each of the four tests (the lower the score the better the performance). There were no instances of trips or stumbles for the ambulatory tests.

3.9 Muscle strength: one repetition maximum test

Four to eight days prior to the first one-repetition maximum test (1RM), participants performed a familiarisation session with the resistance training equipment (Life Fitness and CalGym, Caloundra, QLD, Australia). During the familiarisation session, correct lifting and breathing technique were taught and practiced using submaximal and near maximal loads. 1RM is defined as the heaviest weight a participant is able to lift once, using a proper lifting technique, without compensatory movements (Kraemer et al., 2006). 1RM strength was assessed for seven different exercises comprising in order, chest press, leg press, lateral pull-down, triceps pushdown, knee extension, seated row and biceps curl (Appendix B). Exercises involving large muscle groups were performed first, followed by those involving small muscle groups. In order to facilitate recovery and reduce the effects of fatigue, exercises were alternated between upper and lower body. The tests commenced after a light warm-up (three-minute walking at self-selected speeds on a treadmill). The maximal strength test protocol included one set of 10 repetitions at a relatively light load that served as a specific warm-up, followed by a

gradual increase in load until 1RM was achieved. The rate of the gradual increase in load was dependent on the participant's self-perceived capacity, and it ranged from 1-10 kg for biceps curl and triceps pushdown, up to 100 kg for leg press and between 1 to 20 kg for the rest of the exercises. The 1RM was achieved within 3-6 attempts. The rest period between attempts was 60 seconds, and between each specific exercise, volunteers recovered for 120 seconds. Four to eight days after the first 1RM (1RM-A), participants underwent another 1RM test (1RM-B). The 1RM-B test protocol and test conditions were identical for both tests (Kraemer et al., 2000). The best result for each exercise from the two tests was recorded as the 1RM for that individual. Intraclass correlation coefficients (ICC), typical error as a coefficient of variation (TEcv), retest correlation, repeated measures ANOVA, Bland-Altman plots, and estimation of 95% confidence limits were used to assess reliability between the two 1RM tests. The reliability between the two 1RM tests was high for all exercise (ICC \geq 0.99) (See Appendix C for the full reliability study as accepted for publication in the Journal of Science and Medicine in Sport). Total body muscle strength was calculated as the sum of the seven exercises, while relative muscle strength was calculated as the absolute total muscle strength divided by body mass (kg \cdot kg⁻¹). Studies have reported that the 1RM method to assess muscle strength is safe for elderly (Gordon et al., 1995; Shaw et al., 1995) and also for patients with CVD (Featherstone et al., 1993; Ghilarducci et al., 1989).

3.10 Quality of life questionnaire (SF-36)

Self perceived quality of life (QoL) was assessed using the SF-36 questionnaire (Appendix D). SF-36 assesses self-perceived QoL as reflected by perception of physical function and mental health (Brazier et al., 1992; McHorney et al., 1993; Ware, 1997). It has been widely used in studies examining the impact of obesity and other risk factors on health-related QoL (Ko, 2006; Rejeski et al., 2006; Yancy et al., 2002). The data from the SF-36 may assist in understanding the physical and mental burdens associated with chronic conditions (Ware, 1997). The survey contains 36 items that are compiled into eight scales. Four of the scales evaluate physical health dimensions including physical functioning, role physical (limitation due to physical problems), bodily pain and general health. The other four scales evaluate mental health dimensions including vitality, social functioning, role emotional (limitations due to emotional problems) and

mental health (McHorney et al., 1993; Ware, 1997). Each scale is attributed a score from 0 to 100, where a higher score represents a higher level of function and health-related QoL. The survey was completed before the PPT and all questionnaires were administered by a single investigator.

3.11 Resistance training program

The RT program was performed three times per week for 10 weeks with at least 48 hr recovery (range of 48-72 h) between sessions. Training consisted of seven different exercises for the major muscle groups including chest press, leg press, lateral pull-down, triceps pushdown, knee extension, seated row and biceps curl. In addition, participants performed one abdominal exercise (abdominal curl). Each training session included 3 minutes warm-up and 50-60 minutes of resistance exercise. The exercises was based on the recommendations of the American College of Sport Medicine for individuals with insulin resistance and T2DM (ACSM, 2000b). Similar training protocols have been shown to be effective (e.g. increases in muscle strength) (Levinger et al., 2005b) and safe (Levinger et al., 2005a) for patients with chronic heart failure.

The RT program is outlined in Table 3.1. During the first week, participants performed 2 sets of 15-20 repetitions at intensities corresponding to 40-50% 1RM. At week two, participants performed 3 sets of 15-20 repetitions at intensities corresponding to 50-60% of 1RM. Between weeks three and six, the number of repetitions were reduced to 12-15 and intensity increased (60-75% of 1RM). In the final four weeks of training, the number of repetitions ranged from 8 to 12, with intensities corresponding to 75-85% of 1RM. For each session, weights were adjusted according to the current capacity of an individual, with weights increased by 2-5 kg if the participant was able to achieve the maximum number of prescribed repetitions for that week, and decreased by 2-5kg if the minimum number of repetitions was not able to be lifted. All training sessions were supervised by an exercise physiologist or post-graduate students enrolled in a clinical exercise science course.

Table 3.1. Resistance training protocol: duration, volume and intensity.

Time	Variable	% from 1RM	Repetitions	No. of sets	No. of exercises
Baseline testing	Familiarisation				
	Strength test	100	1		7 (not included abdominal curl)
10 weeks of resistance training	1	40-60	15-20	2	8
	2	50-60	15-20	3	8
	3-6	65-75	12-15	3	8
	7-10	75-85	8-12	3	8
Post testing	Strength test	100	1		7

3.12 Ethics approval

The study protocol was approved by the Human Research Ethics Committees of both Victoria University (Approval No. HRETH:05/63) and Austin Health (Approval No. H2005/02242) and has been registered under the Australian Clinical Trials Registry (ACTR): ACTRN012606000207516.

Chapter 4

Study 1. Characteristics of individuals with HiMF and LoMF

4.1 Introduction

The prevalence of metabolic risk factors associated with MetS and T2DM and their links with obesity (Kearney et al., 2005; Zimmet et al., 2003; Zimmet et al., 2005), have increased considerably over the past two decades in both sexes (Ford, 2005). It has been reported that muscle strength and aerobic fitness are inversely correlated with increases in cardiovascular risk profile (Jurca et al., 2004; LaMonte et al., 2005). In addition, low exercise capacity, impaired capacity to perform ADL's (Jurca et al., 2004; Lee et al., 2005) and lower self-perceived physical, emotional and social QoL (Chambers et al., 2002; Doll et al., 2000; Katz et al., 2000; Ko, 2006; Rejeski et al., 2006) are each thought to be associated with increased cardiovascular risk profiles. However, these studies included patients who had already developed overt cardiac disease, including coronary artery disease and heart failure. It is possible that these reductions in the capacity to perform ADL's and QoL were skewed by the influence of symptomatic CVD. It remains unclear if individuals with various clusters of risk factors for MetS, in the absence of symptomatic heart disease also have impaired capacities to perform ADL's and lower self-perceived QoL.

4.2 Purpose

The main purpose of Study One was to examine different characteristics between individuals with HiMF and those with low number (≤ 1) of metabolic risk factors (LoMF) for MetS and T2DM. The characteristics included in this study included anthropometric measurements and traditional (lipids profile, glycaemic control) and emerging (BDNF, hepatic enzymes and inflammatory markers) risk factors. In addition, this study examined whether increased risk profiles in the absence of symptomatic heart disease are linked to reductions in capacity to perform ADL's and/or impaired QoL in

this population as a whole, and also according to sex (i.e men with HiMF versus men with LoMF and women with HiMF versus women with LoMF), thereby providing early warnings that may motivate individuals to seek early medical treatments and/or early adoption of healthy lifestyle behaviours.

4.3 Hypotheses

The following hypotheses were tested:

1. Individuals with HiMF will have lower capacity to perform ADL's and self-perceived QoL, compared to individuals with LoMF.
2. The capacity to perform ADL's and QoL will be adversely affected in both men and women with HiMF, compared to those with LoMF.
3. The emerging risk factors examined in this study are associated with the traditional risk factors studied, and both will be significantly elevated in individuals with HiMF.

4.4 Methodology

4.4.1 Participants

See General methods Section "3.2 Participants".

4.4.2 Study design

Participants underwent a series of anthropometric measurements, fasting blood test, assessment of their aerobic power (VO_{2peak}), muscle strength, physical performance test to assess functional capacity, and a self-perceived QoL questionnaire (SF-36). The series of tests were all completed within 3-4 weeks for each individual.

4.4.2.1 Three-day dietary logs

See General methods Section " 3.3 Three-day dietary logs"

4.4.2.2 Anthropometric measurements

See General methods Section “3.4 Anthropometric measurements”

4.4.2.3 Standard overnight blood test

See General methods Section “3.5 Blood sample”

4.4.2.4 Blood pressure

See General methods Section “3.6 Blood pressure”

4.4.2.5 Aerobic power (VO_{2peak})

See General methods Section “3.7 Aerobic power (VO_{2peak})”

4.4.2.6 Physical Performance Test

See General methods Section “3.8 Physical Performance Test”.

4.4.2.7 Muscle strength: one repetition maximum test

See General methods Section “3.9 Muscle strength: one repetition maximum test”.

4.4.2.8 Quality of life questionnaire (SF-36)

See General methods Section “3.10 Quality of life questionnaire (SF-36)”

4.4.2.9 Statistical analyses

Multivariate-analysis of variance (MANOVA) was used to assess differences between the HiMF and LoMF men and women. Comparisons included anthropometric measurements, risk factors, aerobic power, strength and the capacity to perform ADL's and QoL. Multiple comparisons were corrected using the Bonferroni method. Spearman

Rho correlations were conducted to assess the relationship between selected variables. All data are reported as mean \pm standard deviation and all statistical analyses were conducted at the 95% level of significance.

4.5 Results

4.5.1 Age, sex, anthropometric measurements, dietary intake and hemodynamics of individuals with HiMF and LoMF

The physical characteristics of the LoMF and HiMF groups are shown in Table 4.1. There were no significant age or height differences between the groups. Participants in HiMF had higher body mass, waist circumference, total body fat and higher LBM ($p < 0.01$) and reported significantly ($p < 0.05$) higher total energy (KJ) (by 22.2%) and fat (g) (by 26.6%) uptake, and tended to increase ($p = 0.10$) protein uptake (by 20.9%) (Table 4.2). In addition, the HiMF group had higher SBP, DBP and RPP (Table 4.3).

Table 4.1. Anthropometric characteristics: comparison between individuals with HiMF and LoMF.

Variable	LoMF N=25	HiMF M=30	p
Sex (M/F)	8/17	20/10	-----
Age (yrs)	49.5 \pm 6.5	51.9 \pm 6.4	0.16
Age (range)	40-61	40-69	-----
Height (cm)	166.9 \pm 9.1	170.3 \pm 9.9	0.19
Mass (kg)	67.3 \pm 11.5	89.5 \pm 13.8	<0.01
Waist (cm)	81.1 \pm 8.5	101.5 \pm 10.6	<0.01
BMI (kg·m ⁻²)	24.1 \pm 3.2	30.8 \pm 4.1	<0.01
Total Fat (%)	34.6 \pm 9.0	37.8 \pm 8.8	0.12
Total Fat (kg)	22.4 \pm 6.8	32.6 \pm 8.9	<0.01
Total LBM (kg)	42.5 \pm 10.2	53.7 \pm 10.9	<0.01

BMI (body mass index), LBM (lean body mass).

Table 4.2. Dietary compositions: comparisons between individuals with HiMF and LoMF.

Variable	LoMF	HiMF	p
Total energy (KJ)	6710.5±1997.2	8201.6±2197.9	0.03
Carbohydrates (g)	161.2±76.0	196.0±66.7	0.14
Protein (g)	70.4±22.9	85.1±30.6	0.10
Fat (g)	61.0±20.6	77.2±20.8	0.02

Table 4.3. Resting heart rate, blood pressure and rate-pressure product comparisons between individuals with HiMF and LoMF.

Variable	LoMF	HiMF	p
Resting HR (bpm)	73.0±9.9	70.7±10.3	0.40
SBP (mmHg)	116.7±11.7	133.3±13.3	<0.01
DBP (mmHg)	77.0±6.8	87.6±8.8	<0.01
RPP (SBP×HR) ·100 ⁻¹	85.2±14.7	94.1±16.8	0.04

HR (heart rate), SBP (systolic blood pressure), DBP (diastolic blood pressure), RPP (rate pressure product).

4.5.2 Lipids profile and glycaemic measurements of individuals with HiMF and LoMF

The aggregate data for the HiMF group demonstrated elevated total cholesterol, triglyceride and LDL levels, and lower HDL (Table 4.4). In addition they had lower glycaemic control as reflected by higher fasting glucose levels, HbA1c, insulin levels and HOMA-IR (p<0.05).

Table 4.4. Lipids, glucose, HbA1c and insulin resistance, comparisons between individuals with HiMF and LoMF.

Variable	LoMF	HiMF	p
Total Cholesterol (mmol·L ⁻¹)	5.0±1.0	5.9±1.0	<0.01
Triglyceride (mmol·L ⁻¹)	0.7±0.4	1.5±0.6	<0.01
LDL (mmol·L ⁻¹)	2.8±1.0	3.8±1.0	<0.01
HDL (mmol·L ⁻¹)	1.8±0.6	1.5±0.5	0.02
Glucose (mmol·L ⁻¹)	5.0±0.3	5.8±0.8	<0.01
HbA1 _c (%)	5.2±0.2	5.6±0.4	<0.01
Insulin (pmol·L ⁻¹)	27.6±21.8	55.9±33.7	<0.01
HOMA-IR	0.9±0.7	2.0±1.3	<0.01

LDL (low density lipoprotein), HDL (high density lipoprotein), HbA1c (glycated-haemoglobin), HOMA-IR (homeostasis model assessment for insulin resistance).

4.5.3 Inflammatory markers, BDNF and hepatic enzymes of individuals with HiMF and LoMF

Individuals with HiMF demonstrated significantly elevated inflammatory markers, compared to individuals with LoMF. These markers included elevated IL-6 (51.4%), TNF- α (57.4%) and CRP (133.3%) (all $p < 0.05$, Table 4.5). IL-1 β and IL-8 were also elevated but did not reach statistical significance. GGT, ALT and BDNF also were significantly elevated in volunteers with HiMF, compared to volunteers with LoMF (82.3%, 146.6% and 27.5% respectively $p < 0.05$). Alcohol intake was similar between the two groups (HiMF 5.6±6.3 and LoMF 4.3±6.3 alcohol drinks per week $p = 0.46$), suggesting that GGT and ALT was elevated in the HiMF group independent of alcohol intake.

Table 4.5. Differences in emerging risk factors between individuals with HiMF and LoMF.

Variable	LoMF	HiMF	p
IL-1 β (pg·ml ⁻¹)	4.9 \pm 3.5	6.5 \pm 4.5	0.17
IL-6 (pg·ml ⁻¹)	14.8 \pm 11.2	22.4 \pm 13.3	0.04
IL-8 (pg·ml ⁻¹)	7.2 \pm 5.0	10.5 \pm 8.2	0.11
TNF- α (pg·ml ⁻¹)	4.7 \pm 2.1	7.4 \pm 5.6	0.05
CRP (mg·L ⁻¹)	1.2 \pm 1.0	2.8 \pm 1.7	<0.01
GGT (U·L ⁻¹)	19.8 \pm 19.1	36.1 \pm 24.4	<0.01
ALT (U·L ⁻¹)	20.4 \pm 8.9	50.3 \pm 42.0	<0.01
BDNF (pg·ml ⁻¹)	709.6 \pm 239.8	904.9 \pm 270.8	0.01

IL (interleukin), TNF α (tumor necrosis factor alpha), CRP (C-reactive protein), GGT (gammaglutamyltransferase), ALT (alanine aminotransferase). Proinflammatory cytokines and BDNF data are reported for 50 volunteers, as 5 individuals chose not to undertake an additional blood sample.

4.5.4 Aerobic power, capacity to perform ADL's and quality of life in participants with high and low numbers of metabolic risk factors

No significant differences were observed between HiMF and LoMF for VO_{2peak} (ml·kg⁻¹·min⁻¹), muscle strength relative to body mass or any of the PPT measures (Table 4.6). Significantly higher values (p<0.01) were observed for absolute VO_{2peak} (+ 31.3%) and absolute muscle strength (+ 35.4%) in HiMF, compared to LoMF (Table 4.6). No significant difference was observed between the groups for any of the scales of the SF-36 (Table 4.7).

Table 4.6. *VO₂peak, strength and functional capacity differences between individuals with high and low metabolic risk factors.*

Variable	LoMF	HiMF	p
VO ₂ peak (L·min ⁻¹)	1.6±0.5	2.1±0.6	<0.01
VO ₂ peak (ml·kg ⁻¹ ·min ⁻¹)	23.9±5.5	23.1±5.2	0.56
Muscle strength (kg)	379.6±134.1	513.9±144.8	<0.01
Muscle strength (kg·kg ⁻¹)	5.5±1.3	5.7±1.4	0.62
15 m walk (sec)	5.9±0.7	5.9±1.2	0.81
Up and go (sec)	5.1±0.6	4.9±0.8	0.51
Ascending stairs (sec)	8.4±1.6	8.2±1.7	0.71
Descending stairs (sec)	8.0±1.9	7.6±1.7	0.46
Total PPT (sec)	27.4±4.3	26.7±5.0	0.57

VO₂peak (peak oxygen consumption), muscle strength-kg (absolute weight lifted, sum of seven exercises), muscle strength-kg·kg⁻¹ (muscle strength relative to body mass), PPT (physical performance test, lower total time represents better performance in the functional tests).

Table 4.7. *Self-perceived quality of life (SF-36) comparison between individuals from HiMF and LoMF.*

Variable	LoMF	HiMF	p
Physical function	87.0±12.1	86.8±12.5	0.96
Role physical	84.0±28.8	87.5±26.9	0.64
Bodily pain	81.4±18.8	71.8±25.2	0.12
General health	70.2±20.8	73.0±17.8	0.60
Vitality	61.2±17.8	62.0±17.0	0.87
Social function	90.0±17.2	89.3±17.2	0.87
Role emotional	86.7±30.4	92.2±18.9	0.41
Mental health	76.2±15.6	80.0±13.7	0.33
Physical health dimension	76.7±15.7	76.2±15.6	0.90
Mental health dimension	76.8±14.8	79.3±12.7	0.52

Role physical refers to role limitations attribute to physical problems. Role emotional refers to limitations attribute to emotional problems).

4.5.5 Correlation between selected variables

The actual number of risk factors were significantly correlated with absolute VO_{2peak} ($r=0.41$, $p<0.01$) and with total muscle strength ($r=0.49$, $p<0.01$). No correlation was found between the number of risk factors and VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$), or muscle strength relative to body mass. In addition, no significant correlation was found between the number of risk factors and the capacity to perform ADL's or QoL. VO_{2peak} (both absolute and relative) were correlated with muscle strength and the capacity to perform ADL's, but not with QoL. Relative muscle strength was the only variable that tended to correlate with both the mental and the physical aspects of the SF-36 (Table 4.8).

Table 4.8. Correlations between the number of metabolic risk factors and variables of exercise capacity.

	VO_{2peak} ($L \cdot min^{-1}$)	VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	Muscle strength (kg)	Muscle strength ($kg \cdot kg^{-1}$)	PPT (sec)	PHD	MHD
N risk factors	$r=0.41$ $p<0.01$	N/S	$r=0.49$ $p<0.01$	N/S	N/S	N/S	N/S
VO_{2peak} ($L \cdot min^{-1}$)	-----	$r=0.67$ $p<0.01$	$r=0.85$ $p<0.01$	$r=0.63$ $p<0.01$	$r=-0.56$ $p<0.01$	N/S	N/S
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	-----	-----	$r=0.44$ $p<0.01$	$r=0.66$ $p<0.01$	$r=-0.49$ $P<0.01$	$r=0.23$ $p=0.09$	N/S
Muscle strength (kg)	-----	-----	-----	$r=0.81$ $p<0.01$	$r=-0.73$ $p<0.01$	N/S	N/S
Muscle strength ($kg \cdot kg^{-1}$)	-----	-----	-----	-----	$r=-0.82$, $p<0.01$	$r=0.24$ $p=0.07$	$r=0.23$ $p=0.09$
Total PPT (sec)	-----	-----	-----	-----	-----	N/S	N/S
PHD	-----	-----	-----	-----	-----	-----	$r=0.78$ $p<0.01$

PPT (physical performance test), PHD (physical health dimension), MHD (mental health dimension).

4.5.6 Correlation between BDNF and other risk factors

BDNF levels were positively correlated with the actual number (0,1,2,3,4 or 5) of metabolic risk factors ($r=0.31$, $p=0.03$), triglyceride ($r=0.38$, $p<0.01$), fasting plasma

glucose levels ($r=0.36$, $p<0.01$), HbA1c($r=0.34$, $p=0.01$), plasma insulin level ($r=0.35$, $p=0.01$), HOMA-IR ($r=0.37$, $p<0.01$) and abdominal fat ($r=0.28$, $p=0.05$). BDNF was negatively correlated with HDL ($r=-0.33$, $p=0.02$). No significant correlation was found between BDNF and blood pressure ($p>0.05$). When factors were taken together within one stepwise multiple regression model, triglyceride was the strongest predictor for BDNF levels ($r=0.45$, $p<0.01$).

4.5.7 Correlation between hepatic enzymes and inflammatory markers and other risk factors

Of all blood parameters investigated, only CRP, GGT and ALT were correlated with the actual numbers of metabolic risk factors ($r=0.48$, $r=0.51$ and $r=0.57$ respectively, all $p<0.01$). CRP, GGT and ALT were also correlated with anthropometric measurements and metabolic risk factors (Table 4.9). A stepwise multiple regression model indicated that HDL and LDL correlated most strongly with GGT, and triglyceride and total body fat were correlated most strongly with CRP (all $p<0.05$). ALT did not correlate with other risk factors when all variables were analysed in one model.

Table 4.9. Correlations between markers of proinflammatory markers, hepatic enzymes and conventional metabolic risk factors.

	CRP	GGT	ALT
Waist circumference (cm)	0.41	0.58	0.60
Abdominal fat (g)	0.52	0.50	0.46
Fasting glucose ($\text{mmol}\cdot\text{L}^{-1}$)	0.32	0.40	0.29
HbA1c (%)	0.33	0.35	0.31
HOMA	0.36	0.46	0.54
SBP (mmHg)	0.35	0.33	0.26
LDL ($\text{mmol}\cdot\text{L}^{-1}$)	0.37	0.44	0.38
Triglycerides ($\text{mmol}\cdot\text{L}^{-1}$)	0.55	0.50	0.49
HDL ($\text{mmol}\cdot\text{L}^{-1}$)	NS	-0.51	-0.60

For all reported data $p<0.05$. CRP (C-reactive protein), GGT (gamma-glutamyltransferase), ALT (alanine aminotransferase), HbA1c (glycosylated haemoglobin), HOMA (homeostasis model assessment of insulin resistance), SBP (systolic blood pressure), LDL (low density lipoprotein), HDL (high density lipoprotein), NS (not significant, $p>0.05$).

4.5.8 Anthropometric, metabolic, physical fitness, functional capacities and quality of life of men and women with HiMF and LoMF.

In order to ensure that the metabolic differences between the HiMF and LoMF groups are because of a real metabolic alteration in individuals with 2 or more metabolic risk factors and not because of sex differences between the groups, groups were divided into four subgroups including men with HiMF and LoMF and women with HiMF and LoMF. As shown in Table 4.10, both men and women with HiMF were heavier, had larger waist circumference and higher total fat and LBM contents. In addition, the HiMF groups had higher total cholesterol, triglyceride and LDL. Similarly, both HiMF groups have elevated fasting glucose level and HbA1c and they more insulin resistant (Table 4.11). CRP was significantly elevated in women with HiMF ($p<0.01$), and in men it tended to be elevated ($p=0.10$).

Table 4.10. Anthropometric characteristics for men and women from HiMF and LoMF groups.

Variable	Men			Women		
	LoMF N=8	HiMF M=20	p	LoMF F=17	HiMF F=10	p
Age (yrs)	49.9±7.1	51.6±7.5	0.58	49.3±6.5	52.6±3.5	0.15
Age (range)	40-60	40-69	-----	40-61	47-58	-----
Height (cm)	176.6±6.7	175.1±7.9	0.63	162.3±5.9	160.8±5.6	0.51
Mass (kg)	77.6±8.9	92.8±13.3	<0.01	62.5±9.3	82.7±12.9	<0.01
Waist (cm)	88.4±6.9	104.2±9.6	<0.01	77.7±7.0	96.1±10.9	<0.01
BMI (kg·m ⁻²)	24.9±2.7	30.2±3.8	<0.01	23.7±3.4	32.0±4.6	<0.01
Total Fat (%)	26.2±6.5	32.8±5.2	<0.01	38.5±7.2	47.8±4.8	<0.01
Total Fat (kg)	19.9±5.7	29.9±8.3	<0.01	23.5±7.2	38.0±8.0	<0.01
Total LBM (kg)	55.5±6.6	60.1±6.3	0.09	36.4±3.8	40.9±5.3	0.02

BMI (body mass index), LBM (lean body mass).

Table 4.11. Metabolic characteristics for men and women from HiMF and LoMF groups.

Variable	Men			Women		
	LoMF	HiMF	p	LoMF	HiMF	p
SBP (mmHg)	117.3±10.0	132.0±14.1	0.01	116.5±12.7	135.8±12.1	<0.01
DBP (mmHg)	75.0±5.3	87.8±10.2	<0.01	78.0±7.3	87.2±5.5	<0.01
Total Cholesterol (mmol·L ⁻¹)	4.5±1.3	5.8±1.1	0.02	5.2±0.8	6.3±0.8	<0.01
Triglyceride (mmol·L ⁻¹)	0.9±0.4	1.7±0.	0.01	0.7±0.3	1.4±0.5	<0.01
LDL (mmol·L ⁻¹)	2.6±1.3	3.9±1.1	0.02	2.9±0.8	3.7±0.9	0.04
HDL (mmol·L ⁻¹)	1.5±0.6	1.2±0.3	0.10	2.0±0.6	2.0±0.4	0.89
CRP (mg·L ⁻¹)	1.2±1.1	2.3±1.6	0.10	1.2±1.1	3.8±1.6	<0.01
Glucose (mmol·L ⁻¹)	5.1±0.3	5.9±0.8	0.02	4.9±0.3	5.5±0.6	<0.01
HbA1c (%)	5.3±0.3	5.6±0.4	0.04	5.2±0.2	5.6±0.5	0.01
Insulin (pmol·L ⁻¹)	36.2±29.1	63.7±34.6	0.06	23.5±17.0	40.5±27.0	0.06
HOMA-IR	1.2±1.0	2.3±1.4	0.04	0.7±0.6	1.4±1.0	0.04

SBP (systolic blood pressure), DBP (diastolic blood pressure) LDL (low density lipoprotein), HDL (high density lipoprotein), CRP (C-reactive protein), HbA1c (glycosylated-haemoglobin), HOMA-IR (homeostasis model assessment for insulin resistance).

No significant difference was observed for VO_{2peak} between HiMF men and women compared to their LoMF peers, although women with HiMF tended to have higher absolute VO_{2peak} (L·min⁻¹) (p=0.07) (Table 4.12). Similarly, no significant difference was observed for muscle strength or the capacity to perform ADL's. It is important to note however, that women with HiMF tended to have lower relative muscle strength (-14%, p=0.06) and longer time to complete that ADL's activities (10%, p=0.07) compared to their LoMF peers (Table 4.12).

Table 4.12. Aerobic power, strength and functional capacities for men and women from HiMF and LoMF groups.

Variable	Men			Women		
	LoMF	HiMF	p	LoMF	HiMF	p
VO _{2peak} (L·min ⁻¹)	2.1±0.5	2.3±0.5	0.42	1.4±0.3	1.6±0.3	0.07
VO _{2peak} (ml·kg ⁻¹ ·min ⁻¹)	27.3±6.8	24.7±5.0	0.82	22.4±4.2	19.8±4.0	0.13
Muscle strength (kg)	527.0±126.4	594.6±98.6	0.14	310.3±63.5	352.4±59.9	0.10
Muscle strength (kg·kg ⁻¹)	6.8±1.2	6.4±1.0	0.49	5.0±0.9	4.3±0.8	0.06
15 m walk (sec)	5.2±0.7	5.2±0.9	0.99	6.2±0.5	7.1±0.6	<0.01
Up and go (sec)	4.7±0.8	4.6±0.6	0.61	5.2±0.5	5.6±0.7	0.12
Ascending stairs (sec)	7.2±0.7	7.4±1.1	0.69	9.0±1.6	9.9±1.4	0.13
Descending stairs (sec)	7.0±1.3	6.9±1.2	0.78	8.5±2.0	9.2±1.5	0.36
Total PPT (sec)	24.2±2.8	24.1±3.2	0.93	28.9±4.1	31.8±3.6	0.07

VO_{2peak} (peak aerobic power), muscle strength-kg (absolute weight lifted, sum of seven exercises), muscle strength-kg·kg⁻¹ (muscle strength relative to body mass), PPT (physical performance test, lower total time represents better performance in the functional test).

No differences between groups were observed in any of the components of the SF-36 with the exception of the bodily pain scale, with more self-reported pain in HiMF women, compared to LoMF women (Table 4.13).

Table 4.13. Self-perceived quality of life (SF-36) for men and women from HiMF and LoMF groups.

Variable	Men			Women		
	LoMF	HiMF	p	LoMF	HiMF	p
Physical function	87.5±10.0	90.0±10.5	0.57	86.7±13.3	80.5±14.2	0.26
Role physical	81.3±37.2	90.0±24.8	0.47	85.3±25.1	82.5±31.3	0.80
Bodily pain	79.0±22.8	75.9±26.3	0.77	82.5±17.2	63.7±22.1*	0.02
General health	61.5±22.1	75.2±15.8	0.08	74.35±19.4	68.6±21.5	0.48
Vitality	61.3±18.1	66.8±15.0	0.42	61.2±18.2	52.5±17.7	0.24
Social function	90.6±18.6	92.6±11.7	0.74	89.8±17.2	82.6±24.4	0.38
Role emotional	100.0±0.0	95.0±16.3	0.40	80.4±35.5	86.7±23.3	0.62
Mental health	79.5±13.3	83.2±12.1	0.48	74.6±16.7	73.6±14.9	0.88
Physical health dimension	74.0±18.6	79.5±14.2	0.41	77.9±14.7	69.6±17.1	0.19
Mental health dimension	78.5±11.8	82.6±9.3	0.35	76.1±16.3	72.7±16.1	0.61

* Indicates $p < 0.05$ between HiMF and LoMF in each sex. Role physical refers to role limitations attribute to physical problems. Role emotional refers to limitations attribute to emotional problems).

4.5.8.1 Correlation between selected variables

In women, but not in men, the actual number (0, 1, 2, 3, 4 or 5) of metabolic risk factors was positively correlated with the time taken to perform ADL's ($r=0.50$, $p=0.01$) (Figure 4.1) and negatively correlated with aerobic power ($r=-0.52$, $p<0.01$), and the physical components of the SF-36 including physical functioning ($r=-0.47$, $p=0.01$), bodily pain ($r=-0.55$, $p<0.01$) and physical health dimension ($r=-0.40$, $p=0.04$) (Figure 4.1). In both sexes, the number of risk factors had no associations with the mental aspects of the SF-36.

When muscle strength was expressed relative to body mass, there was a significant negative correlation with the risk profile ($r=-0.50$, $p=0.01$) in women only. For both women and men, relative muscle strength was correlated with the time taken to perform ADL's ($r=-0.70$ and $r=-0.62$, respectively) and relative aerobic power ($r=0.77$, $p<0.01$ and $r=0.36$, $p=0.06$, respectively). Relative muscle strength did not correlate with QoL for either sex.

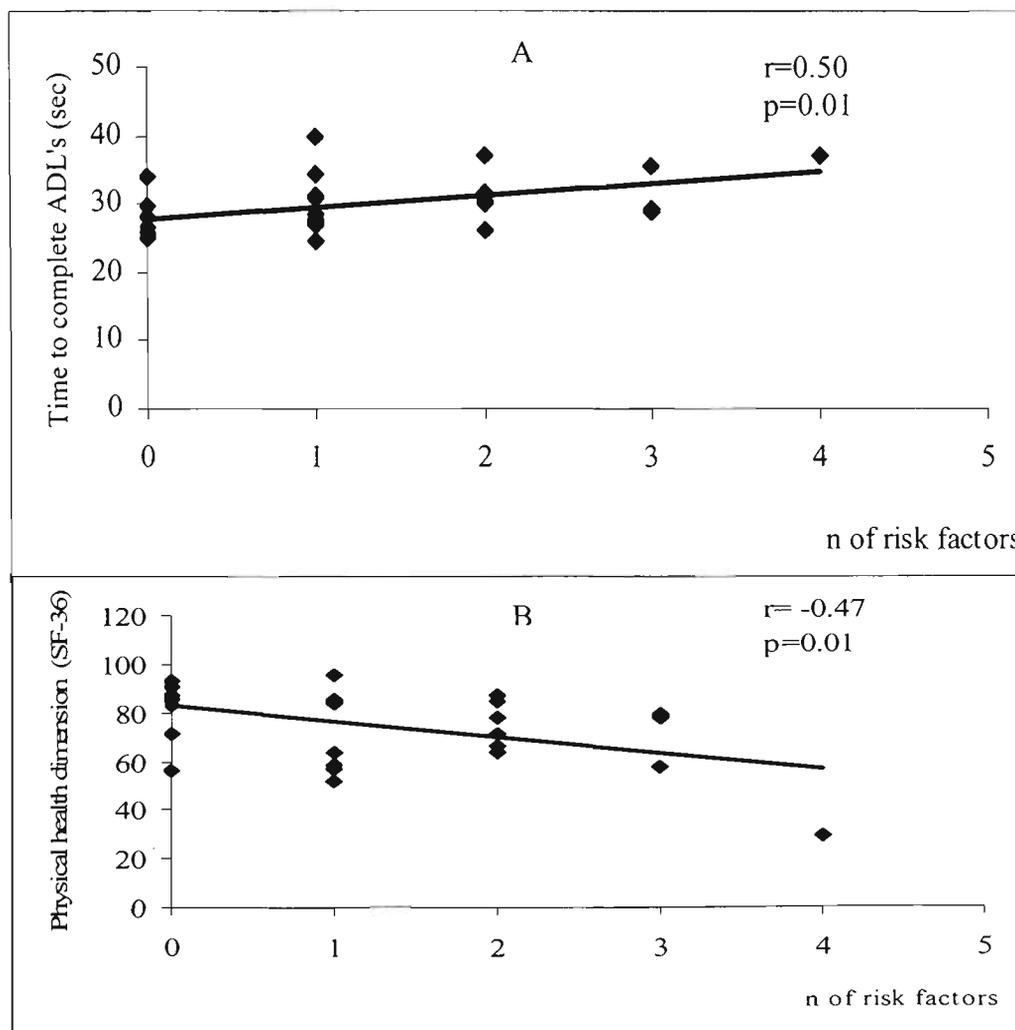


Figure 4.1. Correlation between the numbers of risk factor and time to complete the ADL's (activities of daily living) (A) and Physical health dimension (SF-36) (B) in women.

4.6 Discussion

4.6.1 The effect of HiMF and LoMF on functional capacity and quality of life.

An important finding of Study One was that despite the higher number of risk factors for the HiMF group compared to LoMF, no differences between the groups were observed for aerobic power, muscle strength relative to body mass, the capacity to perform ADL's or QoL. These findings were evident before and after groups were divided according to sex. However, women with HiMF reported more perceived bodily pain, compared to women with LoMF and the actual number of the metabolic risk factors correlated with the capacity to perform ADL's and the physical aspect of the SF-36.

Several previous studies have reported that people with clusters of metabolic risk factors and heart disease are usually less physically active (Chen et al., 2004; Lakka et al., 2003), and have lower aerobic and functional capacities (Lakka et al., 2003) and lower QoL (Doll et al., 2000; Katz et al., 2000; Rejeski et al., 2006; Yancy et al., 2002). In the current study, the group with HiMF demonstrated similar capacity to perform ADL's and QoL compared to individuals with LoMF, despite a significant higher risk of MetS and T2DM. Similar findings occurred for the men after the groups had been analysed separately according to sex. There are at least three possible explanations for the similar capacity to perform ADL's and QoL in individuals with HiMF and LoMF. First, the participants in the current study were free from symptomatic heart disease, suggesting that functional status and QoL are relatively unaffected until after the onset of signs and symptoms of such disease. Second, although the HiMF groups had significantly higher body mass and BMI, physical functioning was similar to the LoMF group (especially in men). Even though the self-reported physical activity patterns of the two groups were similar, when the heavier individuals did move, they derived a greater exercise stimulus due to greater body mass, and this may have served to normalise the exercise capacities of these relatively inactive groups of individuals. Finally, the findings of the current study may support Crisp and McGuinness (1976) "Jolly Fat" hypothesis. According to that hypothesis, some overweight and obese individuals have lower levels of depression and anxiety, that in turn may lead to higher self perception QoL, than lean people (Crisp and McGuinness, 1976; Li et al., 2004;

Palinkas et al., 1996). As a result, obesity and other risk factors may have little or no impact on physical and emotional function or self-perceived QoL (Fontaine et al., 1997; Lapidus et al., 1989; Palinkas et al., 1996).

It has been reported that skeletal muscle strength is an important factor contributing to the capacity to perform ADL's, aerobic power and to the maintenance of QoL in healthy elderly and those with chronic diseases (Fiatarone et al., 1994; Levinger et al., 2005b; Maiorana et al., 2002). An important finding of the current study is that in women with clusters of metabolic risk factors, even in the absence of symptomatic heart disease, there is a significant correlation between the risk profile and a reduction in some physical functioning capacities including relative muscle strength, aerobic power, ADL's and self-perceived capacity to perform physical activities. In addition, women with HiMF reported increased sensitivity to bodily pain, compared to women with LoMF. This finding is similar to Fontaine et al. (1996) who reported that the main effect of obesity is on bodily pain (indicates increase in pain). Furthermore, an increase in bodily pain is a common finding in obese individuals and it may be used as an independent predictor for self-perceived QoL (Barofsky et al., 1997). This may provide a possible explanation as to why women are more likely to consult a medical or allied health practitioner earlier in the disease process than men (Australian Bureau of Statistics, 2006; Leon, 2003). As women's clinical profiles may have an adverse effect on their daily physical performance, they may be more likely to seek medical intervention before the risk factors develop to fully evolved heart disease.

In contrast, men in this study did not demonstrate a significant correlation between risk profile and aerobic power or the capacity to perform ADL's. In addition, the risk profile did not translate into reductions in self-perceived QoL (both physical and mental aspects) in men with HiMF, compared to men with LoMF. The findings of this study may explain why men often live with risk factors for years before symptoms appear (Harris, 1993; Mooy et al., 1995; Mykkanen et al., 1993; Thomas et al., 2005b). In the absence of any deterioration in the capacity to perform ADL's and/or QoL, men with HiMF but without symptomatic disease, may not receive forewarning of impending health problems and thus not actively seek medical intervention or engage in self-help through lifestyle modification until later in the disease progression. Therefore, in contrast to women, the factors for MetS, T2DM and CVD have less impact on daily

activities of men and as such, they may not seek medical help in the early stage of the development of heart disease.

In summary, in women there is a correlation between the actual number of the metabolic factors associated with the MetS and T2DM and the capacity to perform ADL's and the physical aspect of QoL. In addition, women with HiMF have more self-perceived bodily pain compared to women with LoMF. In men however, it appears that the number of risk factors did not affect the capacity to perform ADL's or QoL. For men, the significance of this part of the study was that impaired functional capacities or reduced QoL may accompany or follow the emergence of symptomatic heart disease, but may not be early warnings of future disease.

4.6.2 The association between BDNF level and other risk factors in individuals with HiMF and LoMF

An important finding of the current study is that BDNF was significantly elevated in individuals with HiMF who are free from overt CVD. In addition, BDNF was positively correlated with the number of metabolic risk factors, and with abdominal fat, triglyceride, fasting plasma glucose, HbA1c, plasma insulin and insulin resistance and was negatively correlated with HDL in this population.

Recently, it has been shown that BDNF may play a role in the development of risk factors associated with the MetS, also called "Metabolic Syndrome-Neurotrophic Hypothesis" (Hristova and Aloe, 2006). It appears that BDNF levels and its associations with other risk factors may change with the duration of metabolic risk factor exposure and the prevalence of other chronic diseases such as T2DM. For instance, normal or elevated BDNF levels have been described at early stages of T2DM, and low levels as the disease progresses (Geroldi et al., 2006; Hristova and Aloe, 2006). In the current study, similar to Suwa et al. (2006), higher levels of BDNF were found for individuals with HiMF, compared to LoMF. This rise may have a compensatory role in partly negating hyperphagia (Suwa et al., 2006) that is common in these individuals. As was observed from the dietary logs, the HiMF group had higher total energy and fat intakes, compared to LoMF. The compensatory mechanism theory is supported by other studies that suggested that elevated levels of BDNF may suppress appetite and may assist in glucose homeostasis (Lebrun et al., 2006; Nakagawa et al., 2000; Nonomura et al.,

2001; Ono et al., 1997). In addition, BDNF infusions have been shown to suppress appetite and increase weight loss (Pelleymounter et al., 1995). In the current study, a positive correlation was found between BDNF and other metabolic risk factors in individuals who had not yet developed overt disease. Similarly, Suwa et al. (2006) reported a significant positive correlation between BDNF and BMI ($r=0.54$), percentages of body fat ($r=0.56$), triglyceride levels ($r=0.47$), fasting glucose levels ($r=0.44$) and insulin resistance ($r=0.51$) in newly diagnosed females with T2DM. In addition, they reported that BDNF levels were elevated in females with T2DM, compared to those with normal glucose tolerance.

However, an increase in BDNF levels through hyper-secretion at an early stage may lead to an imbalance in the autonomic nervous system in later stages of disease progression. It has been previously shown that altered interactions between the neuro-immuno-endocrine systems may lead reduce BDNF levels, compared to healthy controls (Hristova and Aloe, 2006). This may help to explain why individuals with longstanding T2DM (Geroldi et al., 2006; Krabbe et al., 2007) and neuropsychiatric disorders (Tsai, 2003) exhibit lower levels of BDNF, compared to healthy controls. In addition, negative correlations of BDNF with BMI ($r=-0.12$), HbA1c ($r=-0.11$) and triglyceride ($r=-0.21$), and a positive correlation with HDL ($r=0.34$), have been reported in patients with long standing metabolic risk factors (Geroldi et al., 2006).

4.6.3 The association between hepatic enzymes, inflammatory markers and risk factors in individuals with HiMF and LoMF

An important finding of the current study is that inflammatory markers, especially IL-6, TNF- α and CRP and the hepatic enzymes GGT and ALT, were elevated in individuals with HiMF, in the absence of overt T2DM and CVD. Previous studies have shown that GGT, ALT (Lee et al., 2006; Lim et al., 2004; Onat et al., 2006; Ruttman et al., 2005; Wannamethee et al., 2005) and inflammatory markers are elevated in individuals with MetS, T2DM and CVD (Duncan et al., 2003; Festa et al., 2000; Hak et al., 2001; Han et al., 2002; Herder et al., 2006; Hotamisligil et al., 1993; Laaksonen et al., 2004; Lechleitner et al., 2002; Pradhan et al., 2001; Rutter et al., 2004; Tracy, 1998). The data from the current study indicated that inflammatory markers and hepatic enzymes were also elevated in the presence of as few as two metabolic risk factors in the absence of

overt disease. These findings suggest that increased markers of inflammation and hepatic enzymes are elevated at earlier stages of the disease process than has been previously reported. It may also indicate that markers of inflammation, GGT and ALT may be used as early signs for metabolic disease in this population. These data support finding by other investigators who have suggested that these markers may be useful in clinical practice to identify individuals at high risk for developing T2DM and CVD (De Lorenzo et al., 2007; Emdin et al., 2005; Perry et al., 1998; Ridker et al., 2004).

In the current study, GGT, ALT and most of the inflammatory markers that were examined were elevated or tended to be elevated in individuals with HiMF. GGT, ALT and CRP were the only analytes that were significantly correlated with anthropometric and metabolic parameters such as waist circumference, body fat, abdominal fat, lipids, fasting glucose level and insulin resistance. Therefore, in combination with these anthropometric and metabolic variables, CRP and hepatic enzymes may assist in identifying early risk of developing MetS, T2DM and CVD. Longitudinal studies would be necessary to confirm this hypothesis. Although proinflammatory cytokines were higher in individuals with HiMF it appears that measurements of these may not add any additional clinical information. This is significant given the high cost of measuring proinflammatory cytokines.

4.6.4 Conclusions

Study One has examined some of the biochemical characteristics and functional capacities in individuals with high and low numbers of metabolic risk factors associated with MetS, T2DM and CVD. In particular, this study has examined the associations between traditional metabolic risk factors and functional capacity, the capacity to perform ADL's and QoL in these populations. In addition, some emerging risk factors were compared for individuals with HiMF and LoMF, and there were also examined in association with several traditional risk factors. This study showed that in addition to alterations in the traditional metabolic risk factors for HiMF, hepatic enzymes and inflammatory markers were also elevated even in individuals with 2 or more metabolic risk factors but free from overt disease. In addition, the present study has also provided a rationale for adding GGT, ALT and the inflammatory marker CRP, to the list of factors defining MetS and contributing to the development of T2DM and CVD, and

may be monitored regularly in clinical practice together with glucose, lipids levels and BP. A particularly novel finding was that BDNF was elevated in individuals with HiMF, compared to those with LoMF, and also correlated with risk factors for MetS and T2DM. This rise may have a useful compensatory role in partly negating hyperphagia that is common in individuals with HiMF. This finding may also be associated with a relatively early stage of risk factor exposure and absence of chronic overt disease.

However, despite the clear differences in both traditional and emerging risk factors between the HiMF group and the LoMF group, both groups exhibited similar muscle strength and VO_{2peak} , (both relative to body mass), as well as capacity to perform ADL's and self perceived QoL. These results were also evident even after the groups were stratified according to sex, especially in men. This important finding suggests that increases in the number of risk factors for metabolic disease may not always translate into reductions in the capacity to perform ADL's and QoL.

In women with HiMF, there were trends for reductions in muscle strength relative to body mass, and the capacity to perform ADL's ($p=0.06$ and 0.07 respectively), with no difference in VO_{2peak} . Self-reported bodily pain was significantly higher in women with HiMF, compared to women with LoMF. In women, there was also a significant correlation between the actual number of metabolic risk factors and the capacity to perform ADL's and self-perceived physical capacity. The implication for women is that impairment in functional capacity and self-perceived bodily pain for those with HiMF may provide some early warning signs, and this may translate into earlier visits to their medical practitioners than would otherwise be the case.

Primary prevention of MetS, T2DM and CVD depends on the early detection of risk factors, early medical intervention and, independent of these, early adoption of healthy lifestyle. This emphasises the importance of regular medical check-ups, combined with education and motivation strategies to promote long-term self-management of healthy lifestyle.

Chapter 5

Study 2. Effect of resistance training on body composition, functional capacities and quality of life

5.1 Introduction

Loss of muscle mass and strength are common in apparently healthy middle-aged and elderly individuals and also individuals with HiMF and T2DM (Iannuzzi-Sucich et al., 2002; Willey and Fiatarone-Singh, 2003). Increases in muscle strength and mass should be goals for exercise interventions for healthy middle-aged and elderly individuals, as well as those with chronic disease.

Whilst the benefits of aerobic training are well documented for HiMF and T2DM, more studies are needed to examine the effects of RT for these populations (Eriksson, 1999; Willey and Fiatarone-Singh, 2003). RT has been shown to be an effective mode of exercise training to combat age-related loss of muscle mass and strength (Fiatarone-Singh, 1998; Hurley and Roth, 2000). Increases in muscle strength, are the most common findings as a result of RT. It has been reported that increases in skeletal muscle strength may improve functional capacity and reduce physical impairment in elderly people (Brandon et al., 2000). Improvement in the capacity to perform ADL's has been proposed as a surrogate for QoL (Pennix et al., 2001). Improvements in the capacity to perform ADL's may also improve self-reported QoL (Poehlman, 1999). Although some investigators have reported improvements in QoL for elderly individuals following RT (Rejeski et al., 2002), others have reported no such improvements (Perrig-Chiello et al., 1998).

To date, there are limited data on the effects of RT alone on the capacity to perform ADL's and QoL for middle-aged individuals with HiMF, or the comparative effects of RT for individuals with HiMF, compared to those LoMF.

5.2 Purpose

The purpose of Study Two was to compare the effects of RT as a single intervention on the capacity to perform ADL's and QoL of middle-aged individuals with HiMF and LoMF. In addition, this study assessed the relationship between changes of muscle strength, VO_{2peak} and body composition and their contributions to any improvements seen in the capacity to perform ADL's and QoL in these two populations.

5.3 Hypotheses

The following hypotheses were tested:

1. RT improves muscle strength and in turn the capacity to perform ADL's for individuals with either HiMF or LoMF.
2. RT will produce favourable changes to body composition for individuals with either HiMF or LoMF.
3. RT will improve QoL for individuals with either HiMF or LoMF.

5.4 Methodology

5.4.1 Study design and participants

See General methods Sections "3.1 Study design" and "3.2 Participants".

5.4.1.1 Three-day dietary logs

See General methods Section "3.3 Three-day dietary logs".

5.4.1.2 Anthropometric measurements

See General methods Section "3.4 Anthropometric measurements".

5.4.1.3 Standard overnight blood test

See General methods Section "3.5 Blood sample"

5.4.1.4 Blood pressure

See General methods Section “3.6 Blood pressure”.

5.4.1.5 Aerobic power (VO_{2peak})

See General methods Section “3.7 Aerobic power (VO_{2peak})”.

5.4.1.6 Physical Performance Test

See General methods Section “3.8 Physical Performance Test”.

5.4.1.7 Muscle strength: one repetition maximum test

See General methods Section “3.9 Muscle strength: one repetition maximum test”.

5.4.1.8 Quality of life questionnaire (SF-36)

See General methods Section “3.10 Quality of life questionnaire (SF-36)”.

5.4.1.9 Resistance training program

See General methods Section “3.11 Resistance training program”.

5.4.2.10 Statistics

MANOVA was used to examine the differences of the metabolic risk factors between HiMF and LoMF before each group was randomised to training or the non-exercise control groups. In addition MANOVA was used to examine the groups’ characteristics at baseline after randomisation (i.e. HiMFT versus HiMFC and LoMFT versus LoMFC). The exercise training data were analysed by the repeated measured ANOVA model that was constructed to analyse the effect of primary interest by time (pre- and post-) for each group. Repeated measures ANOVA was also used to examine the effect of exercise training over time between LoMFT versus LoMFC and also between HiMFT and HiMFC (referred as p “Group × Time”) and between the two training

groups (LoMFT versus HiMFT). Spearman Rho correlations were conducted to assess correlations between changes in muscle strength and QoL, and changes in muscle strength and the capacity to perform ADL's. All data are reported as mean \pm standard deviation and all statistical analyses were conducted at the 95% level of significance.

5.5 Results

5.5.1 Metabolic differences between the HiMF and LoMF

As was reported in Study One, individuals with HiMF had higher waist circumference (101.5 ± 10.6 versus 81.1 ± 8.5 cm, $p < 0.01$), higher systolic (133.3 ± 13.3 versus 116.7 ± 11.7 mmHg, $P < 0.01$) and diastolic 87.6 ± 8.8 versus 77.0 ± 6.8 mmHg, $p < 0.01$) blood pressure, higher triglyceride levels (1.5 ± 0.6 versus 0.7 ± 0.4 mmol·L⁻¹, $p < 0.01$), and lower HDL levels (1.5 ± 0.5 versus 1.8 ± 0.6 mmol·L⁻¹, $p = 0.02$), compared to the LoMF group. In addition the HiMF group had higher fasting glucose (5.8 ± 0.8 versus 5.0 ± 0.3 mmol·L⁻¹, $p < 0.01$) and insulin levels (55.9 ± 33.7 versus 27.6 ± 21.8 pmol·L⁻¹, $p < 0.01$).

5.5.2 Baseline comparisons

Before commencing the exercise intervention, there were no significant differences between LoMFC and LoMFT, or between HiMFC and HiMFT for sex, age, weight, height, total body fat percentages and total LBM (all $p > 0.05$, Table 5.1).

Table 5.1. Baseline comparison between LoMFC versus LoMFT groups and HiMFC versus HiMFT groups.

Variable	LoMFC N=13	LoMFT N=12	p	HiMFC N=15	HiMFT N=15	p
Sex (M/F)	4/9	4/8	-----	10/5	10/5	-----
Age (yrs)	48.5±7.7	50.6±5.1	0.43	52.3±5.8	51.6±7.1	0.78
Height (cm)	166.4±8.3	167.4±10.2	0.80	170.9±8.8	169.7±11.1	0.75
Mass (kg)	67.8±12.6	66.8±10.6	0.84	88.3±14.8	90.6±13.4	0.64
Waist (cm)	81.3±8.5	80.9±8.9	0.90	99.0±10.6	104.1±10.4	0.20
BMI (kg·m ⁻²)	24.3±3.4	23.8±3.1	0.70	30.0±3.7	31.6±4.4	0.28
Total Fat (%)	34.6±8.0	34.6±10.4	0.99	36.3±8.9	39.3±8.7	0.36
Total Fat (kg)	22.6±7.1	22.1±6.8	0.85	31.1±9.1	34.2±8.8	0.35
Total LBM (kg)	42.6±10.2	42.4±10.7	0.95	54.3±11.4	53.1±10.7	0.76
N of risk factors						
Obesity	4	5	----	14	15	----
Dyslipidemia	0	0	----	9	7	----
Hypertension	2	1	----	12	11	----
IFG	0	0	----	8	8	----
T2DM	0	0	----	1	1	----

LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (High metabolic factor control), HiMFT (high metabolic factor training), BMI (body mass index), LBM (lean body mass).

5.5.3 Resistance training

5.5.3.1 Participation in training

Three participants from the training groups (one from LoMFT and two from HiMFT) withdrew from the study due to medical or personal reasons (unrelated to the study) and their data were quarantined from the training study. The adherence to exercise training for the HiMFT group was 88±8.3% with a mean attendance of 26.5±2.5 training sessions, and for the LoMFT group was 96±6.5% with a mean attendance of 28.8±1.9 training sessions. At baseline, one participant from the LoMFT, three from the HiMFC and one from the HiMFT did not complete the 1RM test for the leg extension exercise because each possessed strength exceeding the available loads on the machine.

Therefore, the strength test for leg extension was not conducted at endpoint in these individuals. One other participant from the HiMFT group did not perform the leg extension exercise because of an unrelated injury to the knee.

5.5.3.2 Diet comparison

No changes in total energy intake were observed during the course of the study within each group ($p>0.20$), between LoMFC versus LoMFT ($p=0.65$) or between HiMFC versus HiMFT ($p=0.76$). No significant differences were observed also between the two training groups ($p=0.50$). Also no change was observed for the energy macronutrient composition within or between groups before and at the end of the study (Table 5.2).

Table 5.2. Total energy at baseline and after 10 weeks of intervention for both LoMF and HiMF groups.

Variable	Group	Pre	Post	p group×time
Total energy intake (Kj)	LoMFC	6173.3±1581.4	6035.9±808.4	0.65
	LoMFT	7100.9±2242.9	6666.6±1846.7	
	HiMFC	8513.4±2663.3	8332.2±2521.8	0.76
	HiMFT	7889.8±1699.7	7912.8±1612.0	
Carb (g)	LoMFC	139.9±31.4	158.1±16.5	0.37
	LoMFT	176.7±95.2	164.4±76.8	
	HiMFC	207.5±68.0	214.4±89.1	0.91
	HiMFT	184.4±66.8	187.9±55.1	
Protein (g)	LoMFC	67.4±23.0	60.9±13.0	0.85
	LoMFT	72.5±23.7	67.5±15.1	
	HiMFC	84.0±30.4	78.4±29.3	0.40
	HiMFT	86.2±32.4	88.7±29.0	
Fat (g)	LoMFC	58.6±26.0	51.8±19.4	0.79
	LoMFT	62.7±16.9	58.8±18.1	
	HiMFC	79.5±22.1	70.8±20.3	0.23
	HiMFT	74.9±20.4	78.1±29.4	

LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (High metabolic factor control), HiMFT (high metabolic factor training), Carb (carbohydrate).

5.5.3.3 The effect of resistance training on body composition

In both HiMFT and LoMFT groups, training had no effect on body mass ($p>0.05$). For the LoMFT group, training had positive effects on waist circumference, total fat percentage and fat mass (kg) (Table 5.3). For both LoMFT and HiMFT, training

significantly increased LBM, compared to the corresponding control groups (2.6% and 2.1%, respectively, both $p=0.03$), with no significant difference between the two training groups ($p=0.94$) (Table 5.3).

Table 5.3. The effect of resistance training on body composition of individuals with LoMF and HiMF.

Variable	Group	Pre	Post	p group×time
Body mass (kg)	LoMFC	67.8±12.6	68.5±13.1	0.82
	LoMFT	66.5±11.1	67.1±12.0	
	HiMFC	88.3±14.8	88.2±15.3	0.90
	HiMFT	88.6±12.3	88.7±12.1	
BMI (kg·m ⁻²)	LoMFC	24.3±3.4	24.6±3.5	0.83
	LoMFT	23.8±3.3	24.0±3.3	
	HiMFC	30.0±3.7	30.1±3.9	0.79
	HiMFT	31.4±4.7	31.4±4.6	
Waist (cm)	LoMFC	81.3±8.5	82.9±8.5*	0.05
	LoMFT	79.9±8.7	79.6±9.1	
	HiMFC	99.0±10.6	99.3±11.3	0.11
	HiMFT	102.3±9.9	100.8±9.8	
Hip (cm)	LoMFC	99.7±8.5	99.8±8.5	0.98
	LoMFT	97.6±5.8	97.7±6.8	
	HiMFC	106.3±8.9	105.4±9.3	0.98
	HiMFT	108.8±10.5	108.2±10.6	
Abdominal fat (kg)	LoMFC	2.0±0.6	2.0±0.6	0.13
	LoMFT	1.8±0.8	1.8±0.8	
	HiMFC	3.3±0.9	3.2±0.9	0.49
	HiMFT	3.4±1.1	3.4±1.0	
Total fat (%)	LoMFC	34.6±8.0	34.9±8.2	0.02
	LoMFT	35.0±10.8	33.5±10.5*	
	HiMFC	36.3±8.9	36.2±8.3	0.46
	HiMFT	39.8±9.2	39.2±9.3	
Total fat (kg)	LoMFC	22.6±7.1	23.0±7.2	0.08
	LoMFT	22.2±7.1	21.5±7.2	
	HiMFC	31.1±9.1	30.9±9.1	0.91
	HiMFT	33.9±9.1	33.5±8.6	
Total LBM (kg)	LoMFC	42.6±10.2	42.7±10.3	0.03
	LoMFT	41.8±11.1	42.9±10.9*	
	HiMFC	54.3±11.4	54.0±11.1	0.03
	HiMFT	51.3±10.3	52.4±11.0*	

* Indicates $p\leq 0.05$ between pre-and-post within each group. LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training), BMI (body mass index), LBM (lean body mass).

5.5.3.4 The effect of resistance training on aerobic power and the capacity to perform ADL's

For LoMFT, training had a positive effect on both absolute and relative $\text{VO}_{2\text{peak}}$ (Table 5.4). Total time to complete the PPT was significantly reduced by 8.8% for the LoMFT and 9.7% for the HiMFT, compared to the controls (both $p < 0.01$), with no difference between the two training groups ($p = 0.78$) (Table 5.4). In addition, training significantly improved most of the individual components of PPT ($p < 0.05$) for both training groups, with the exception of the up-and-go test for HiMFT compared to HiMFC ($p = 0.14$). No differences between the two training groups were observed for any of the components of the PPT.

Table 5.4. The effect of resistance training on fitness and the capacity to perform ADL's of individuals with LoMF and HiMF.

Variable	Group	Pre	Post	p group×time
Time (sec)	LoMFC	548.8±225.3	502.7±137.1	0.01
	LoMFT	561.9±216.3	628.0±219.1*	
	HiMFC	587.9±96.9	577.2±96.1	<0.01
	HiMFT	557.2±133.5	602.9±143.7*	
VO _{2peak} (L·min ⁻¹)	LoMFC	1.6±0.4	1.5±0.4	0.02
	LoMFT	1.6±0.6	1.7±0.6*	
	HiMFC	2.0±0.4	2.1±0.5	0.65
	HiMFT	2.1±0.7	2.1±0.7	
VO _{2peak} (ml·kg ⁻¹ ·min ⁻¹)	LoMFC	23.4±3.8	22.5±3.4	0.02
	LoMFT	24.1±7.7	25.8±7.6*	
	HiMFC	22.8±4.2	23.2±4.9	0.56
	HiMFT	23.2±6.5	24.1±6.1	
15 m walk (sec)	LoMFC	5.8±0.6	6.0±0.7	0.03
	LoMFT	6.2±0.9	5.9±0.9*	
	HiMFC	5.8±0.9	5.8±0.9	0.04
	HiMFT	6.1±1.4	5.7±1.3*	
Up and go (sec)	LoMFC	5.0±0.7	4.9±0.7	0.05
	LoMFT	5.1±0.6	4.6±0.5*	
	HiMFC	4.8±0.5	4.5±0.6	0.14
	HiMFT	5.2±1.0	4.6±0.7*	
Ascending stairs (sec)	LoMFC	8.3±1.2	8.4±1.5	<0.01
	LoMFT	8.7±2.0	8.0±1.8*	
	HiMFC	7.8±1.3	7.7±1.6	<0.01
	HiMFT	8.9±2.1	8.1±1.7*	
Descending stairs (sec)	LoMFC	7.7±1.8	7.8±2.0	<0.01
	LoMFT	8.4±2.2	7.7±1.9*	
	HiMFC	7.2±1.5	7.1±1.8	<0.01
	HiMFT	8.1±2.0	7.3±1.7*	
Total PPT (sec)	LoMFC	26.8±3.6	27.1±4.3	<0.01
	LoMFT	28.4±5.0	26.1±4.7*	
	HiMFC	25.7±3.8	25.3±4.1	<0.01
	HiMFT	28.3±6.1	25.8±5.1*	

* Indicates p≤0.05 between pre-and-post within each group. LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training), PPT (physical performance test, as lower the time indicates better performance).

5.5.3.5 The effect of resistance training on skeletal muscle strength

Muscle strength improved for all seven exercises for both training groups, compared to their controls (all $p < 0.01$) (Table 5.5). HiMFT improved more than LoMFT in chest press (24.4% versus 20.3%, $p = 0.04$), leg press (33.9% versus 28.5%, $p = 0.01$) and total strength (25.0% versus 23.7%, $p = 0.03$) (Table 5.5), but for none of the others.

The change of total muscle strength was negatively correlated with the changes of total time to complete the PPT for both HiMF (pooled HiMFT and HiMFC, $r = -0.53$, $p < 0.01$) and LoMF (pooled LoMFT and LoMFC, $r = -0.47$, $p = 0.02$). In addition, changes in total muscle strength for the pooled HiMF group, but not the pooled LoMF group, correlated with changes in self-reported physical and mental health ($r = 0.59$, $p < 0.01$ and 0.45 , $p = 0.02$ respectively).

Table 5.5. The effect of resistance training on muscle strength of individuals with LoMF and HiMF.

Variable	Group	Pre	Post	p group×time
Chest press (kg)	LoMFC	41.8±23.7	40.7±24.1	<0.01
	LoMFT	43.5±18.8	54.6±24.2*	
	HiMFC	69.8±28.7	67.2±29.5	<0.01
	HiMFT	58.5±23.7	77.4±31.6*	
Leg press (kg)	LoMFC	165.8±60.6	166.8±63.9	<0.01
	LoMFT	178.0±92.5	249.0±97.7*	
	HiMFC	239.2±81.1	241.2±81.4	<0.01
	HiMFT	200.1±63.9	303.1±82.6*	
Lateral pull-down (kg)	LoMFC	42.5±15.8	42.7±16.3	<0.01
	LoMFT	42.0±13.2	49.8±12.5*	
	HiMFC	62.6±17.1	61.2±17.4	<0.01
	HiMFT	54.8±15.7	63.6±17.1*	
Triceps push-down (kg)	LoMFC	23.6±10.2	23.1±9.1	<0.01
	LoMFT	22.1±8.5	26.3±8.3*	
	HiMFC	33.7±10.1	33.5±10.4	<0.01
	HiMFT	30.7±10.2	36.2±11.9*	
Leg extension (kg)	LoMFC	42.9±13.6	41.0±13.0	<0.01
	LoMFT	41.3±12.7	53.8±13.8	
	HiMFC	53.9±15.5	53.6±17.9	<0.01
	HiMFT	54.6±13.3	69.1±18.7*	
Seated row (kg)	LoMFC	43.4±16.0	41.8±16.2*	<0.01
	LoMFT	42.6±16.4	51.4±16.2*	
	HiMFC	63.0±18.4	62.4±18.4	<0.01
	HiMFT	54.1±15.9	64.4±17.9*	
Biceps curl (kg)	LoMFC	15.9±7.2	15.7±8.0	<0.01
	LoMFT	14.0±6.2	18.0±6.7*	
	HiMFC	24.1±8.6	22.5±8.6	<0.01
	HiMFT	21.6±10.1	24.9±10.4*	
Total strength (kg)	LoMFC	376.1±136.5	371.7±143.4	<0.01
	LoMFT	378.6±135.4	496.3±137.3*	
	HiMFC	535.4±150.8	530.9±153.5	<0.01
	HiMFT	468.8±133.7	628.1±172.9*	

* Indicates $p \leq 0.05$ between pre-and-post within each group. LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training).

5.5.3.6 The effect of resistance training on quality of life

RT had no effect on any of the SF-36 subscales, nor either the physical nor mental health dimensions for LoMFT (all $p > 0.05$) (Table 5.6). In contrast, for HiMFT, training increased the perception of both physical and mental health (14.8% and 9.1%, respectively), compared to HiMFC (Table 5.6). In addition, training improved the scores of the some of the subscales of the SF-36 for HiMFT, specifically physical function (8.5%), general health (15.5%) and social function (10.5%). The role of physical scale (i.e. role limitations due to physical problems) tended to improve in HiMFT, compared to HiMFC (+16.6% and -10.5% respectively, $p = 0.08$). Training had contrasting influences on the perception of bodily pain between the two training groups. The bodily pain score for LoMFT decreased (-8.2%, indicating more perception of bodily pain) after training, while the bodily pain score for HiMFT increased (improved) by 16.8% ($p = 0.04$) (Table 5.6). Similarly, training had more positive effects on the self-perceived physical health dimension of the HiMFT group, compared to the LoMFT group (+14.8% and +3.3% respectively, $p = 0.06$).

Table 5.6. The effect of resistance training on quality of life of individuals with LoMF and HiMF.

Variable	Group	Pre	Post	p group×time
Physical function	LoMFC	88.1±13.2	88.1±13.3	0.42
	LoMFT	87.3±10.6	90.0±15.7	
	HiMFC	91.7±9.0	90.3±9.5	0.01
	HiMFT	81.5±13.6	88.5±11.8*	
Role physical	LoMFC	82.7±27.7	78.8±33.6	0.30
	LoMFT	93.2±16.2	97.7±7.5	
	HiMFC	95.0±10.4	85.0±31.1	0.08
	HiMFT	80.8±37.0	94.2±15.0	
Bodily pain	LoMFC	80.5±19.2	80.1±21.6	0.43
	LoMFT	85.3±17.1	78.3±17.6	
	HiMFC	80.9±19.9	80.3±26.2	0.21
	HiMFT	59.4±28.0	69.4±25.9	
General health	LoMFC	68.4±16.9	68.8±18.5	0.96
	LoMFT	77.0±19.6	77.2±23.4	
	HiMFC	79.4±17.6	74.0±16.4	<0.01
	HiMFT	64.2±15.9	74.2±15.7*	
Vitality	LoMFC	55.0±16.2	60.7±17.3	0.53
	LoMFT	70.0±19.9	70.1±12.2	
	HiMFC	68.0±17.2	66.7±20.8	0.13
	HiMFT	54.6±15.7	65.0±10.8	
Social function	LoMFC	91.4±11.8	83.7±27.1	0.15
	LoMFT	92.1±19.4	97.7±7.5	
	HiMFC	93.4±12.3	84.3±24.6	0.04
	HiMFT	82.8±21.4	91.5±14.7	
Role emotional	LoMFC	82.1±32.3	79.5±39.8	0.47
	LoMFT	90.9±30.2	97.0±9.9	
	HiMFC	93.3±18.7	86.7±24.6	0.32
	HiMFT	92.3±20.0	94.9±12.4	
Mental health	LoMFC	76.0±15.1	77.8±16.5	0.95
	LoMFT	76.4±17.6	77.8±12.6	
	HiMFC	83.5±13.6	77.9±21.3	0.29
	HiMFT	75.1±13.7	76.3±14.0	
Physical health dimension	LoMFC	74.8±14.3	75.2±17.3	0.99
	LoMFT	82.5±12.3	82.8±11.5	
	HiMFC	82.9±10.9	79.1±17.1	0.01
	HiMFT	68.2±17.7	78.3±10.9*	
Mental health dimension	LoMFC	74.5±12.8	74.0±20.5	0.60
	LoMFT	81.4±16.3	84.1±9.6	
	HiMFC	83.5±11.8	77.8±18.4	0.03
	HiMFT	73.7±12.8	80.4±10.7	

* Indicates $p \leq 0.05$ between pre-and-post within each group. LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training).

5.6 Discussion

The main finding of Study Two was that RT did not reduce whole body fat content or improve aerobic power (VO_{2peak}) for HiMFT, but did improve QoL. In contrast, there were improvements in whole body fat stores and aerobic power for LoMFT, in the absence of improvements to QoL. RT improved the capacity to perform ADL's to a similar extent in individuals both HiMFT and LoMFT.

Muscle weakness is a common finding in adult clinical populations (Willey and Fiatarone-Singh, 2003; Yki-Jarvinen and Koivisto, 1983) and is also a consequence of normal ageing (Iannuzzi-Sucich et al., 2002; Mishra and Misra, 2003). RT is the preferred training regimen to increase muscle strength and mass that are important for the performance of ADL's in many populations including young, elderly and those who suffer from insulin resistance/T2DM (Kraemer et al., 2001; Maiorana et al., 2002; Pollock et al., 2000). It is well documented that an increase in muscle strength can improve the capacity to perform ADL's and reduce disability in elderly people (Brandon et al., 2000; Fiatarone et al., 1994; Pennix et al., 2001). Similarly, this study showed that RT increased muscle strength in individuals with both high and low numbers of metabolic risk factors. The changes in muscle strength were correlated with improvements in the capacity to perform ADL's in both training groups.

Although both groups improved in the capacity to perform ADL's, improvements in QoL were observed only for HiMF. It is possible that training exerted positive influences on QoL for HiMF, since overweight individuals with and without chronic diseases have lower QoL scores, compared to lean individuals or those with less morbidity (Katz et al., 2000; Rejeski et al., 2006). In the present study, HiMFT exhibited small positive changes in QoL, whilst the control group exhibited modest declines, with significant differences between these groups. For the LoMF arm of the study, the QoL of the control group did not decline, and the group difference (control versus training) was not significantly different. It may be that QoL declines for individuals with HiMF who are not involved in a regular physical activity, and this is not as apparent for individuals with LoMF. It is possible that in relatively healthy middle-aged and elderly individuals, longer periods of training should be performed in order to improve QoL (Perrig-Chiello et al., 1998). It has been suggested that the capacity to perform ADL's may be used as a surrogate for QoL in elderly individuals

(Pennix et al., 2001) and those with chronic diseases, such as CVD (Tyni-Lenne et al., 2001). The current study suggests that there are associations between muscle strength, ADL's and QoL for individuals with multiple numbers of metabolic risk factors. However, the improvements in the capacity to perform ADL's and QoL were not related to changes in aerobic power or body fat content. ADL's do not depend on high levels of endurance capacity, but are better classified as needing short bursts of effort (such as rising from a chair, climbing stairs, dressing and carrying groceries). Therefore, improvements in muscle strength may be more indicative of improved capacity to perform ADL's and QoL, compared to endurance-type training which improve aerobic power. The finding of the current study that RT has little or no effect on aerobic power is similar to other studies that examined the effect of RT on middle-aged individuals (Hagberg et al., 1989; Pollock et al., 1991).

RT had a positive effect on LBM for both training groups. This finding is concordant with other studies that examined the effect of RT for individuals with metabolic disorders, such as T2DM (Castaneda et al., 2002; Dunstan et al., 2002). In the present study, it appears that training had more favorable effects on total fat content for the LoMFT group. For LoMFT, waist circumference did not change, but increased for LoMFC. RT reduced total fat and fat percentages for LoMFT, compared to LoMFC. In contrast, RT had no effect on any of the fat measurements in the HiMF groups (training and control). There are at least two factors that may limit fat loss following RT in overweight individuals and those with other metabolic risk factors, including insulin resistance. First, the HiMF groups had higher fasting insulin levels, compared to the LoMF groups. It has been reported that increases in insulin levels are associated with lower rates of lipolysis and promotion of fat storage by inhibiting lipase activity (McMurray and Hackney, 2005). Second, although obesity and hyperinsulinemia may lead to chronic activation of the sympathetic nervous system (Haynes et al., 1997; Tack et al., 1996), the responsiveness of adipose tissue to sympathetic stimulation is reduced, resulting in an inhibition of fat loss in these individuals (McMurray and Hackney, 2005). An important finding of the current study was that the changes in self-perceived QoL for individuals with HiMF following RT appear to be related to muscle strength and the capacity to perform ADL's, rather than body fat levels and aerobic capacity.

In conclusion, RT increased muscle strength and the capacity to perform ADL's in individuals with low and high metabolic risk factors for MetS and T2DM. QoL

improved for the HiMF group, and this was independent of changes to body fat content or aerobic power. In contrast, there were improvements in whole body fat and aerobic power for LoMFT, in the absence of improvements to QoL. Longer training regimens may be needed in order to improve QoL in individuals with LoMF.

Chapter 6

Study 3. Effect of resistance training on traditional and emerging metabolic risk factors

6.1 Introduction

Physical inactivity has been identified as a major risk factor for the development of both HiMF and T2DM (Cameron et al., 2003; Hu et al., 2001a; Hu et al., 2004a) and CVD (Fletcher et al., 1996). Aerobic training is the most frequently prescribed mode of exercise for those individuals (Eriksson, 1999; Pescatello et al., 2004; Rissanen and Fogelholm, 1999). The benefits of aerobic training for those individuals are well documented (Perez-Martin et al., 2001). However, aerobic training has a limited effect on preservation of muscle mass and strength. Muscle is the most insulin-sensitive tissue in the body (Deen, 2004) and is the major organ which disposes of glucose (Katz et al., 1983; Shulman et al., 1990). It has been suggested that a training regimen that does not alter muscle mass and strength, such as aerobic training, has a limited effect on glucose control (Eriksson et al., 1997). Moreover, it has been suggested that the capacity of individuals with HiMF to perform aerobic exercise is limited due to obesity and other conditions common to individuals with HiMF and T2DM (such as arthritis) and low motivation. In recent years, RT has been of great interest for individuals with elevated fasting blood glucose, insulin resistance and T2DM. Some studies reported that RT improved fasting blood glucose (Balducci et al., 2004; Maiorana et al., 2002), HbA1c (Brooks et al., 2007; Dunstan et al., 2002; Maiorana et al., 2002), insulin resistance (Brooks et al., 2007; Ishii et al., 1998; Ryan et al., 1996) and BP (both systolic and diastolic) (Blumenthal et al., 1991). However, other studies reported no change in the above metabolic risk factors after RT (Cornelissen and Fagard, 2005; Cuff et al., 2003; Dunstan et al., 1998; Rice et al., 1999). It is difficult to assess the role of RT in individuals with clusters of metabolic risk factors, as some of the above studies involved either hybrid exercise training regimens (i.e. combined aerobic and resistance exercise) or double interventions (e.g. including diet). Currently there is a lack of randomised controlled data on the effects of RT as a single intervention in these individuals (Willey and Fiatarone-Singh, 2003). Castaneda et al. (2002) and Sigal et al.

(2007) reported that RT improved glycaemic control (a reduction in HbA1c), with no change in fasting glucose levels, lipid profiles or BP in elderly individuals with T2DM. Banz et al. (2003) reported a reduction in body fat after 10 weeks of RT without changes in glucose, lipid profiles or BP, in individuals with HiMF.

To date, limited and conflicting findings have arisen from studies examining the effect of RT alone on inflammatory markers for individuals with HiMF and T2DM (Kohut et al., 2006; Olson et al., 2007; Reynolds et al., 2004). Furthermore, no studies have examined the effect of RT, as a single intervention, on plasma GGT, ALT and BDNF activities in individuals with HiMF. As such, the effects of RT on the emerging metabolic risk factors in individuals with HiMF and LoMF are currently unclear.

6.2 Purpose

The purpose of Study Three was to examine the effects of 10 weeks RT as a single intervention on conventional and emerging metabolic risk factors including, glycaemic control and insulin resistance, lipids profile and blood pressure, inflammatory markers, hepatic enzymes and BDNF for individuals with HiMF and LoMF associated with the MetS and T2DM.

6.3 Hypotheses

The following hypotheses were tested:

1. Emerging and traditional metabolic risk factors are correlated.

Ten weeks of RT:

1. Improves the metabolic risk profiles of individuals with HiMF.
2. Improves the clinical profiles of individuals with LoMF.

6.4 Method

6.4.1 Study design and participants

See General methods Sections “3.1 Study design” and “3.2 Participants”.

6.4.1.1 Power calculation

The formula of Cohen (Cohn, 1988) was applied to estimate the minimum sample sizes to permit the testing of all hypotheses of this study at a power of 0.8 (Pagano, 1986). The power calculation was as follows: $d = \text{mean } x_1 - \text{mean } x_2 / \sqrt{[(SD_1)^2 + (SD_2)^2] / 2}$, where mean x_1 and SD_1 represent pre-training data and mean x_2 and SD_2 represent post training data.

Sample sizes were determined after conducting statistical analyses using three criteria ($p = 0.05$ and mean and standard deviation) of key variables (such as, lipids, fasting glucose and HbA1c), obtained from previous studies in the literature. For instance, the data from Park et al. (2003) were used to calculate the power for triglyceride as follows: $d = 148.8 - 85.8 / \sqrt{[5.82^2 + 5.03^2] / 2} = 11.6$. The data from Castaneda et al. (2002) were used to calculate the power for HbA1c as follows: $d = 8.7 - 7.6 / \sqrt{[0.3^2 + 0.9^2] / 2} = 4.2$. For the range of examined variables, the minimum sample size $n=8$ for each group was needed (or 32 participants overall). As most studies used for the power calculation included patients with long standing T2DM a further 23 participants were recruited (overall 55 participants). This strengthened the statistical analyses and allowed for withdrawals of some volunteers before completion of the study.

6.4.1.2 Anthropometric measurements

See General methods Section “3.4 Anthropometric measurements”.

6.4.1.3 Blood sample

See General methods Section “3.5 Blood sample”.

6.4.1.4 Blood pressure

See General methods Section “3.6 Blood pressure”.

6.4.1.5 Resistance training program

See General methods Section “3.11 Resistance training program”.

6.4.1.6 Statistics

See Chapter Five (Study Two) Section “5.4.2.10 Statistics”.

6.5 Results

6.5.1 Baseline comparison

No differences were found between LoMFC and LoMFT, or between HiMFC and HiMFT for sex, age, weight, height, total body fat percentages and total LBM (all $p < 0.05$ see Study Two Table 5.1). In addition, no differences at baseline were found between the groups (LoMFC versus LoMFT, or between HiMFC versus HiMFT) for BP, lipids profile, glycaemic control, inflammatory markers and/or GGT level (all $p > 0.05$). However, at baseline, BDNF was higher for HiMFC compared to HiMFT ($p = 0.01$) (Table 6.5 and Figure 6.1). This was outside of the control of the researcher and not due to study biases.

6.5.2 The effects of resistance training

6.5.2.1 The effect of resistance training on traditional metabolic risk factors

6.5.2.1.1 The effect of resistance training on anthropometric measurements

As was reported previously (Study Two, Table 5.3.), training had no significant effect on body mass, BMI or abdominal fat in both HiMFT and LoMFT. Fat percentage and waist circumference were significantly improved for LoMFT only. LBM increased significantly in both HiMFT (1.1 kg) and LoMFT (1.1 kg).

6.5.2.1.2 The effect of resistance training on resting blood pressure and heart rate

For both HiMFT and LoMFT training had no significant effect on SBP or DBP compared to their controls ($p>0.05$). Training improved SBP ($p=0.03$) and tended to improve DBP ($p=0.06$) for LoMFT compared HiMFT. That was due to an interaction effect of a reduction in SBP for LoMFT (by 7 mmHg) and increase in SBP (2 mmHg) for HiMFT. Similarly, DBP dropped by 3 mmHg in the LoMFT while it was increase by 2 mmHg in the HiMFT (Table 6.1). Resting HR was significantly lower after training in HiMFT group, compared to HiMFC (Table 6.1)

Table 6.1. The effect of resistance training on resting blood pressure and heart rate of individuals with HiMF and LoMF.

Variable	Group	Pre	Post	p group×time
Resting HR (bpm)	LoMFC	72.9±10.7	70.5±8.5	0.56
	LoMFT	73.2±10.0	68.5±6.1	
	HiMFC	71.6±10.2	74.6±9.3	0.02
	HiMFT	70±10.8	65.1±8.4*	
SBP (mmHg)	LoMFC	116.5±12.4	114.5±12.8	0.19
	LoMFT	116.9±11.9	110.0±10.2*	
	HiMFC	134.9±12.5	136.2±12.8	0.92
	HiMFT	130.6±15.7	132.2±13.0	
DBP (mmHg)	LoMFC	76.3±5.5	73.2±7.6	0.95
	LoMFT	77.8±8.6	74.5±9.0	
	HiMFC	87.9±7.7	89.9±8.2	0.62
	HiMFT	87.5±11.2	90.8±12.7	

* Indicates $p\leq 0.05$ between pre-and-post within each group. HR (heart rate), SBP (systolic blood pressure), DBP, LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training).

6.5.2.1.3 The effect of resistance training on lipids profile of individuals with HiMF and LoMF

Both HiMFT and LoMFT training had no effect on total cholesterol, triglyceride, LDL or HDL compared to their respective controls (all $p>0.05$, Table 6.2). Small but significant increases in LDL ($p<0.05$) was observed after training in the HiMFT, compared to baseline levels but not compared to HiMFC (Table 6.2).

Table 6.2. The effect of resistance training on the lipid profile of individuals with LoMF and HiMF.

Variable	Group	Pre	Post	p group×time
Total cholesterol (mmol·L ⁻¹)	LoMFC	4.9±1.0	5.0±1.1	0.67
	LoMFT	5.0±1.1	5.2±1.4	
	HiMFC	6.2±1.0	6.2±1.0	0.74
	HiMFT	5.6±1.0	5.7±0.8	
Trig (mmol·L ⁻¹)	LoMFC	0.8±0.4	0.9±0.3	0.70
	LoMFT	0.6±0.3	0.7±0.2	
	HiMFC	1.6±0.8	1.6±1.0	0.74
	HiMFT	1.4±0.4	1.4±0.7	
LDL (mmol·L ⁻¹)	LoMFC	2.9±0.8	3.1±0.8	0.44
	LoMFT	2.8±1.2	3.1±1.3	
	HiMFC	4.1±0.9	4.3±0.9	0.38
	HiMFT	3.3±1.0	3.6±0.9*	
HDL (mmol·L ⁻¹)	LoMFC	1.6±0.5	1.5±0.5	0.46
	LoMFT	2.0±0.6	1.8±0.6	
	HiMFC	1.4±0.4	1.2±0.4	0.66
	HiMFT	1.7±0.5	1.5±0.3	

* Indicates $p \leq 0.05$ between pre-and-post within each group. Trig (triglyceride), LDL (low density lipoprotein), HDL (high density lipoprotein), LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training).

6.5.2.1.4 The effect of resistance training on glycaemic control of individuals with HiMF and LoMF

Glycaemic control did not improve for either HiMFT or LoMFT, compared to their controls, reflected by no significant changes in fasting glucose, HbA1c or insulin resistance (Table 6.3). However, in the HiMFT, insulin resistance (HOMA-IR), tended to increase compared to the pre training level ($p=0.07$, Table 6.3). The increase in insulin resistance levels in the HiMFT group was probably due to a significant increase in insulin levels after training, compared to baseline levels.

Table 6.3. The effect of resistance training on fasting glucose, HbA1c and insulin resistance.

Variable	Group	Pre	Post	p group×time
Fasting glucose (mmol·L ⁻¹)	LoMFC	4.9±0.4	5.1±0.4	0.13
	LoMFT	5.1±0.2	5.0±0.3	
	HiMFC	5.8±0.9	5.8±1.0	0.61
	HiMFT	5.7±0.6	5.8±0.6	
HbA1c (%)	LoMFC	5.2±0.3	5.2±3.0	0.25
	LoMFT	5.2±0.1	5.3±0.2	
	HiMFC	5.5±0.4	5.5±0.4	0.73
	HiMFT	5.7±0.5	5.7±0.5	
Insulin (pmol·L ⁻¹)	LoMFC	29.4±25.0	30.5±15.7	0.64
	LoMFT	19.9±13.2	24.4±19.8	
	HiMFC	64.2±38.3	75.3±45.1	0.32
	HiMFT	46.1±28.5	71.2±48.8*	
HOMA-IR	LoMFC	0.9±0.8	1.0±0.5	0.70
	LoMFT	0.6±0.4	0.8±0.6	
	HiMFC	2.4±1.6	2.7±1.7	0.27
	HiMFT	1.6±1.1	2.6±2.0	

* Indicates $p < 0.05$ compared to baseline levels. LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training) HbA1c (glycosylated-haemoglobin), HOMA-IR (homeostasis model assessment of insulin resistance, $[(\text{fasting glucose (mmol}\cdot\text{L}^{-1}) \times \text{fasting insulin (mIU/L)})] \cdot 25^{-1}$).

6.5.2.2 The effect of resistance training on emerging metabolic risk factors

6.5.2.2.1 The effect of resistance training on inflammatory markers of individuals with HiMF and LoMF

In the HiMFT group, training did not significantly alter plasma CRP or cytokine concentrations. However, relative to the HiMFC group, training tended to reduce the plasma concentrations of IL-1 β (HiMFT -7.4% versus +19.7% for the HiMFC, time \times group $p = 0.08$) and TNF- α (HiMFT -10% versus +16.6% for the HiMFC, time \times group $p = 0.10$) (Table 6.4). Training did not significantly alter plasma CRP and cytokines concentrations for the LoMFT group, and these variables did not differ significantly between the LoMFT and LoMFC groups.

Table 6.4. The effect of resistance training on inflammatory markers of individuals with HiMF and LoMF

Variable	Group	Pre	Post	p group×time
IL-1 β (pg·mL ⁻¹)	LoMFC	6.6±3.6	6.9±2.8	0.50
	LoMFT	4.0±2.8	3.9±2.5	
	HiMFC	6.6±4.9	7.9±6.1	0.08
	HiMFT	6.8±4.4	6.3±4.3	
IL-6 (pg·mL ⁻¹)	LoMFC	14.0±11.4	18.3±11.2	0.94
	LoMFT	11.6±11.6	11.7±11.1	
	HiMFC	25.6±14.9	26.9±14.9	0.76
	HiMFT	19.1±10.7	19.5±11.5	
IL-8 (pg·mL ⁻¹)	LoMFC	7.5±3.7	8.8±6.9	0.43
	LoMFT	6.4±6.5	6.4±6.7	
	HiMFC	13.1±10.0	13.9±9.0	0.58
	HiMFT	7.4±4.7	7.3±4.4	
TNF- α (pg·mL ⁻¹)	LoMFC	5.2±2.8	5.7±2.9	0.32
	LoMFT	4.4±1.4	4.4±1.1	
	HiMFC	6.6±6.6	7.7±6.9	0.10
	HiMFT	8.0±5.0	7.2±3.3	
CRP (mg·L ⁻¹)	LoMFC	1.2±1.1	1.0±1.1	0.08
	LoMFT	1.2±1.1	1.6±1.1	
	HiMFC	2.5±1.6	3.7±4.5	0.47
	HiMFT	3.2±1.9	3.5±2.8	

LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training), IL (interleukin), TNF (tumor necrosis factor), CRP (C-reactive protein).

6.5.2.2.2 The effect of resistance training on hepatic enzymes and BDNF levels of individuals with HiMF and LoMF

RT had no significant effect on GGT, ALT or BDNF levels within training groups or compared to their respective controls (all $p > 0.05$, Table 6.5 and Figure 6.1). Also, no significant difference was observed also between the two training groups.

Table 6.5. The effect of resistance training on GGT and BDNF levels of individuals with HiMF and LoMF.

Variable	Group	Pre	Post	p group×time
GGT (U·L ⁻¹)	LoMFC	16.4±9.5	15.9±9.4	0.22
	LoMFT	24.5±26.6	19.6±18.4	
	HiMFC	40.7±28.2	40.6±28.04	0.56
	HiMFT	29.8±17.7	27.0±10.6	
ALT (U·L ⁻¹)	LoMFC	19.3±5.8	23.2±12.3	0.60
	LoMFT	22.3±12.0	23.4±11.2	
	HiMFC	62.5±54.5	58.3±46.0	0.36
	HiMFT	38.8±20.2	41.5±38.1	
BDNF (pg·mL ⁻¹)	LoMFC	673.1±198.1	656.9±272.4	0.43
	LoMFT	716.6±283.1	645.4±137.2	
	HiMFC	1075.6±406.4	1225.7±1011.7	0.81
	HiMFT	768.8±201.3*	838.7±251.4	

* Indicates p<0.01 at baseline for HiMFT versus HiMFC). LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training), GGT (gammaglutamyltransferase), ALT (alanine aminotransferase). BDNF (brain-derived neurotrophic factor). BDNF and inflammatory markers are reported for 50 volunteers, as 5 individuals chose not to provide an additional blood sample (in addition to the fasting blood sample).

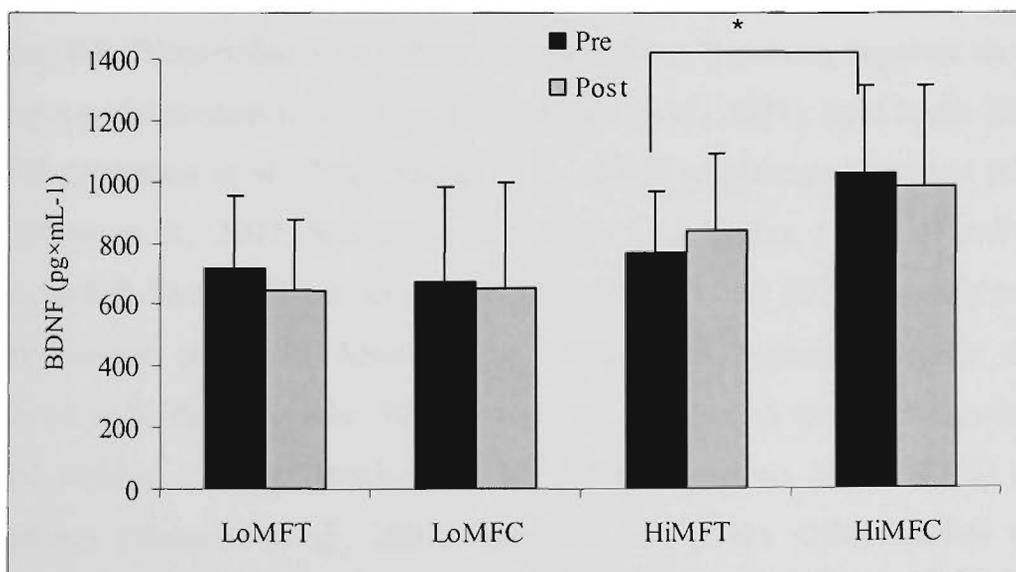


Figure 6.1. BDNF level before (pre) and after (post) 10 week of RT for HiMFT, HiMFC, LoMFT and LoMFC.

* Indicates p=0.01 at baseline between HiMFT and HiMFC.

6.6 Discussion

The main finding of this study was that 10 weeks of RT for middle-aged individuals with and without clusters of metabolic risk factors associated with the MetS and T2DM did not improve either the conventional or emerging metabolic risk profile of the participants.

Physical inactivity is strongly associated with the development of MetS, T2DM and CVD (Hu et al., 2001c; Hu et al., 2004b). The rationale for RT for overweight individuals and those with impaired glycaemic control is that skeletal muscle is an important tissue for glucose disposal (Katz et al., 1983; Shulman et al., 1990) and an increase in muscle mass should lead to improved glucose homeostasis and increase glycogen storage (Castaneda et al., 2002; Sanchez and Leon, 2001). Previous studies examining the effect of RT on metabolic risk factors reported a wide range of physiological benefits including improvements in glycaemic control and insulin resistance (Balducci et al., 2004; Brooks et al., 2007; Dunstan et al., 2002; Maiorana et al., 2002), reductions in body mass, waist circumference, and fat content (Dunstan et al., 2002; Joseph et al., 2001), reductions in total cholesterol, LDL and triglycerides levels (Cauza et al., 2005b; Honkola et al., 1997) and increased HDL (Cauza et al., 2005b; Eriksson et al., 1998). Also reductions in BP (both systolic and diastolic) were reported following RT (Blumenthal et al., 1991). Other studies, however, reported no change to body mass or fat content (Ishii et al., 1998; Olson et al., 2007), lipid levels (Eriksson et al., 1997; Maiorana et al., 2002; Olson et al., 2007) or glycaemic control (Cuff et al., 2003; Olson et al., 2007; Stewart et al., 2005) in a similar group of individuals in response to RT. These differences are probably related to the different study populations and intervention protocols. Most of the studies that reported benefits of RT for individuals with HiMF and/or T2DM were in response to double interventions that included aerobic training (Balducci et al., 2004; Maiorana et al., 2002) or dietary interventions (Dunstan et al., 2002; Joseph et al., 2001). Other studies used non-controlled experimental designs or no non-active control group (Eriksson et al., 1997; Honkola et al., 1997; Ryan et al., 1996; Smutok et al., 1994).

The present study demonstrated that RT as a single intervention had no effects on conventional metabolic risk factors such as body fat levels, waist circumference, glycaemic control, lipid profiles or BP or emerging risk factors including inflammatory

markers and hepatic enzymes. In addition, RT did not increase BDNF levels as was expected for HiMFT, even though BDNF levels were relatively low at baseline for this group, compared to HiMFC.

Training increased insulin levels and insulin resistance (HOMA-IR) for HiMFT. It is not clear why RT had this undesirable effect on insulin resistance. However, a recent review suggested that many untrained individuals who become involved in physical activity may experience “exercise-induced muscle damage” (Tee et al., 2007). This in turn, may increase muscle inflammation levels. Increase in inflammation is associated with a reduction in some insulin-signalling proteins such as tyrosine phosphorylation of IRS-1 (Plomgaard et al., 2005), phosphorylated Akt (Krook et al., 1998) and phosphorylation of AS160 (Jager et al., 2007; Plomgaard et al., 2005), all of which may increase insulin resistance. In the current study for the HiMFT group, no significant changes were observed for plasma levels of inflammatory markers after training. However, it is possible that localised intramuscular increases in inflammation, may affect insulin-signalling proteins (Tee et al., 2007) and, in turn leads to increase insulin resistance. Similarly, it has been previously reported that RT may increase both insulin and glucose levels even in healthy individuals (Kraemer et al., 2004). As such, RT that is not combined with diet control for individuals with impaired glycaemic control may actually increase insulin resistance. In addition, some investigators have reported that insulin action is reduced in response to acute bouts of resistance exercise. This may be because resistance exercise reduces basal AS160 phosphorylation (Howlett et al., 2007). The effects of RT on insulin resistance and insulin-signalling proteins will be discussed in detail in Chapter Seven (Study Four).

Results from other randomised controlled studies that have examined the effect of RT in individuals with T2DM and metabolic risk factors are inconclusive. In the work of Castaneda et al. (2002), LBM increased by 1.2 kg, a similar magnitude to the increase in LBM in the current study (1.1kg). However, in contrast to the current study, Castaneda et al. (2002) reported reductions in HbA1c from 8.7 ± 0.3 to $7.6\pm 0.2\%$ and SBP of 9.7 mmHg after RT in elderly individuals (mean age=66 yr) with T2DM. Similarly, Sigal et al. (2007) reported a significant reduction in HbA1c after RT (from 7.48 to 7.35%). It is possible that the improvements in HbA1c in response to RT in the study of Castaneda et al. (2002) and Sigal et al. (2007) could be explained because the participant had already long standing T2DM, with higher baseline levels of HbA1c, compared to the

levels for participants in the current study (5.5%). Similarly, baseline SBP was higher in the study of Castaneda et al. (2002) by 10 mmHg, compared to the SBP in the current study. It appears that RT may improve some risk factors for elderly patients with overt metabolic diseases such as T2DM. The current study results are concordant with those of Banz et al. (2003) who reported that RT did not change glucose, lipids profile or BP for middle-age individuals (mean age=48 yr) HiMF. It is important to note however, that Banz et al. (2000) did not include a non-exercise control group. Similarly, Olson et al. (2007) reported that 1 year of moderate RT did not change metabolic risk factors (glycaemic control, lipids profile and BP) in overweight female (mean age =39 yr). As RT had no significant effect on metabolic risk factors of individuals with HiMF, it is not surprising that RT had limited effects on individuals with LoMF.

In the present study, 10 weeks of RT, as a single intervention (i.e. no change to diet), did not significantly modify proinflammatory markers, GGT or ALT levels. However, TNF- α and IL-1 β tended to decrease after training in the HiMFT group. A longer training period may lead to larger changes in these cytokines. Similar to the current study findings, others have also reported no change to plasma GGT concentration in patients with T2DM following six weeks of single leg RT (Holten et al., 2004). Together, these findings indicate that two-to three months of whole body RT – at least on its own – is insufficient to modify plasma hepatic enzymes concentration for individuals with HiMF or T2DM.

Limited published data currently exist relating to the effects of RT on inflammatory markers. The few existing studies generally indicate that RT exerts little or no effect on inflammatory markers (DiPenta et al., 2007). For example, Reynolds et al. (2004) reported that 16 weeks of moderate RT (2 sets of 10-12 reps, 3 days/wk) improved insulin sensitivity without altering proinflammatory markers (e.g. plasma TNF- α concentration) in elderly people with hypertension. Kohut et al. (2006) examined the effect of aerobic training versus combined strength, flexibility and balance training in elderly individuals with and without health problems such as hypertension and T2DM. They reported that serum IL-18, IL-6 and CRP concentrations decreased following aerobic training, but not following the combined strength, flexibility and balance training, while serum TNF- α concentration decrease following both modes of training. In contrast, Brooks et al. (2007) reported that 16 weeks of RT plus standard care in the treatment of elderly with T2DM reduces plasma CRP concentration by 20% (from 3.5

mg·L⁻¹ to 2.8 mg·L⁻¹), compared to standard care alone. Similarly, Olson et al. (Olson et al., 2007) reported that 1 year of RT significantly reduces plasma CRP concentration (mean decrease of 3.0 mg·dl⁻¹), compared to baseline levels in overweight women, with no change in plasma IL-6 concentration. Importantly, however, the reduction in plasma CRP concentration was not statistically significant when compared to the non-active control group (Olson et al., 2007).

Collectively, the data from the present study and others suggest that RT has the potential to improve some inflammatory markers. However, other studies have reported that weight reduction protocols that included also aerobic training significantly reduced plasma CRP and ALT concentration, in addition to other metabolic risk factors such as lipids profile, BP and insulin resistance (Okita et al., 2004). Similar reductions in hepatic enzymes concentrations (Volek et al., 2000) and proinflammatory markers (Ryan and Nicklas, 2004) were reported following dietary modifications. The mechanism by which aerobic training reduces proinflammatory markers is not fully understood. Exercise increases the release of the myokine IL-6 (from working muscles), which can in turn suppress other proinflammatory markers (such as TNF- α). In addition, the release of IL-6 during exercise can promote lipolysis as well as fat oxidation (Febbraio, 2007; Febbraio and Pedersen, 2005; Petersen and Pedersen, 2005). Therefore, available evidence suggests that to reduce some proinflammatory markers and hepatic enzymes, RT should be combined with other non-pharmacological interventions such as aerobic exercise training and/or dietary modifications.

The main findings of the study suggest that RT as a single intervention has little or no influence on conventional and emerging metabolic risk factors in middle-aged individuals with clusters of metabolic abnormalities in the absence of overt disease. This suggests that the physiological benefits from this form of training that have been reported previously, were probably due to other factors such as, the inclusion of aerobic training, dietary interventions and/or the inclusion of elderly individuals and those with long standing T2DM. As such, RT may not be sufficiently efficacious as a single preventative exercise intervention for improving metabolic risk profile in middle-aged individuals who are yet to develop overt disease. Alternatively, it is possible that longer training durations may be needed in order to elicit improvements in metabolic risk factors in individuals with HiMF.

Chapter 7

Study 4. The effect of resistance training on insulin-signalling proteins and glycogen content

7.1 Introduction

Akt and AS160 are two downstream proteins in the PI3-K pathway (see Figures 2.6 and 2.7), and they form an important link between insulin-signalling and glycogen and protein synthesis, and the translocation of GLUT4 from the cytoplasm to the membrane (Krook et al., 2004; Le Roith and Zick, 2001; Miranda et al., 2005). Some studies, but not all (Holten et al., 2004; Krisan et al., 2004), have reported that obesity (Goodyear et al., 1995b) and diabetes impairs the PI3-K pathway (Krook et al., 2000; Krook et al., 2004), partly by reducing phosphorylation of the insulin-signalling proteins Akt and AS160 (Jager et al., 2007; Krook et al., 1998).

Although it is accepted that exercise training has the capacity to improve insulin action, insulin sensitivity and glucose disposal (Frosig et al., 2007; Wojtaszewski et al., 2000), to date, most studies have utilised aerobic exercise. In addition, it has been shown that aerobic training may improve the metabolic risk profile of individuals with clusters of metabolic risk factors and T2DM (Borghouts and Keizer, 2000; Christ-Roberts et al., 2004; Colwell, 2003; Couillard et al., 2001; Dela et al., 1995b; Kraus et al., 2002). The effect of RT on insulin sensitivity and insulin-signalling proteins is unclear (Coffey and Hawley, 2007). Some investigators have reported an increase in Akt phosphorylation from 10 min to 72 h after an acute bout of resistance exercise (Creer et al., 2005; Leger et al., 2006), while others have reported no change after 1 to 40 h (Coffey et al., 2006; Eliasson et al., 2006; Krisan et al., 2004). Furthermore, recently Howlett et al. (2007) reported significantly reduced insulin sensitivity and glucose disposal, as well as reduced AS160 phosphorylation (~40%) and tendency for a reduction in phosphorylated Akt (exact value was not reported) immediately after an acute bout of resistance exercise. This was not evident 24 h after repeated bouts of resistance exercises (3 exercise sessions over a week) (Howlett et al., 2007). Despite this reduction in AS160 phosphorylation, insulin stimulation was still able to elicit an increase in AS160 phosphorylation by two-to-three fold, suggesting that the reduction in phosphorylated

AS160 and phosphorylated Akt does not necessarily translate into a reduced ability to respond to insulin stimulation. The authors speculated that the reduction in insulin sensitivity immediately after an acute bout of resistance exercise may be temporary as other studies have reported an increase in insulin sensitivity 24 h after acute resistance exercise (Fenicchia et al., 2004; Koopman et al., 2005). In contrast, other studies have reported a reduction in insulin sensitivity up to 48 h after acute resistance exercise (Asp et al., 1996; Asp and Richter, 1996; Asp et al., 1997).

The number of studies that have examined the effects of prolonged RT on insulin-signalling proteins is limited. Some investigators have suggested that the increase in insulin sensitivity following training is probably because of an increase in insulin receptor protein content, PKB- α/β (Akt 1/2) and glycogen synthase (content and activity) (Holten et al., 2004). Others, however, have reported that RT does not change total or phosphorylated Akt (Krisan et al., 2004). It is important to note that these studies have measured insulin-signalling 16 to 40 h after the last training session and as such, the measurements may be influenced by the acute response to the last training session rather than representing a chronic adaptation to training. The conflicting results in regard to the effects of resistance exercise and RT on Akt bring into question the current understanding of the role Akt plays in exercise induced training adaptation (Coffey and Hawley, 2007). To date, there are no studies examining the effects of whole body RT on basal AS160 (total or phosphorylated). Furthermore, most of the above studies have reported insulin sensitivity and insulin-signalling proteins under insulin load or contraction stimulation and not in the rested basal state. As individuals are at rest (basal levels) during most hours of the day, it is important to examine the effects of RT on the basal levels of insulin-signalling proteins. Previous studies have taken their post-training muscle samples 0-48 h after the last exercise session (Holten et al., 2004; Howlett et al., 2007; Krisan et al., 2004). It has been previously shown, however, that protein turnover can remain elevated for up to 48 h after an acute bout of resistance exercise (Phillips et al., 1997). Thus, the results from these previous studies, where muscle samples were obtained within the first 48 h, may not represent the true new basal conditions. Currently, there are no studies that have looked at basal levels of Akt and AS160 beyond 48 h after the last training bout.

An increased risk profile and increased levels of inflammatory markers may lead to abnormal glucose homeostasis, insulin resistance and T2DM (Duncan et al., 2003; Festa

et al., 2000; Hak et al., 2001; Han et al., 2002; Hotamisligil et al., 1993; Rutter et al., 2004). Individuals with HiMF are also characterised by increased levels of inflammatory markers. It has been reported that inflammation may lead to insulin resistance via increased serine phosphorylation of IRS-1 (Kanety et al., 1995). The increase in serine phosphorylation interferes with insulin-induced tyrosine phosphorylation of IRS-1 and may impair insulin action (Hotamisligil et al., 1994; Hotamisligil et al., 1996; Kanety et al., 1995; Peraldi et al., 1996). To date there are no data on the correlation between inflammatory markers and total and phosphorylated forms of Akt and AS160.

7.2 Purpose

The purpose of Study Four was to investigate the effects of RT on Akt, AS160 and muscle glycogen stores for individuals with HiMF or LoMF. Akt and AS160 were measured in the skeletal muscle of resting individuals before RT and 4-5 days following their most recent training session. In addition, this study examined the correlation between the insulin-signalling proteins Akt and AS160, risk factors and inflammatory markers in these populations.

7.3 Hypotheses

The following hypotheses were tested:

1. RT will increase total and phosphorylated Akt and AS160
2. RT will increase muscle glycogen content
3. Markers of systemic inflammation will be correlated with the levels of phosphorylated AS160 and Akt

7.4 Methods

7.4.1 Participants and study design

Thirty-two untrained men (n=15) and women (n=17) aged 51.4 ± 6.5 (range 40-69 yr), volunteered to undergo muscle biopsies in addition to other anthropometric and clinical

measures before and after 10 weeks of RT. For study design and participants See General methods Sections “3.1 Study design” and “3.2 Participants” for inclusion and exclusion criteria. Participants were randomly allocated to one of four groups: HiMFT, HiMFC, LoMFT and LoMFC (Table 7.1)

7.4.2 Study protocol

7.4.2.1 Anthropometric measurements

See General methods Section “3.4 Anthropometric measurements”.

7.4.2.2 Blood sample

See General methods Section “3.5 Blood sample”.

It is important to note, the blood sample for fasting lipid profile, glucose and insulin levels was taken one to two days before the muscle biopsy, but the muscle and blood results were neither compared nor analysed together. Therefore the different timings of the muscle and blood samples did not compromise the Results or the Discussion for this Study. The blood sample for proinflammatory cytokines was taken on the same day but just prior to the muscle biopsy.

7.4.2.3 Blood pressure

See General methods Section “3.6 Blood pressure”.

7.4.2.4 Muscle strength: one repetition maximum test

See General methods Section “3.9 Muscle strength: one repetition maximum test”.

6.4.2.5 Muscle biopsy

Muscle biopsies were taken from the vastus lateralis under local anaesthesia with Xylocaine 1%, utilising the percutaneous needle biopsy technique (Evans et al., 1982). The samples were weighed and immediately frozen in liquid nitrogen and then transferred to a -80°C freezer until analysis. The biopsies were conducted at baseline and 4-5 days after the last training session. The methods for muscle biopsy sampling and

tissue storage are well established in the School of Human Movement Recreation and Performance, Victoria University (Aughey et al., 2006; Williams et al., 2004).

6.4.2.6 Glycogen analysis

The muscle sample (5-30 μg) was freeze-dried before analysis. Total muscle glycogen was analysed using an acid hydrolysis method. Muscle samples were hydrolysed in 0.5 ml of 2M HCl and then were boiled for 30 min. After 30 min, tubes were cooled at room temperature and HCl was neutralised with 1.5 ml 0.67M NaOH. Small muscle extracts (7.5-20 μl) were transferred into a glass culture tubes (10 \times 75 mm) containing 1 ml of cocktail (50 $\text{mmol}\cdot\text{L}^{-1}$ Tris 8.8 pH, 1 $\text{mmol}\cdot\text{L}^{-1}$ MgCl_2 , 0.5 $\text{mmol}\cdot\text{L}^{-1}$ DDT, 0.3 $\text{mmol}\cdot\text{L}^{-1}$ ATP, 0.05 $\text{mmol}\cdot\text{L}^{-1}$ NADP, 1U $\cdot\text{ml}^{-1}$ HK, 0.1 U ml^{-1} P-6-PDH). Tubes were then incubated in the dark for 15 min. Extracts and glucose standard were analysed as triplicates by fluorimeter (SEQUOIA-TURNER Corporation, Model 112, CA, USA).

6.4.2.7 Akt and AS160 analyses

Preparation of muscle sample: muscle (25-47 mg) was homogenised (Kinematica Polytron, Brinkmann, CT) in ice-cold lysis buffer consisting of (in mM) (20 Tris-HCl, 5 EDTA, 10 Na-pyrophosphate, 100 NaF, 2 Na_3VO_4 , and 1% Nonidet P-40 (NP-40), and protease inhibitor tablet (Roche, Lewes, Sussex, UK). The homogenised muscle was then incubated for 30 min at 4°C and then centrifuged at 13000 g for 30 min. The supernatant was then removed and stored at -80°C.

Total protein determination: Homogenised sample (10 μl) was diluted 20-fold and total protein concentration was determined using BCA Pearce protein assay kit (Pierce Biotechnology, IL, USA) using BSA standard.

Antibodies: phospho-Akt (Ser473) antibody and total Akt antibody were purchased from Cell Signaling Technology (Beverly, MA) and total Anti-AS160 (Rab-GAP) was purchased from Upstate (NY, USA).

Blotting: Equal amounts of muscle protein (60 μg) were separated using 8% sodium dodecyl sulfate -polyacrylamide gel electrophoresis (SDS-PAGE) (9.4 ml ddH₂O, 5 ml 1.5 M Tris-HCl pH 8.8, 5.3 ml 30% Acrylamide, 200 μl 10% SDS, 200 μl 10% Ammonium-peroxidsulfate (APS) and 20 μl N,N,N,N-Tetramethyl-ethylene diamine

(TEMED)) and were then transferred to nitrocellulose membranes. The membranes were blocked with 5% BSA in Tris-buffered saline with 0.5% Tween (TBST) at room temperature for 1 h. Then, membranes were incubated overnight at 4°C with antibodies to Akt and AS160, diluted (1:1000) in blocking buffer. Membranes were washed with TBST and protein was detected by using secondary HRP-conjugated antibody (Cell Signaling Technology, MA, USA) at room temperature for 1 h. Proteins were viewed by chemiluminescence (Western Lighthing Chemiluminescence Reagent Plus, Perkin Elmer, Boston, MA) and bands were quantified using Kodak Imaging software (Kodak ID 3.5, Boston, MA).

7.4.2.8 Resistance training program

See General methods Section “3.11 Resistance training program”.

6.4.2.9 Statistics

See Chapter Five (Study Two) Section “5.4.2.10 Statistics”. In addition, Spearman Rho correlations were conducted to assess the relationship between Akt, AS160 and glycogen content and metabolic risk factors.

7.5 Results

7.5.1 Baseline comparison

7.5.1.1 Participant characteristics

No significant differences were found between LoMFC and LoMFT or between HiMFC and HiMFT for sex, age, anthropometric measurements or metabolic risk factors (Table 7.1).

Table 7.1. Group characteristics at baseline.

Variable	LoMFC n=5	LoMFT n=6	p	HiMFC n=11	HiMFT n=10	p
Sex (M/F)	1/4	1/5	-----	M=7 / F=4	M=6 / F=4	-----
Age (yrs)	53.8±7.8	50.2±4.9	0.43	51.1±5.7	51.4±8.0	0.92
Waist (cm)	81.7±4.3	81.4±10.0	0.63	99.4±12.3	100.4±9.5	0.84
BMI (kg·m ⁻²)	23.4±2.7	24.9±3.3	0.68	30.3±4.1	31.2±5.2	0.65
Glucose (mmol·L ⁻¹)	4.9±0.4	5.1±0.2	0.54	5.6±0.4	5.8±0.6	0.58
Trig (mmol·L ⁻¹)	0.7±0.4	0.7±0.4	0.66	1.8±0.8	1.5±0.4	0.27
HDL (mmol·L ⁻¹)	1.5±0.5	1.7±0.4	0.13	1.3±0.5	1.6±0.6	0.22
SBP (mmHg)	122.0±10.9	119.7±14.1	0.81	134.2±13.5	129.0±16.5	0.44
DBP (mmHg)	78.0±1.4	81.0±8.3	0.30	87.5±7.8	85.8±8.9	0.65
HbA1c (%)	5.2±0.3	5.3±0.2	0.65	5.5±0.3	5.7±0.5	0.15
HOMA-IR	0.9±0.8	0.7±0.9	0.21	2.3±1.6	1.5±1.0	0.61

LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training), BMI (body mass index), Trig (triglyceride), HDL (high-density lipoproteing), SBP (systolic blood pressure), DBP (diastolic blood pressure), HbA1c (glycosylated-haemoglobin), HOMA-IR (homeostasis model assessment of insulin resistance, [(fasting glucose (mmol·L⁻¹)×fasting insulin (mIU/L)]·25⁻¹).

7.5.1.2 Baseline Glycogen, Akt and AS160 levels

At baseline, no significant differences were found between HiMF (pooled HiMFT and HiMFC) and LoMF (pooled LoMFT and LoMFC) for glycogen content, Akt and AS160 (all p>0.05). Also, at baseline, despite randomization, HiMFT participants had elevated levels of phosphorylated Akt, compared to HiMFC individuals (Table 7.2). The AS160 data for one participant from HiMFC and for one LoMFC participant were excluded due to abnormal values (values>3 SD from the mean).

Table 7.2. Glycogen stores, Akt and AS160 at baseline, comparisons between HiMFT versus HiMFC and LoMFT versus LoMFC.

Variable	LoMFC n=4	LoMFT n=6	p	HiMFC n=11	HiMFT n=10	p
Glycogen (μ mol glucosyl units/gram wet)	61.7 \pm 8.9	62.5 \pm 17.1	0.93	70.8 \pm 22.5	73.4 \pm 15.6	0.77
Phosphorylated-Akt (A.U)	23.5 \pm 13.5	24.3 \pm 11.2	0.92	19.8 \pm 5.5	37.3 \pm 17.5	<0.01
Total Akt (A.U)	182.3 \pm 57.6	175.7 \pm 50.9	0.85	180.3 \pm 54.5	172.5 \pm 50.2	0.91
Phosphorylated - AS160 (A.U)	108.1 \pm 62.6	55.1 \pm 17.8	0.08	66.9 \pm 42.7	95.1 \pm 57.6	0.23
Total AS160 (A.U)	160.0 \pm 51.2	170.1 \pm 107.3	0.87	182.2 \pm 76.6	223.2 \pm 101.6	0.32

LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training).

7.5.1.3 Baseline correlation between Akt and AS160 and metabolic risk factors

For all groups together (pooled HiMF and LoMF groups), total AS160 was correlated with both total and phosphorylated Akt ($r=0.59$, $p<0.01$ and $r=0.46$, $p=0.01$ respectively). Similarly, phosphorylated AS160 was correlated with phosphorylated and total Akt ($r=0.64$, $p<0.01$ and $r=0.42$, $p=0.02$ respectively).

For the HiMF group, (training and control pooled together), baseline IL6 and IL8 levels were negatively correlated with baseline total AS160 ($r=-0.51$ and $r=-0.52$, $p=0.02$) and p-AS160 ($r=-0.49$ and $r=-0.45$, $p<0.05$). HOMA-IR was negatively correlated with baseline phosphorylated Akt ($r=-0.44$, $p=0.05$).

7.5.2 The effects of resistance training

7.5.2.1. Adherence to training

Details of participants' adherence to training are discussed in Chapter 5 (5.5.3.1 Participation in training). The muscle sample from one volunteer (HiMFC) was analysed for Akt and AS160 only (not for glycogen content) due to the small muscle sample.

7.5.2.2 The effect of resistance training on glycogen content, Akt and AS160

The effect of RT on muscle glycogen is illustrated in Figure 7.1. In both HiMFT and LoMFT, training improved muscle glycogen content compared to baseline (by 22.3%, $p=0.06$ and 34.4%, $p=0.03$).

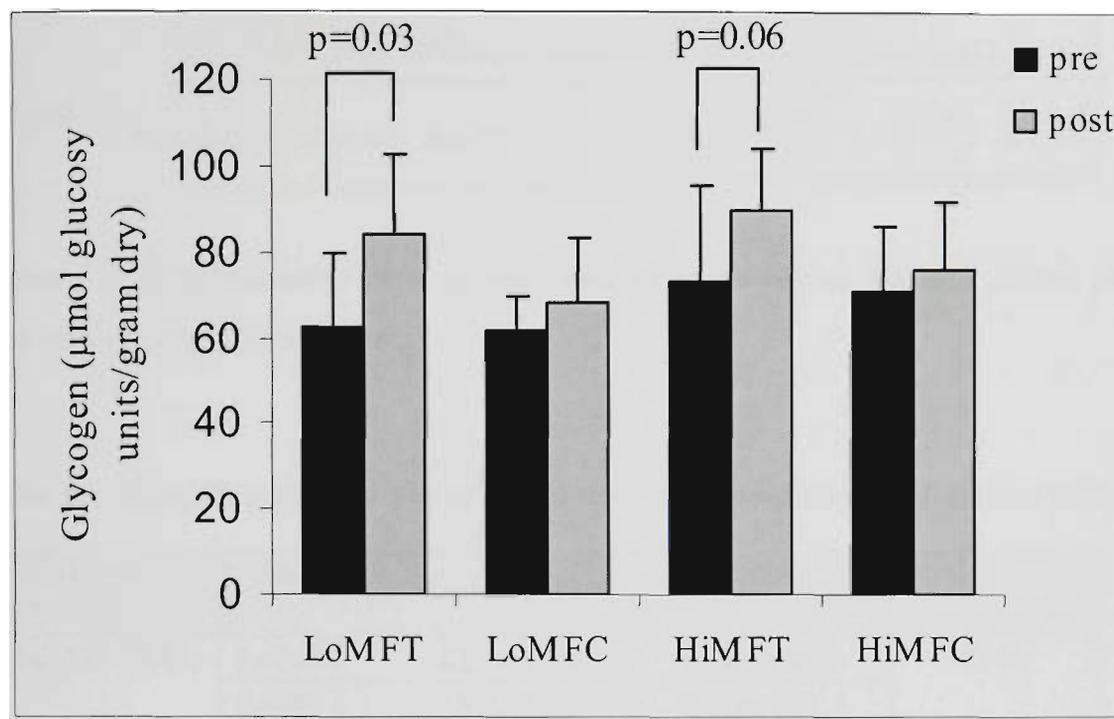


Figure 7.1. The effect of resistance training on glycogen content.

LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training).

Representative blots of total and phosphorylated Akt and AS160 before (pre) and after (post) training for the same two participants are shown in Figure 7.2. For LoMFT, training did not change Akt and AS160 levels (both total and phosphorylated) (Table 7.3) For HiMFT, RT significantly increased total Akt (by 25.1%) compared to baseline levels ($p<0.02$) which was almost significantly different from HiMFC ($p=0.06$). Training however, significantly reduced phosphorylated AS160 (by -24.8%) for the HiMFT both compared to baseline ($p=0.02$) and compared to controls ($p=0.01$) (Table 7.3).

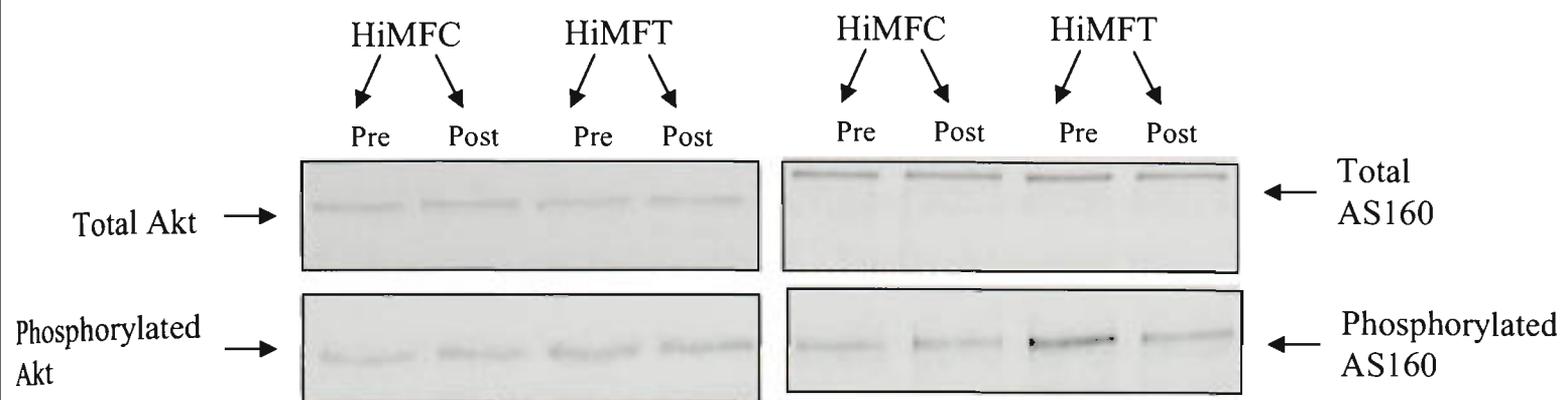


Figure 7.2. Representative blots of total and phosphorylated Akt and AS160 pre and post 10 weeks of interventions.

Table 7.3. The effects of 10 weeks of RT on total and phosphorylated Akt and AS160.

Variable	Group	Pre	Post	p group×time
Total Akt (A.U)	LoMFC	182.3±57.6	184.3±46.9	0.40
	LoMFT	175.7±50.9	217.6±111.1	
	HiMFC	180.3±54.5	182.2±59.1	0.06
	HiMFT	172.5±50.2	215.8±85.6*	
Phosphorylated Akt (A.U)	LoMFC	23.5±13.5	22.8±2.0	0.68
	LoMFT	24.3±11.2	26.7±11.3	
	HiMFC	19.8±5.5	25.1±13.7	0.08
	HiMFT	37.3±17.5	31.7±8.4	
Total AS160 (A.U)	LoMFC	160.0±51.2	170.3±76.1	0.91
	LoMFT	170.1±107.3	176.5±71.4	
	HiMFC	182.2±76.6	187.3±78.9	0.37
	HiMFT	223.2±101.6	207.6±77.1	
Phosphorylated AS160 (A.U)	LoMFC	108.1±62.6	108.8±77.1	0.90
	LoMFT	55.1±17.8	52.9±18.2	
	HiMFC	66.9±42.6	77.9±50.6	0.01
	HiMFT	95.1±57.6	71.5±41.7*	

* Indicates $p < 0.05$. LoMFC (low metabolic factor control), LoMFT (low metabolic factor training), HiMFC (high metabolic factor control), HiMFT (high metabolic factor training).

7.5.2.3 Correlation between Akt and AS160 and metabolic risk factors effects of training

When all groups were pooled together (pooled HiMF and LoMF), the change in total Akt (percentage of change from pre to post) was correlated with the change in total AS160 ($r=0.47$, $p<0.01$). The change in phosphorylated Akt was correlated with both total AS160 ($r=0.54$, $p<0.02$) and phosphorylated AS160 ($r=0.66$, $p<0.01$).

In the HiMF group (training and control subgroups pooled together) the percentage change in phosphorylated AS160 and the percentage change in total AS160 were negatively correlated the number of metabolic risk factors at baseline (i.e. pre-training data) ($r=-0.51$, $p=0.02$ and $p=-0.41$, $r=0.04$, respectively) and abdominal fat (kg) at baseline ($r=-0.46$, $p=0.04$ and $p=-0.45$, $r=0.05$, respectively). For the HiMFT, the percentage change in phosphorylated AS160 was negatively correlated with the number of metabolic risk factors ($r=-0.81$, $p<0.01$) and with baseline plasma HbA1c ($r=-0.74$, $p=0.02$) (Figure 7.3).

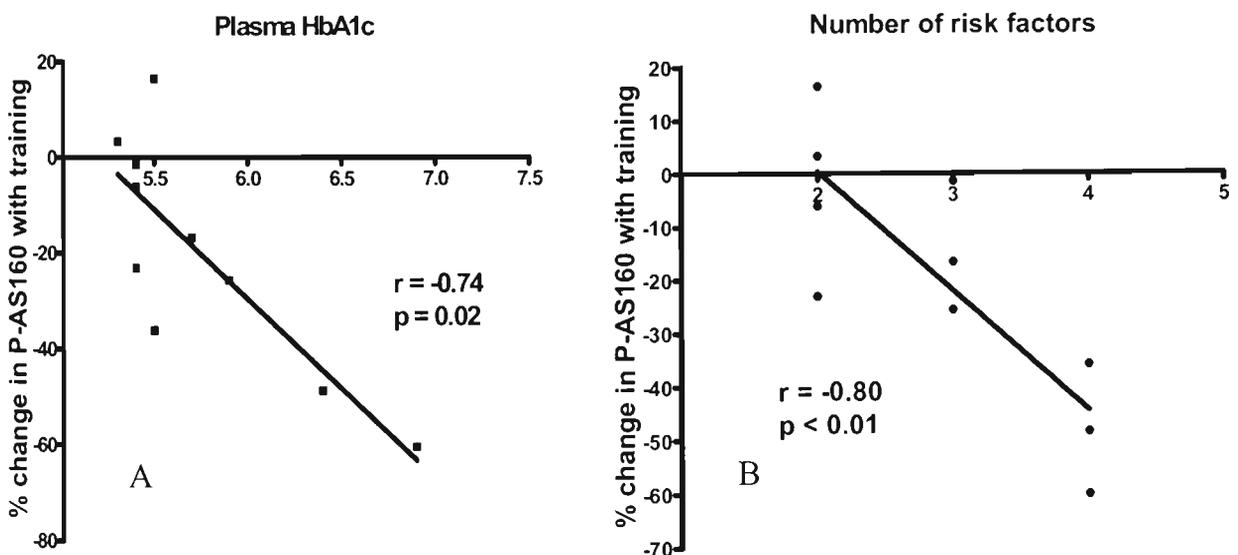


Figure 7.3. Correlation between percentage change in phosphorylated AS160 and HbA1c (A) and the number of metabolic risk factors (B) in the HiMFT group.

7.6 Discussion

7.6.1 Akt, AS160 and glycogen stores at baseline: differences between individuals with HiMF and LoMF

An important finding from the current study was that there were no significant differences between individuals with HiMF and LoMF in regard to the pre-training glycogen stores, and the total and phosphorylated Akt and AS160. It is not clear from the literature if individuals with HiMF and T2DM have lower levels of total and phosphorylated insulin-signalling proteins. Some studies have reported that obesity (Goodyear et al., 1995b) and diabetes impaired the PI3-K pathway (Krook et al., 2000; Krook et al., 2004), including reductions in Akt (Krook et al., 1998) and AS160 phosphorylation (Jager et al., 2007). Others, however, have reported no significant differences in total Akt, total IRS-1 and also total glycogen synthase between healthy individuals and patients with T2DM (Holten et al., 2004), or between normal weight and obese rodents (Krisan et al., 2004). The findings of the current study are similar to these latter studies in that no significant differences were observed between individuals with HiMF and LoMF at baseline for Akt and AS160 (both total protein and phosphorylation). The differences between the studies listed above may be related to the different populations and/or different study methodologies. These conflicting findings suggest that obesity, insulin resistance and T2DM are not simple phenomena related solely to alterations (reductions) in insulin-signalling proteins (content and activity).

7.6.2 The effects of resistance training on Akt and AS160 in individuals with HiMF and LoMF

An important finding of Study Four was that RT did not change (LoMFT) and even reduced (HiMFT) the post-training resting levels of the phosphorylated insulin-signalling protein AS160 and phosphorylated Akt, with the samples taken 4-5 days after the most recent training session. In addition, metabolic risk factors and inflammatory markers were negatively correlated with both total and phosphorylated Akt and AS160.

Some studies have previously reported that RT may have the potential to improve insulin sensitivity, insulin resistance and glucose homeostasis in young and elderly people (Dela and Kjaer, 2006; Poehlman et al., 2000), and also in people who are

overweight with and without clusters of metabolic risk factors and T2DM (Albright et al., 2000; Dela and Kjaer, 2006; Shaibi et al., 2006). However, the mechanism through which training stimulates an improvement in insulin resistance and glucose homeostasis is not fully understood (Cartee and Wojtaszewski, 2007; Jessen and Goodyear, 2005; Tomas et al., 2002). Holten et al. (2004) have reported that six weeks of one-leg RT increased leg glucose clearance (in the trained leg) under insulin stimulation and muscle glycogen content for healthy individuals and those with T2DM. The authors suggested that the mechanisms behind those training effects include an increase in protein content of the insulin receptor, Akt, glycogen synthase (protein content and activity) and an increase in GLUT4 density. Similarly, Krisan et al. (2004) reported that 12 weeks of RT (rat model) increased IRS-1 and GLUT4 protein. However, they did not find changes in total and phosphorylated Akt in the basal state and or under insulin stimulation after RT. As there are limited studies that have examined the effects of RT on basal Akt and no studies on AS160 it is difficult to compare the results from the current study with others. In the current study, no significant changes in basal Akt and AS160 (total and phosphorylated) were observed for LoMFT. For HiMFT however, total Akt was significantly increased after training, compared to both baseline and HiMFC. Phosphorylated Akt for HiMFT did not change compared to baseline but tended to be reduced ($p=0.08$), compared to HiMFC. This may be related to HiMFC having a small, non-significant, increase in phosphorylated Akt and HiMFT exhibiting a small, non-significant, decrease in phosphorylated Akt. This finding (small reduction in phosphorylated Akt) is in contrast to studies using aerobic training, which have shown an increase in total and phosphorylated Akt (Frosig et al., 2007). The apparently discordant findings in the current study (i.e. an increase in total Akt but a reduction in phosphorylated Akt) warrant further studies to fully elucidate the influences of RT on Akt. The discordant findings are also apparent in studies that have examined the acute effect of resistance exercise on phosphorylated Akt. Some studies have reported an increase in phosphorylated Akt after an acute bout of resistance exercise (Creer et al., 2005; Leger et al., 2006), while others have reported no change (Coffey et al., 2006; Deshmukh et al., 2006; Eliasson et al., 2006; Krisan et al., 2004) or a reduction in phosphorylated Akt (by up to 57%) after acute resistance exercise (Howlett et al., 2007; Terzis et al., 2008). It is important to note however, that it is possible that a reduction in basal phosphorylated Akt may not inhibit an increase in phosphorylated Akt following insulin stimulation or muscle contraction (Howlett et al., 2007).

Previous studies have reported that immediately following acute resistance exercise there is a significant reduction in AS160 phosphorylation (by up to 40%) in healthy young volunteers (Howlett et al., 2007). In addition, a reduction in insulin action, and a reduction in GLUT4 protein content (up to 39%) has been reported up to two days after resistance exercise (Asp et al., 1996; Asp and Richter, 1996; Asp et al., 1997). The current study is the first to report that the reduction in basal phosphorylated AS160 may not be only a transient response to an acute bout of resistance exercise, but may persist even 4-to-5 days after the last exercise session for individuals with HiMF. These data suggest that the reduction in phosphorylated AS160 is not a short term or temporary phenomenon (up to 48 h after resistance exercise), but rather may indicate a new basal state.

It is not clear why RT led to a reduction in phosphorylated AS160. A possible link may be related to the high levels of inflammatory markers in individuals with HiMF even after training, and the possible associations with insulin-signalling proteins. It has been shown that HiMF, insulin resistance and T2DM are associated with increased inflammation (Duncan et al., 2003; Festa et al., 2000; Hak et al., 2001; Han et al., 2002; Hotamisligil et al., 1993; Rutter et al., 2004) and that insulin-signalling may be altered by inflammation (Kanety et al., 1995). It has been reported that inflammation can increase serine phosphorylation of IRS-1 (Kanety et al., 1995) which in turn may impair insulin action, and therefore, lead to insulin resistance (Hotamisligil et al., 1994; Hotamisligil et al., 1996; Kanety et al., 1995; Peraldi et al., 1996). Similarly, the data from this study suggest that there is an association between inflammatory markers, insulin-signalling proteins (total and phosphorylated), insulin resistance (HOMA-IR) and also between metabolic risk factors and insulin-signalling proteins, indicating that diversion from a healthy clinical profile may lead to impaired insulin-signalling. In addition, it may suggest that the increase in insulin levels and HOMA-IR in the HiMFT, compared to baseline levels, that has been reported previously (Study Three, Table 6.3) may be related to the reduction in phosphorylated AS160.

Furthermore, as previously discussed (Study Three, Discussion), for some individuals resistance exercise may lead to muscle damage that in turn increases inflammation (Tee et al., 2007). An increase in inflammation is associated with a reduction in the phosphorylation form of some insulin-signalling proteins (such as Akt and AS160) (Jager et al., 2007; Krook et al., 1998; Plomgaard et al., 2005), all of which may lead to

increased insulin resistance. Although in the current study the HiMFT group did not exhibit significant changes in plasma levels of inflammatory markers after training (Study Three) it is possible that localised intramuscular increases in inflammation (Tee et al., 2007) may affect the phosphorylation of Akt and AS160 following training.

7.6.3 The effect of resistance training on glycogen stores

Participants in the RT groups exhibited a significant increase in muscle glycogen (LoMFT) or tended to increase muscle glycogen stores (HiMFT, $p=0.06$). Investigators have reported that Akt is an important insulin-signalling protein involved in the phosphorylation and activation of glycogen synthase kinase 3 (GSK3) which in turn activates the glycogen synthase activity (Le Roith and Zick, 2001; Miranda et al., 2005; Myers and White, 2002; Saltiel, 1996; Virkamaki et al., 1999) leading to an increase in glycogen content. In the current study muscle glycogen content was increased after RT even in the presence of lower basal (resting) levels of the phosphorylated forms of Akt and AS160 after training. This result could be interpreted as RT increasing muscle glycogen independently of basal levels of phosphorylated Akt or AS160. However, it is more likely, that glycogen content increases in the first 48 h or so after a training bout in response to insulin in post-prandial periods. The finding in the current study that RT increased basal total Akt, suggests a greater potential for higher levels of Akt phosphorylation and hence higher GSK-3 activation in the presence of increased insulin levels, leading to increased glycogen levels. Due to the small amounts of muscle taken in the biopsy samples, only two insulin-signalling proteins were selected to be analysed, as well as glycogen stores. In order to have a better understanding of the effects of RT on insulin-signalling proteins, other proteins (such as GLUT4, GSK3, IRS-1 and AMPK) may also need to be examined.

In conclusion, elevated systemic markers of inflammation and increased metabolic risk factors may inhibit insulin-signalling protein phosphorylation and in turn, increase insulin resistance as well. Metabolic risk factors may counter the training-induced adaptations in total and phosphorylated forms of Akt and AS160. Despite reduced levels of phosphorylated Akt and phosphorylated AS160 at 4-5 days after completing the training program for HiMFT, total Akt and glycogen content increased. The increase in total Akt after training may increase the potential for insulin-signalling protein phosphorylation during exercise and/or insulin stimulation.

Chapter 8

8.0 General discussion

8.1 Major findings

The prevalence of HiMF, T2DM and CVD has escalated worldwide over the past two decades, accompanied by the obesity epidemic (Elabbassi and Haddad, 2005; Miranda et al., 2005; World Health Organization, 2003a; Zimmet et al., 2003). Poor lifestyle, including physical inactivity, contributes to the development of these conditions. Therefore, increases in physical activity level have the potential to improve functional capacity, QoL and the clinical outlook of those individuals (Colwell, 2003; Hu et al., 2004a; Hu et al., 2001b; Torgerson et al., 2004). This thesis examined the physical characteristics of individuals with HiMF compared to those with LoMF, as well as the capacity to perform ADL's, functional capacities and QoL in these populations (Study One). The other studies examined the effects of RT on body composition, functional capacities and QoL (Study Two) as well as the effects of RT on metabolic risk factors (Study Three) and insulin-signalling proteins including Akt and AS160 and muscle glycogen content (Study Four). These studies provide novel information in regard to the effects and benefits from RT as a single intervention to individuals with HiMF. In addition, the findings from this thesis highlight the strengths and the limitations of RT for this population, particularly a training regimen similar to the 10-week program used in this thesis.

An important finding was that despite the fact that individuals with HiMF diverge more from healthy clinical profiles, compared to those with LoMF, no differences between the groups were observed for aerobic power, muscle strength relative to body mass, and the capacity to perform ADL's or QoL. These findings were evident even after groups were divided according to sex, but especially in men. In women with HiMF, there is an association between risk profile and reduction in relative muscle strength, aerobic power, ADL's and self-perceived capacity to perform physical activities. Furthermore, women with HiMF reported more bodily pain, compared those with LoMF. This finding may have clinical importance in that women may use a decrease in functional capacity and/or increased self-perceptions of pain as early warnings, and therefore seek medical

intervention earlier in the risk factor exposure, compared to men (Australian Bureau of Statistics, 2006). In addition, as HiMF does not affect functional capacity and QoL of men (or they chose to ignore those signs. The present data raise the possibility that men should regularly consult their medical practitioner for check-ups and adoption of healthier lifestyle before risk factors progress to overt disease such as T2DM, coronary artery disease or heart failure.

Muscle weakness and sarcopenia are common findings in adult clinical populations (Willey and Fiatarone-Singh, 2003; Yki-Jarvinen and Koivisto, 1983) and are also a consequence of normal ageing (Iannuzzi-Sucich et al., 2002; Mishra and Misra, 2003). In addition, muscle weakness may lead to increased disability and reduce the capacity to perform ADL's in the elderly. The findings of this thesis confirm that RT can improve skeletal muscle strength and mass and the capacity to perform ADL's both in individuals with HiMF and individuals with LoMF. In addition, RT improved the QoL of individuals with HiMF. These findings highlight the important role RT may have in combating the loss of muscle strength and mass, and the potential of RT to improve the capacity to perform ADL's and QoL in those with HiMF. It is possible that longer training durations are needed to improve QoL in individuals with LoMF. Because RT has such positive effects on muscle mass, strength, the capacity to perform ADL's and QoL, it is recommended that RT be added to exercise interventions for these populations. This can probably be generalised to many more chronic medical conditions.

It has been suggested that both Akt and AS160 are the most distal proteins in the insulin-signalling chain (Cartee and Wojtaszewski, 2007) and both have metabolic effects on proteins synthesis, GLUT4, and glycogen synthesis. A novel finding was that RT reduced the post-training resting levels of phosphorylated AS160 and phosphorylated Akt for the HiMFT, with the samples taken 4-5 days after the most recent training session. As such, the reduction in resting phosphorylated AS160 and Akt may not be only a response to an acute bout as reported previously (Howlett et al., 2007) but may indicate a new basal state. However, the reduction in resting phosphorylated AS160 and Akt may not inhibit an increase in phosphorylated forms of these proteins following insulin stimulation or muscle contraction (Howlett et al., 2007). In contrast to the phosphorylated forms of Akt, total Akt increased following RT in HiMFT. The increase in total Akt may suggest a greater potential for higher levels of

Akt phosphorylation and hence higher GSK-3 activation in the presence of increased insulin levels or muscle contraction, leading to increased glycogen levels. Finally, an important finding was that elevated inflammatory markers and increased metabolic risk factors may inhibit phosphorylation of AS160 and Akt. This in turn may increase insulin resistance. It appears that metabolic risk factors may counter the training-induced adaptations in total and phosphorylated forms of Akt and AS160.

Despite the significant benefits of RT for muscle strength and mass and muscle glycogen content and the capacity to perform ADL's and QoL, no change to the clinical profiles of participants with HiMFT was observed. It was not expected that RT will improve the metabolic risk profile in the LoMFT group, as they are already considered to have normal/healthy clinical profile. As reported in Study Three, RT did not change the traditional metabolic risk factors, such as body fat content and waist circumference, systolic or diastolic BP, lipid profile or fasting glucose or HbA1c in the HiMFT, nor the emerging risk factors such as inflammation markers, hepatic enzymes or BDNF levels. In addition, the insulin resistance state for the HiMFT was even increased following training compared to baseline levels. Previous studies with similar populations have shown that training interventions that include both RT and aerobic training (Balducci et al., 2004; Maiorana et al., 2002) or RT and diets (Dunstan et al., 2002; Joseph et al., 2001) have significant effects on clinical outcomes including improvements in glycaemic control and insulin resistance and reductions in body mass, waist circumference, and fat content. Improvements in lipid profiles (Cauza et al., 2005b; Honkola et al., 1997) and a reduction in BP (Blumenthal et al., 1991) were also reported. As such, it appears that in order to target the metabolic risk factors in individuals with HiMF and T2DM using exercise training interventions, it will be the most efficient to combine RT with other interventions such as aerobic training and/or diet.

8.2 Thesis limitations

A potential limitation of the thesis is the possibility for sex bias between HiMF (male:female 20:10) and LoMF (8:17) groups. It is important to note that of the total sample of 55 volunteers, 28 were male and 27 female. The allocation to HiMF or LoMF groups was based on objective IDF criteria, with more men allocated to HiMF and more

women to LoMF. In the training studies, participants were randomised and stratified according to sex to ensure near equal numbers of males and females in each study subgroup and the sex split for LoMFC and LoMFT (male:female 4:9 versus 4:8) and HiMFC and HiMFT (10:5 versus 10:5) was nearly identical. Therefore, any biases based on sex may apply for the comparisons of HiMF and LoMF but it did not apply to any other comparisons in the thesis (LoMFC versus LoMFT and HiMFC versus HiMFT).

Another limitation is the duration of the training protocol. It is possible that longer training protocol will elicit greater training benefits for individuals with HiMF and LoMF, including improvements in clinical outcomes for individuals with HiMF and improvement in QoL for individuals with LoMF.

Finally, some of the biological markers (especially the insulin signalling proteins) have large variability. This large variability may affect the results and may also prevent to reach to statistical significant following training.

8.3 Recommendation for future research

The results from the current thesis raise several questions in regard to the role of exercise training as a therapeutic intervention:

- What is/are the cause/s for the reduction in total and phosphorylation Akt and AS160 after resistance exercise and RT?
- What is the mechanism behind the increase in muscle glycogen content?
- What is the optimal RT protocol (intensity, volume, frequency and duration) that should be used in order to improve the metabolic risk profile in individuals with HiMF?
- What is the optimal training protocol (eg hybrid program of RT plus aerobic training, RT alone, RT plus diet) to improve metabolic risk factors in the HiMF population?
- What will be the best way to encourage people to increase their physical activity level?
- Do men and women respond and adapt similarly to similar training regimes?

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Appendices

Appendix A

Three days dietary log

Instructions For a Three Day Food Diary

Name Weight..... kg
Age Height cm
Date

Keeping a food record is like having your swimming stroke or your golf swing analysed videoed. The most important concern is that it captures what you REALLY or NORMALLY do.

1. **Above all, try to eat normally while you are recording.**
 - a) Do not try to eat better (or worse) to impress (or shock).
 - b) Do not just eat foods that are convenient to record.
 - c) Don't adjust your food quantities so that it looks tidier on paper, or fits into round numbers- e.g. exactly two cups of Cornflakes, exactly one cup of milk.
2. Complete the food diary for two weekdays and one weekend day.
3. Also indicate at what time of the day you have exercised/trained and give an estimate of the duration and intensity of the training completed.
4. Carry the food record around with you at all times and fill in all foods/drinks at the time they are eaten. Don't rely on your memory and judgment by waiting until the end of the day or the recording period.
5. Include all food, drinks, medication and supplements.
6. Accurate details about the quantity of each food/drink is important: Tell us in terms of:
 - a) Food weight- you may know the weight/volume of a food because it is written on the packet or because you have easy access to scales. Make sure that you specify whether the food is cooked or uncooked (e.g. for meats) and whether it includes bones, skins and cores (e.g. for chops or pieces of fruit).
e.g.: Mars bar - 70 g; Sara Lee muffin - 65g.
 - b) Teaspoons and tablespoons: gently heaped.
e.g.: Tsp of margarine on toast; 2 Tbsp of mashed potato.
 - c) Cups: Level cups.
e.g.: cup of Weenies; 2 cups of cooked pasta.
 - d) Measure the outline using the grid attached.

Don't guess sizes! Don't label simply as small, medium large.

e.g.: T-bone steak, 15 X 8 X 1.5 cm; Grannysmith apple, 6 cm diameter.

7. In describing food it is sufficient simply to name foods that are well known and standard items. You may not even have to bother to measure foods that came in standard sizes. However, remember special features such as whether foods were sweetened/unsweetened, full cream/low fat, wholemeal/white or toasted/untoasted bread.

An indication of the number of grams of fat, protein and carbohydrate per serve of per 100 gm, from the nutrition panel is extremely useful

As there are many varieties of muesli or cereal bar, an indication of the fat, carbohydrate and protein content is very useful.

Indicate if a slice of bread was sandwich or toast thickness.

1 Tim-tam biscuit;

1 cup Cerola toasted apricot muesli;

1 slice TipTop wholemeal sandwich bread.

8. Where relevant, indicate if the food was purchased outside the home, if the food was commercially prepared or the meal was eaten in a restaurant.

9. If foods vary in their shape and size and composition, and particularly if they are made up from different foods combined together, then you will need to provide more information, such as a stir fry or omelette. Try to list all the ingredients, with the quantities of each. You may need to measure the quantity of foods that come in different and unusual portion sizes or give as many details as possible.

Omelette made from 2 X 60 g eggs,

1 slice Kraft single cheese;

1 slice lean ham, 9 X9 x 0.25 cm

In some cases it may be necessary to give the recipe (attach to the back of the sheet if you wish) and then indicate how much you ate of the finished product.

10. Remember to mention anything that you add to food (e.g. butter, margarine on bread milk on cereal, sugar in tea). And comment on anything that you take away from food (e.g. remove skin from chicken, cut fat from meat).

10. If food is cooked, include the method of cooking.

e.g.: 60 g egg, fried in UP oil; 1 cup of beans, steamed.

**EXAMPLE ONLY
FOOD DIARY DAY _.**

NAME DAY DATE

Time FOOD DESCRIPTION QUANTITY WHERE EATEN

6.30-7.30am TRAINING

Training Running 12 km (50 mins) Easy.

7.45am Breakfast

orange juice	sweetened	2 glasses (200ml)	At home
muesli	toasted	1 cup	
milk	skimmed	1/2 cup	
toast	wholemeal	2 slice	
butter		1 tsp	
jam	strawberry	2 tsp	
coffee	white, no sugar	1 cup	

10 am Morning Tea

banana		12 X 3 cm	AT WORK
apple juice	unsweetened	250 ml	

12 pm Lunch

salad sandwich	white bread	2 slices	AT WORK
	butter	1 tsp	
	lettuce	1 large leaf	
	tomato	1 slice	
	cheddar cheese	1 slice	
corn chips		50 g packet	
flavoured milk coffee Moove		250 ml	

4pm Afternoon snack

snack pack	sultanas, peanuts	25g pack	AT WORK
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7 pm Dinner

satay	chicken	2 satay sticks	
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TAKE-AWAY

peanut sauce		2 tbsp	Resturant
cabbage		4 tbsp	
chicken		1/2 cup,	
Black bean sauce		1 tbsp	
corn kernels	stir fried	1 tbsp	
snow peas	stir fried	1 tbsp	
rice	mashed	2 tbsp	
coffee	instant	1 cup	
banana split	with ice cream	1 banana/ 1 scoop icecream .	

10pm Supper

milo	with Shape milk	1 cup	
		2 tsp milo	

Supplements Vitamin C	tablet	1 X 100 mg	
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Appendix B

Resistance training programme exercises

Following is the description of the resistance exercises used during the 1RM tests and during the training as well as the targeted muscle groups.

Chest press

Description: Participant lies on a bench with hands holding the lower pulleys of the machine. Participant then extends arms almost to full extension and returns to the starting position (Figure B.1).

Primary muscles: pectoralis major, anterior deltoid and triceps.

Start position



Finish position



Figure B.1. Chest press.

Leg press (45°)

Description: Participant seated upright in 45° with both feet on the footplate. Exercise is started from full extension after releasing the footplate from its holding device. Participant then bends knees to approximately 90° (knee flexion), and then pushes the footplate until knees reach full extension again (Figure B.2).

Primary muscles: quadriceps, hamstring and gluteus maximus.

Start position



Finish position

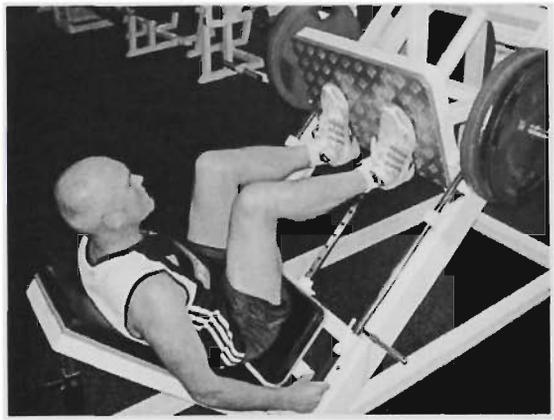


Figure B.2. Leg press (45°).

Lateral pull-down

Description: Participant seated upright with hands holding the bar in wide grip. Participant pulls the bar until it reaches to the level of the chest and then returns to the starting position (Figure B.3).

Primary muscles: latissimus dorsi and biceps brachii.

Start position



Finish position



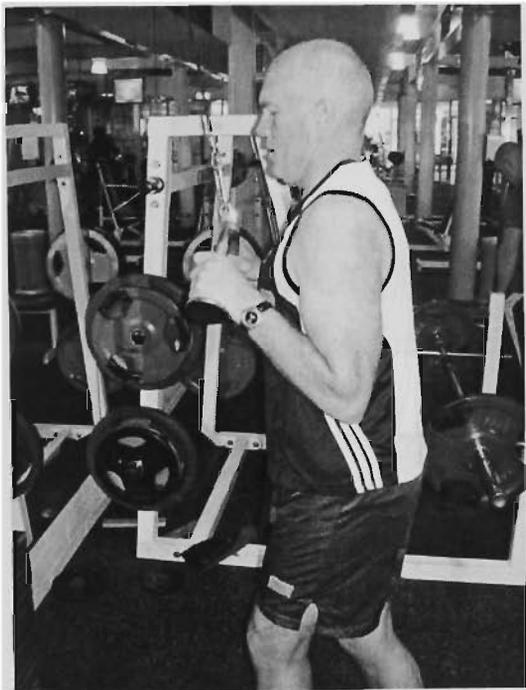
Figure B.3. Lateral pull-down.

Triceps extension

Description: Participant stands with hands holding the bar in pronated grip and at body width. Participant pushes the bar down until elbows reach to full extension and then return to the starting position (Figure B.4).

Primary muscle: triceps brachii.

Start position



Finish position



Figure B.4. Triceps extension.

Knee extension

Description: Participant seated upright with legs inside the pad. Participant extends knees until almost full extension and then returns to the starting position (Figure B.5).

Primary muscle: quadriceps.

Start position



Finish position

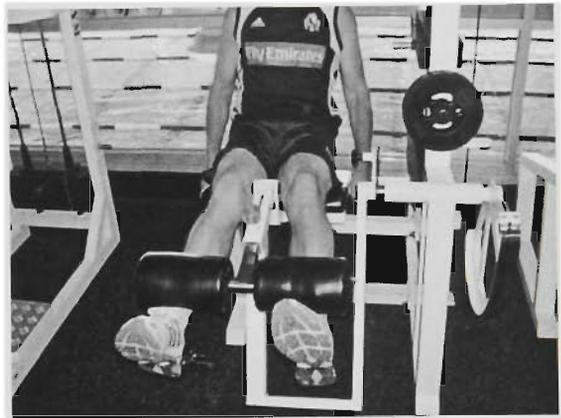


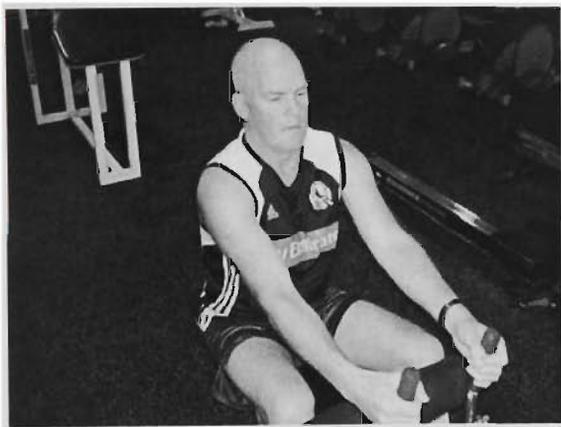
Figure B.5. Knee extension.

Seated row

Description: Participant seated on a bench with knees against the pad. Participant pulls the bar towards body (abdominal area) and then returns to the starting position (Figure B.6).

Primary muscles: trapezius, latissimus dorsi, rhomboids, biceps brachii and posterior deltoid.

Start position



Finish position

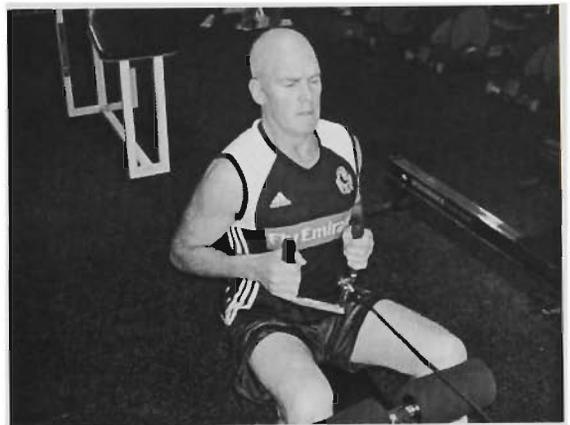


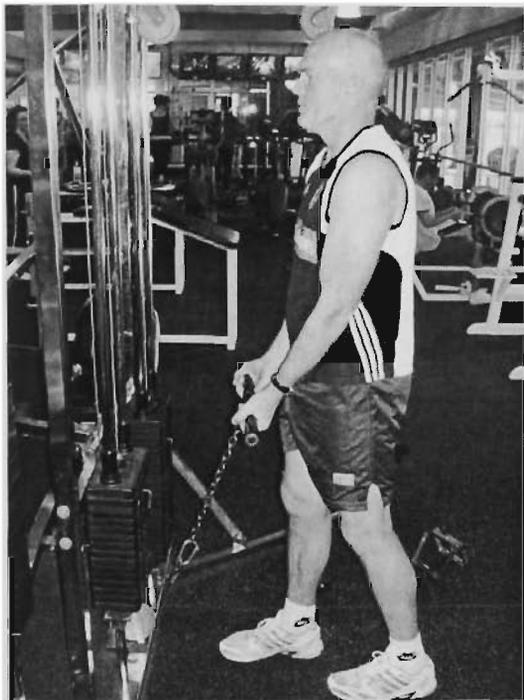
Figure B.6. Seated row.

Biceps curl

Description: Participant stands with hands holding the bar (lower pulley) in supinated grip and body width. Participant pulls the bar until it reaches shoulder level (elbow flexion) and then returns to the starting position (Figure B.7).

Primary muscles: biceps brachii

Start position



Finish position



Figure B.7. Biceps curl.

Appendix C

The reliability of the 1RM strength test for untrained middle-aged individuals

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ABSTRACT

Purpose: The one repetition maximum test (1RM) is considered the gold standard for assessing muscle strength in non-laboratory situations. Since most previous 1RM reliability studies have been conducted with experienced young participants, it is unclear if acceptable test-retest reliability exists for untrained middle-aged individuals. This study examined the reliability of the 1RM strength test of untrained middle-aged individuals. **Methods:** Fifty-three untrained males (n=25) and females (n=28) aged 51.2 ± 0.9 years participated in the study. Participants undertook the first 1RM test (T1) four to eight days after a familiarisation session with the same exercises. 1RM was assessed for seven different exercises. Four to eight days after T1, participants underwent another identical 1RM test (T2). Ten weeks later, 27 participants underwent a third test (T3). Intraclass correlation coefficients (ICC), typical error as a coefficient of variation (TEcv), retest correlation, repeated measures ANOVA, Bland-Altman plots, and estimation of 95% confidence limits were used to assess reliability. **Results:** A high ICC (ICC>0.99) and high correlation ($r>0.9$) were found for all exercises. TEcv ranged from 2.2 to 10.1%. No significant change was found for six of the seven exercises between T1 and T2. Leg press was slightly higher at T2 compared to T1 ($1.6 \pm 0.6\%$, $p=0.02$). No significant change was found between T2 and T3 for any exercise. **Conclusion:** 1RM is a reliable method of evaluating the maximal strength in untrained middle-aged individuals. It appears that 1RM-testing protocols that include one familiarisation session and one testing session are sufficient for assessing maximal strength in this population.

A. INTRODUCTION

Resistance training has been of great interest to exercise scientists and health professionals who study both healthy individuals, and those who suffer from chronic conditions including cardiovascular diseases [1-3], diabetes mellitus [4,5], and overweight/obese individuals [6]. Since an increase in muscle strength is the most common and important benefit of resistance training [7,8], an accurate determination of muscle strength to properly evaluate the efficacy of the training is essential [9]. Laboratory-based methods for evaluating maximal muscle strength include the use of isometric dynamometers [10,11] and isokinetic dynamometers [12-14]. These two methods, however, usually require sophisticated laboratory equipment and personnel trained in their use. Furthermore, these tests are not very specific for the types of movement patterns commonly used in typical fitness regimes. In contrast, the one repetition maximum (1RM) method, defined as the maximal weight that can be lifted once with correct lifting technique, is comparatively simple and requires relatively inexpensive non-laboratory equipment [9]. Moreover, because the 1RM test can be performed using the same patterns as those undertaken by the exercising individuals during their normal training, it is increasingly gaining acceptance as the gold standard for assessing muscle strength [8,9]. Furthermore, previous studies have reported that the 1RM method to assess muscle strength is safe for healthy adults [15,16] and also for patients with cardiovascular disease [17,18]. The test-retest reliability of the 1RM demonstrates high intraclass correlation coefficients (ICC). However, as most 1RM reliability studies have been conducted with experienced healthy young participants (age 18-30 years) [19-21], it is unclear whether this test-retest reliability is applicable to untrained middle-aged individuals who are increasingly the subject of exercise intervention studies. It has been suggested that the reliability of strength tests in older populations may be lower due to decreased muscle strength and joint stability [12]. To date, there is a lack of data on the test-retest reliability of 1RM tests performed by untrained middle-aged individuals for a range of different resistance exercises. Most studies that have examined the test-retest reliability of maximal strength in middle-aged and older populations have used isokinetic dynamometers [12,22,23] and not isoinertial-based (gym) machines.

A familiarisation process prior to 1RM strength testing is essential for ensuring reliable test results [24,25] and minimize learning effect or systematic bias [26]. Furthermore, it

has been shown that without a familiarisation process prior to strength testing, there is a significant increase in the expression of muscle strength between two consecutive strength tests performed a few days apart [24,25]. Some investigators have suggested that older individuals should undergo between 8-9 sessions of 1RM testing in order to increase the consistency of the 1RM measurements [23]. Multiple familiarisation sessions however, may not be practical for training studies that examine strength changes for several different resistance exercises as well as numerous other functional parameters. This would unnecessarily increase the time requirement of each participant and extend the duration of the study, both of which might increase the likelihood of participant dropout. As such, the purpose of this study was to examine the test-retest reliability of the 1RM strength test of untrained middle-aged individuals following one familiarisation session.

B. METHODS

Participants

Fifty-three untrained males (n=25) and females (n=28) aged 51.2 ± 0.9 years volunteered to participate in the study (participants' characteristics are shown in Table 1). Participants were included, whether or not they had cardiovascular risk factors such as overweight/obesity, hypertension, dyslipidemia and hyperglycaemia. Participants were on a range of medications including beta-blockers (2 participants), calcium channel blockers (2), ACE inhibitors (4), diuretics (1), statins (2), metformin (1), and hormone replacement therapy (6). They were only included if they had not been involved in regular aerobic physical activity in the previous six months or resistance training in the previous five years or more. Participants were excluded from the study if they were involved in vigorous regular exercise activity for more than 90 minutes a week or had documented heart disease such as chronic heart failure or coronary artery disease. Each participant received an explanation about the nature of the study and after a medical clearance signed an informed consent document. The study protocol was approved by the Human Research Ethics Committees of both Victoria University and Austin Health.

Table 1. Participants' characteristics (mean±SEM).

	All participants	Subgroup
Gender (M/F)	25/28	13/14
Age (yrs).	51.2±0.9 (40-69)	50.7±1.3 (40-63)
Height (cm).	168.5±1.3 (152.0-186.0)	168.1±1.6 (155-185)
Weight (kg).	78.6±2.3 (40-113.6)	78.5±3.3 (40-112.4)
Waist (cm).	91.9±1.9 (59.1-120.5)	90.9±0.9 (59.1-120.5)
BMI (kg·m ⁻²).	27.5±0.7 (16.7-39.22)	27.5±2.6 (16.7-36.3)

Note: BMI (body mass index).

Study protocol

Four to eight days prior to the first one-repetition maximum test (T1), participants performed a familiarisation session with the resistance training equipment (Life Fitness and CalGym, Caloundra, QLD, Australia). During the familiarisation session, correct lifting and breathing technique were taught and practiced using submaximal and near maximal loads. 1RM was defined as the heaviest weight a participant could lift once with a proper lifting technique, without compensatory movements. 1RM strength was assessed for seven different exercises comprising in order, chest press, leg press, lateral pull-down, triceps pushdown, knee extension, seated row and biceps curl. Exercises involving large muscle groups were performed first followed by those involving small muscle groups. In order to facilitate the recovery and reduce the effect of fatigue, exercises were alternated between the upper and lower body. The tests commenced after a light warm-up (three-minute walking at self-selected speeds on a treadmill). The maximal strength test protocol included one set of 10 repetitions at a relatively light load that served as a specific warm-up, followed by a gradual increase in load until 1RM was achieved. The rate of the gradual increase in load was dependent on the participant's self-perceived capacity, and it ranged from 1-10 kg for biceps curl and triceps pushdown, up to 100 kg for leg press and between 1 to 20 kg for the rest of the

exercises. The 1RM was achieved within 3-6 attempts. The rest period between attempts was 1 minute, and between each specific exercise, volunteers recovered for 2 minutes. Four to eight days after the T1, participants underwent another 1RM test (T2) and, for a subgroup of 27 participants, again after 10 weeks (T3). T2 and T3 test protocols and the test conditions were identical to test T1 [21], and the same investigators conducted the testing on each occasion. The 27 participants from the subgroup were asked not to change their activity level and this was monitored.

Statistical analyses

Reliability in this study was analysed according to the recommendation of Hopkins [26] and Atkinson and Nevil [27]. Intraclass correlation coefficients (ICC) were used as they are a common measurement of reliability that enables comparisons with other studies [27]. The ICC method was based on a repeat measurement of maximal strength (single value) (2, 1) and the same investigator conducted the tests [28]. Retest correlation was measured by Pearson correlation coefficient. Within subject variation was reported as typical error, and was expressed as a coefficient of variation (TEcv). This allows for comparisons between different studies, and is usually not due to machine or operator error [26]. Also, we report the lower and upper confidence limits (95%) of the above measurements. Changes in the means between tests, which examines random change and systematic bias, were assessed by repeated measures ANOVA. Log transformation (multiplied by 100 to maintain precision) was performed prior to the data analyses as data were not normally distributed. Data distribution was examined by normal probability plots and the Kolmogorov-Smirnov test because heteroscedastic errors are the norm in studies in the area of exercise science [27,29]. Log transformation was performed using a spreadsheet designed for this purpose [26,30]. Bland-Altman plots were used to display visual representations of the errors against true values by plotting the difference between T2 and T1 against the mean of T2 and T1 [31]. Data were analyzed using SPSS (Version 15). Data are presented as means \pm standard error of measurements (SEM), unless otherwise stated. All statistical analyses were conducted at the 95% level of significance.

C. RESULTS

No significant injuries occurred during the study, except for mild muscle soreness that is common with unaccustomed exercise for untrained individuals. Some participants reported this mild soreness one to three days after some of the tests.

Raw data of T1 and T2 for all seven exercises (53 participants) is presented in Table 2. Also reported are the ICC and the change in mean, TEcv (%) and the correlation between the two tests. A high ICC (>0.97) and high correlation ($r>0.9$) were found for all exercises and for the total strength (sum of all seven exercises). TEcv (%) indicated typical errors range of 2.2% - 7.2%. In addition, no significant systematic bias was found between total weight lifted at T1 and T2, nor for six of the individual exercises including chest press, triceps pushdown, seated row, leg extension, biceps curl and lateral pull (Table 2). There was a significant but small difference in leg press 1RM with T2 being slightly higher than T1 ($1.6\pm 0.6\%$, $p=0.02$). The Bland-Altman plot within cases for T1 and T2 for total strength demonstrated also that most results for individual participants are within 2 standard deviation (Figure 1A.).

The reliability data of the 27 individuals in the subgroup who performed T1, T2 and T3 are presented in Table 3. ICC was >0.96 between T2 and T1 and T3 and T2. TEcv (%) range was 1.9 to 10.1%. In addition, the retest correlation was >0.9 . No significant systematic bias was found between any of the exercises. Most data points on the Bland-Altman plot for total strength were within 2 standard deviation for T2 versus T3 (Figure 1B).

Table 2. Muscle strength and the reliability for the 53 participants who underwent T1 and T2.

Exercise	T1 (kg±SE)	T2 (kg±SE)	ICC	Reliability after Log-transformation		
				Δ mean (%) (95% CI).	TE as a CV (%) (95% CI)	Retest r
Chest P	52.5±3.5	52.5±3.6	0.99	-0.7 (-3.1 to 1.7)	6.5 (5.4 to 8.1)	0.984
Leg P	195±11.2	198.8±11.4	0.99	1.6 (0.3 to 2.9)*	3.3 (2.8 to 4.1)	0.993
Lat P	50.5±2.3	50.0±2.3	0.99	-1.1 (-2.3 to 0.2)	3.4 (2.8 to 4.2)	0.990
Tri P	27.4±1.4	27.7±1.4	0.98	0.9 (-1.1 to 2.9)	5.3 (4.4 to 6.6)	0.981
Knee E	46.9±2.1	48.0±2.2	0.97	1.7 (-0.7 to 4.2)	6.0 (5.0 to 7.6)	0.969
Seated R	50.8±2.4	50.3±2.4	0.99	-1.1 (-2.4 to 0.2)	3.4 (2.8±4.2)	0.992
Biceps C	18.8±1.1	19.1±1.2	0.98	1.1 (-1.6 to 3.9)	7.2 (6.0 to 9.0)	0.979
All	434.3±21.0	438.2±21.5	0.99	0.7 (-0.2 to 1.6)	2.2 (1.9 to 2.8)	0.997

Note: * indicates $p < 0.05$; ICC (intraclass correlation coefficients), TE (typical error), CV (coefficient of variation), Chest P (chest press), Leg P (leg press), Lat P (lateral pulldown), Tri P (triceps push down), Knee E (knee extension), Seated R (seated row), Biceps C (biceps curl), Total (total weight lifted).

Table 3. Muscle strength and reliability for the 27 participants who underwent T3.

Exercise	T1 (kg±SE)	T2 (kg±SE)	T3 (kg±SE)	ICC (T3-T2)	Reliability after Log-transformation (T3 versus T2)		
					Δ mean (%) (95% CI).	TE as a CV (%) (95% CI)	Retest r
Chest P	53.9±5.6	54.5±5.7	55.0±5.9	0.97	-1.6 (-6.7 to 3.9)	10.1 (7.9 to 14.1)	0.972
Leg P	201.1±15.5	203.4±15.8	209.7±16.6	0.99	1.0 (-1.1 to 3.2)	3.9 (3.0 to 5.4)	0.993
Lat P	52.5±3.6	52.3±3.6	52.6±3.7	0.99	-0.3 (-1.6 to 1.0)	2.4 (1.9 to 3.3)	0.996
Tri P	28.0±2.1	28.4±2.2	28.7±2.2	0.98	0.8 (-2.6 to 4.4)	6.5 (5.0 to 8.9)	0.976
Knee E	46.8±3.1	48.6±3.2	47.3±3.5	0.97	-3.7 (-6.7 to 0.7)	5.4 (4.2 to 7.6)	0.979
Seated R	53.0±3.8	52.4±3.8	52.7±4.0	0.99	-0.5 (-2.0 to 1.1)	2.8 (2.2 to 3.9)	0.995
Biceps C	19.4±1.7	19.6±1.7	19.3±1.7	0.97	-4.2 (-8.1 to -0.1)	7.7 (6.0 to 10.7)	0.978
Total	442.1±31.9	446.2±32.4	458.07±32.7	0.96	1.8 (-2.8 to 6.7)	8.7 (6.8 to 12.1)	0.958

Note: ICC intraclass correlation coefficients), TE (typical error), CV (coefficient of variation), Chest P (chest press), Leg P (leg press), Lat P (lateral pull-down), Tri P (triceps push down), Knee E (knee extension), Seated R (seated row), Biceps C (biceps curl), Total (total weight lifted). Data was analysed after log transformation.

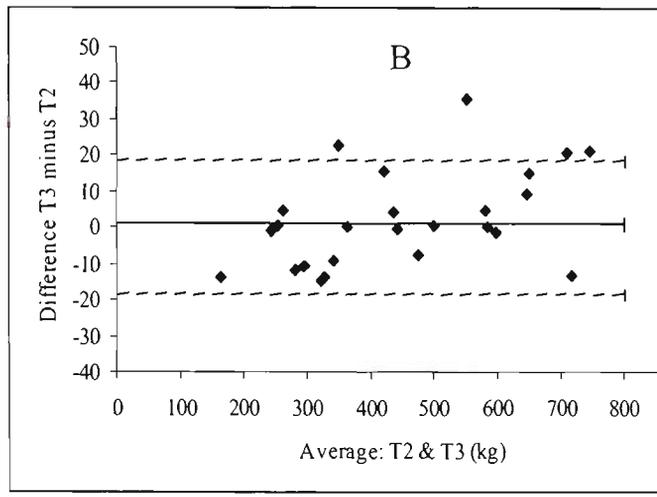
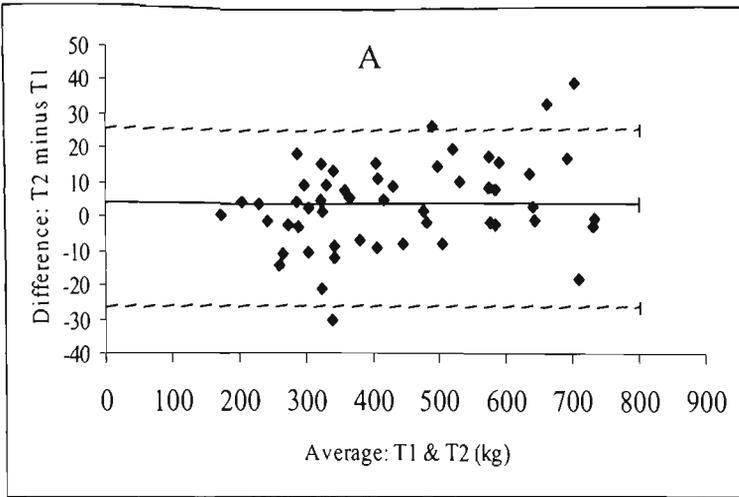


Figure 1. A. Bland-Altman plot for all 53 participants. B. A. Bland-Altman plot for 27 subgroup of participants that also were tests at T3. Solid line represents mean difference between 2 tests. Dashed lines represent Δ difference between 2 tests \pm 2SD. For both panels data point represents comparison for the total strength (sum of all seven exercises).

D. DISCUSSION

Accurate evaluations of muscle strength are important to prescribe safe and effective resistance training intensities and to evaluate the efficacy of training. The main finding of the current study is that the 1RM test, after one familiarisation session, using standard resistance training equipment, is a reliable and simple tool for assessing maximal strength for untrained middle-aged individuals across a wide array of resistance exercises.

To our knowledge, this study is the first to examine the reliability of the 1RM test in a wide range of isoinertial resistance exercises, compared to only one or two exercises in previous studies. The present study had a relatively large sample size ($n= 53$) compared to other studies that examined the reliability of the 1RM test [21,23,32]. The present study demonstrated high ICC across all exercises examined with inexperienced middle-aged individuals. A high ICC was observed both between T1 and T2 and T2 and T3. These results are similar to the reported test-retest reliability of the 1RM test for experienced resistance-trained young individuals. The ICC of 1RM testing is specific to the exercise and ranges between 0.64 and 0.99 for exercises such as leg press

[20,21,32], bench press [20,21,33], lateral pull-down [32] and leg extension [32]. However, it has been suggested that ICC may overestimate reliability, especially when the sample data are heterogeneous [27]. In this study we found high retest correlation ($r>0.9$) for middle-age individuals. Previously, Frontera et al [24] reported a retest correlation in the range of 0.7 to 0.8, using isokinetic dynamometer muscle strength testing in elderly individuals (mean age=60yr, range 45-78). It is important to note that the test protocol of Frontera et al [24] did not include a familiarisation session, and as such, it is possible that one familiarisation session (as used in the current study) improved the correlation (reliability) between the two tests.

Typical error (within subject variation) is an important measure of reliability in the field of exercise and sports science, and it reflects the change in scores between tests [26]. Hopkins (2000) recommended reporting of the typical error as coefficient of variation (TEcv) as it allows direct comparisons between different studies, and it is also less affected by different machines, analysers or diverse cohorts of participants. The lower the TEcv value, the higher the reliability (less variation) [34]. It is difficult to assess if the TEcv in this study indicates high, good or low reliability, as we found only one other study that reported this value for maximal strength testing [34]. Symons et al [34] examined the reliability of concentric, isometric and eccentric isokinetic knee extensor strength in older women. They reported that the TEcv ranged from 7 to 11% for the knee extensors. The authors concluded that the interpretation depends on the precision required but that this range was adequate for assessing muscle strength before training. In the current study, we found lower values between T1 and T2 (2.2 to 6.5%) and between T2 and T3 (2.4 to 10.1%), compared to Symons et al [34]. The difference in the TEcv range may be due to the lack of a familiarisation session in their protocol testing.

Changes in the mean (systematic bias) also indicates consistency between tests. It has been assumed that an increase in muscle strength between two tests can be the result of a learning effect and as such, several familiarisation trials may be necessary before applying an exercise training intervention [26]. In the current study, there were no significant changes in the maximal weight lifted from T1 to T2 for six of seven exercises. The only difference was observed in leg press exercise with the T2 being slightly higher than T1. However, this difference between leg press strength at T1 and T2 was small (representing a difference of only 1.9% or ~3 kg) compared to the expected change in strength following resistance training of least 15% [9]. Further

evidence suggesting that minimal or no learning effects took place in the present study may be seen for the participants that performed a third 1 RM test (T3). No significant improvement was observed for all exercises from T2 to T3 (see Table 3).

Our study also demonstrates that similar to healthy young individuals [32,33], one familiarisation session may be sufficient before assessing maximal strength in an untrained middle-aged population. Previously we have shown that one familiarisation session is adequate for assessing maximal strength (isokinetic dynamometer) in elderly clinical populations [25]. However, Ploutz-Snyder and Giamis [23] reported that older individuals should undergo between 8-9 sessions of 1RM testing (isokinetic dynamometer) in order to increase the consistency of the 1RM measurement. It is important to note, that the Ploutz-Snyder and Giamis [23] protocol included a 1RM test every 48 hours over 2-3 wks. This type of familiarisation protocol may actually induce a training effect due to neural [35], or even musculoskeletal adaptations. In addition repeated maximal strength testing over several days is likely to increase the risk of over-training [36], that could result in blunted adaptations once the training program finally begins. It is important to acknowledge, that in our study 1RM tests were performed on resistance machines that limit the movements to the desired direction. As such, it is possible that more complex movements with “free weights” may require more familiarisation sessions.

Similar to Ploutz-Snyder and Giamis [23], some 1RM test guidelines recommend using multiple familiarisation sessions before assessing maximal strength in order to avoid an improvement in muscle strength due to improved motor coordination or other neural adaptations [9]. This may be valid for investigators who wish to examine increases in muscle strength following resistance training due solely to muscle hypertrophy. However, to our knowledge, most trials with untrained or clinical populations use resistance training as a mode of clinical or therapeutic intervention [37]. As such, changes in motor coordination (i.e. inter-muscular co-ordination) and other neural adaptations should be considered as part of the benefits of the training [38,39]. In other words, if the aim of the study is to examine the early neural adaptations as a result of resistance training, then muscle strength should be assessed before chronic exposure to resistance exercise that occurs with long familiarisation processes.

Furthermore, in training studies with clinical populations, strength testing is usually not the only outcome measure with other physiological, biochemical, functional and

psychological parameters also being evaluated. Due to the complexity of these types of studies, a long familiarisation process may lead to an increase in the drop-out rates of participants, particularly those with low or marginal levels of motivation [40] who would benefit the most from clinical intervention studies.

E. PRACTICAL APPLICATIONS

The data from the current study suggest that the 1RM method is a reliable and simple method to evaluate maximal strength in wide array of resistance exercises in untrained middle-aged individuals. Little or no change was observed in the maximal weights lifted for six of seven exercises between T1, T2 and T3. As such, it appears that 1RM-testing protocols that include one familiarisation session and one testing session separated by 4 – 8 days are sufficient for assessing maximal strength in this untrained population.

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Appendix D

SF-36 questionnaire

Health Survey (SF36)

Today's Date: _____

Name: Last: _____ First: _____ Date of Birth: _____

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer these questions by "check-marking" your choice. Please select only one choice for each item.

1- In general, would you say your health is:

1. Excellent 2. Very good 3. Good 4. Fair 5. Poor

2- Compared to ONE YEAR AGO, how would you rate your health in general NOW?

1. MUCH BETTER than one year ago.
 2. Somewhat BETTER now than one year ago.
 3. About the SAME as one year ago.
 4. Somewhat WORSE now than one year ago.
 5. MUCH WORSE now than one year ago.

3- The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	1. Yes, Limited A Lot	2. Yes, Limited A Little	3. No, Not Limited At All
a) Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
b) Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
c) Lifting or carrying groceries?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
d) Climbing several flights of stairs?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
e) Climbing one flight of stairs?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
f) Bending, kneeling or stooping?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
g) Walking more than a mile ?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
h) Walking several blocks ?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
i) Walking one block?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all
j) Bathing or dressing yourself?	<input type="checkbox"/> 1. Yes, limited a lot	<input type="checkbox"/> 2. Yes, limited a little	<input type="checkbox"/> 3. No, not limited at all

4- During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities *as a result of your physical health*?

	Yes	No
a) Cut down on the amount of time you spent on work or other activities?	<input type="checkbox"/> 1. yes	<input type="checkbox"/> 2. No
b) Accomplished less than you would like?	<input type="checkbox"/> 1. yes	<input type="checkbox"/> 2. No
c) Were limited in the kind of work or other activities?	<input type="checkbox"/> 1. yes	<input type="checkbox"/> 2. No
d) Had difficulty performing the work or other activities (for example it took extra effort)?	<input type="checkbox"/> 1. yes	<input type="checkbox"/> 2. No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the amount of time you spent on work or other activities?	<input type="checkbox"/> 1. yes	<input type="checkbox"/> 2. No
b) Accomplished less than you would like?	<input type="checkbox"/> 1. yes	<input type="checkbox"/> 2. No
c) Didn't do work or other activities as carefully as usual?	<input type="checkbox"/> 1. yes	<input type="checkbox"/> 2. No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1. Not at all 2. Slightly 3. Moderately 4. Quite a bit 5. Extremely

7. How much **bodily pain** have you had during the **past 4 weeks**?

1. None 2. Very mild 3. Mild 4. Moderate 5. Severe 6. Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

1. Not at all 2. A little bit 3. Moderately 4. Quite a bit 5. Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week ...**

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
b) Have you been a very nervous person?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
c) Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
d) Have you felt calm and peaceful?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
e) Did you have a lot of energy?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
f) Have you felt downhearted and blue?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
g) Do you feel worn out?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
h) Have you been a happy person?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time
i) Did you feel tired?	<input type="checkbox"/> 1. All of the time	<input type="checkbox"/> 2. Most of the time	<input type="checkbox"/> 3. A good bit of the time	<input type="checkbox"/> 4. Some of the time	<input type="checkbox"/> 5. A little of the time	<input type="checkbox"/> 6. None of the time

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1. All of the time
- 2. Most of the time.
- 3. Some of the time
- 4. A little of the time.
- 5. None of the time.

11. How TRUE or FALSE is each of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?	<input type="checkbox"/> 1. Definitely true	<input type="checkbox"/> 2. Mostly true	<input type="checkbox"/> 3. Don't know	<input type="checkbox"/> 4. Mostly false	<input type="checkbox"/> 5. Definitely false
b) I am as healthy as anybody I know?	<input type="checkbox"/> 1. Definitely true	<input type="checkbox"/> 2. Mostly true	<input type="checkbox"/> 3. Don't know	<input type="checkbox"/> 4. Mostly false	<input type="checkbox"/> 5. Definitely false
c) I expect my health to get worse?	<input type="checkbox"/> 1. Definitely true	<input type="checkbox"/> 2. Mostly true	<input type="checkbox"/> 3. Don't know	<input type="checkbox"/> 4. Mostly false	<input type="checkbox"/> 5. Definitely false
d) My health is excellent?	<input type="checkbox"/> 1. Definitely true	<input type="checkbox"/> 2. Mostly true	<input type="checkbox"/> 3. Don't know	<input type="checkbox"/> 4. Mostly false	<input type="checkbox"/> 5. Definitely false

Thank you! 