

https://dspace.org/

Evaluation of exercise based intervention programs for metabolic syndrome

Torres, Georgia

2014-09-09
http://hdl.handle.net/10539/15459

Downloaded from a DSpace repository. https://dspace.org/

EVALUATION OF EXERCIS BASED INTERVENTION PROGRAMS FOR METABOLIC SYNDROME

Georgia Torres

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment for the degree of Doctor of Philosophy.

Gauteng, 2014

I, Georgia Torres declare that this research report is my own work, except to the extent indicated in the “Acknowledgements”. It is being submitted for the degree of Doctor of Philosophy, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

The 28th day of March, 2014

DEDICATION

This thesis is dedicated to my Lord and Saviour, Jesus and to my loving family: Luiz, Miguel and Ricardo.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Conference Oral Presentations:

Reproducibility and levels of blood lactate transition thresholds in persons with metabolic syndrome. South African Sports Medicine Association Conference, 2008, Cape-Town, SA

Conference Poster Presentations:

Reproducibility and levels of blood lactate transition thresholds in persons with metabolic syndrome. American College of Sports Medicine World Congress, 2013, Indianapolis, USA.

Papers accepted for publication:

Torres G. Crowther N. Rogers G. Reproducibility and levels of blood lactate transition thresholds in persons with metabolic syndrome. Metabolic Syndrome and Related Disorders. April 2013, 11(2):121-127.

The paper that has been published constitutes Chapter 2 of this Thesis. A version of the paper as it appears in the journal is in the Appendix D.

ABSTRACT

Background

The optimal exercise load/intensity for exercise programs for individuals with metabolic syndrome (MetS) has not been investigated. One method of determining optimal exercise load is to measure the blood lactate transition threshold (BLTT), referred to as the anaerobic threshold (AT). The first part of this thesis (study 1) investigated the reproducibility of BLTT testing and the consequent determination of AT via the Mader method (Mader et al. 1986) and a modified form of the ADAPT method (Cheng et al. 1992) in patients with MetS. Furthermore, a comparison of the reproducibility of the AT determination using the Mader et al. (1986) method as opposed to the ADAPT method has not been investigated in MetS patients.

The effect of specific exercise protocols on the different components of MetS has also not been investigated. Therefore, the second study in the thesis compared the effects on the components of the MetS of an exercise program that uses BLTT (specifically, the AT) to those of a comparable exercise program (not using AT) taken from the literature. The main aim of the study was to design an exercise program that optimized exercise responses and may thus improve metabolic characteristics in individuals with MetS.

The third part of the thesis (study 3) focused on the relationship between cardio-respiratory fitness and the components of the metabolic syndrome. This study developed multiple regression models to find the principal variables that associated with peak

oxygen consumption (VO_2 peak) and AT in persons with MetS. Regression models were also developed to investigate whether these variables were associated with the individual metabolic and cardiovascular components of the metabolic syndrome.

Methods

In study 1, fifteen male patients diagnosed with MetS (age: 43.5 ± 7.52 years) and fifteen healthy, male participants (age: 44.1 ± 6.08 years) each performed a peak oxygen consumption and BLTT test simultaneously using an incremental protocol to exhaustion on a treadmill, at the same daily times, on three different days.

Study 2 used three subject groups. One group consisted of ten participants (male, age: 48.3 ± 7.32 years) with MetS that exercised using the walking program of Leon et al. (1979) (MetSL). A second group consisted of ten participants (male, age: 40.8 ± 8.21 years) with MetS that exercised using velocity at AT to set training intensities (MetSV). A third group consisted of ten participants (male, age: 40.2 ± 7.90 years) without MetS that exercised using velocity at AT to set training intensities (Non-MetSV). Training durations and frequency varied from 20 – 90 minutes and 3 -5 days per week respectively. Height, body mass, waist circumference, blood pressure, fasting plasma triglyceride, total cholesterol, HDL-, LDL- cholesterol, insulin levels, VO_2 peak and BLTT were measured in all groups before, during and after twenty weeks of exercise. In addition, oral glucose tolerance tests (OGTT) were administered to all participants. 0 min, 30 min and 2 hours plasma glucose and insulin levels were measured during the OGTT. HOMA-IR and insulinogenic indices were also calculated. Nutritional data were recorded at week 0, 8 and 20 of training.

In study 3, thirty-one males diagnosed with MetS and twenty-four healthy male participants each performed a VO_2 peak and a BLTT test. Height, mass, waist circumference, blood pressure, fasting plasma triglyceride, total cholesterol, HDL-cholesterol and insulin levels were also measured. In addition, oral glucose tolerance tests (OGTT) were administered to all participants and HOMA indices were calculated.

Results

There was no significant difference in treadmill velocity at AT determined by the Mader method or the Modified ADAPT method within both groups of study 1 ($p > 0.05$). The mean treadmill velocity at AT was higher in the healthy compared to the MetS group using both the Mader and the ADAPT method. Regression analysis and ANCOVA in study 1 demonstrated that this difference was largely due to a higher VO_2 peak in the healthy group. The study also found an association between VO_2 peak and waist circumference. The coefficient of variation of repeat measurements for both the Mader method and the Adapt method was less than 4% indicating good reproducibility. This was confirmed by the typical error method of Hopkins (2000).

Study 2 showed that body mass, BMI and waist circumference decreased significantly in all training groups with the training program using AT and the program not using AT showing similar outcomes in these variables among persons with MetS. Velocity at AT also improved in all training groups. While VO_2 peak increased ($p < 0.05$) in both the MetS groups, it did not change significantly in the group without MetS. Similarly, the blood pressure response was favourable in the groups with MetS yet absent in the group

without MetS. The training group with MetS that used AT was the only group to show significant, positive changes in any of the metabolic parameters (fasting insulin and HOMA). This group also showed the greatest change in the incidence of MetS.

In study 3, presence of MetS, waist circumference and AT were found to associate with VO_2 peak and VO_2 peak was strongly correlated with AT. Age and body mass were found to correlate with fasting glucose, whilst only age correlated with HDL-cholesterol. Age and VO_2 peak both correlated with systolic blood pressure but only VO_2 peak had a significant association with diastolic blood pressure.

Conclusions

Study 1 demonstrated that BLTT tests are reproducible in persons with MetS. Study 2 demonstrated that an endurance exercise program using AT to set intensity is effective in eliciting favourable responses in individuals diagnosed with MetS. In addition, the training program using AT elicited the responses with a reduced exercise frequency and intensity. It also improved insulin sensitivity which was not affected by the walking program. The response to the exercise program that used AT was similar in persons with MetS and in persons without MetS, except in the central cardio-vascular adaptations of VO_2 peak and in the metabolic parameters of fasting insulin and the HOMA index. Study 3 found that the lower VO_2 peak of participants with MetS is associated with their higher waist circumference. The VO_2 peak, in turn, was shown to correlate with anaerobic threshold. Therefore, reducing waist circumference in persons with MetS needs to be a focus of intervention programs for such a group. This study also found that both diastolic and systolic blood pressures were associated with cardio-respiratory fitness (VO_2 peak).

This further supports the benefit of increasing cardio-respiratory fitness in persons with MetS.

The results of these studies showed that BLTT tests are simple, low-cost, reproducible ways of setting exercise intensity for persons with MetS that can be incorporated in the routine cardio-respiratory fitness assessment of an individual. Furthermore, the determination of AT from such tests can be used to design an individualized exercise program that can “reverse” the effects of MetS.

ACKNOWLEDGEMENTS

1) Thank you to my supervisors, Prof Rogers and Prof Crowther. Your inputs and support made this possible.

2) Thank you to the SA Sugar Association. The thesis would have not been possible without their financial support

3) Thank you to Penta Medical Systems for allowing me to use their VO_2 testing apparatus (the Cortex, Metalyzer 3b, CPX on-line system) and the Technogym Wellness Facility for training. Thank you Tony and Kevin Payne for all your support.

4) Thank you to Lancet Pathology Laboratories for their financial support with respect to the blood tests. All blood tests were executed by the pathology laboratory.

5) Thank you Mom, for all your assistance with my family while I was busy with the thesis.

TABLE OF CONTENTS **Page number**

Declaration ii
Dedication iii
Publications and presentations arising from thesis iv
Abstract v
Acknowledgements x
Table of contents xi
List of figures xv
List of tables xvi
Abbreviations xix

Chapter 1. Introduction 1
1. Literature review 6
1.1 Association of metabolic syndrome (MetS) to diabetes and cardiovascular disease 6
1.2 The pathophysiology of metabolic syndrome 7
1.3 Blood lactate transition threshold (BLTT) testing 13
1.4 The effects of endurance training on BLTT 26
1.5 BLTT and prescription of exercise 29
1.6 Exercise intervention programs for the reduction of progressive disease risk factors and effects on components of MetS 35
1.7 Exercise intervention programs for persons with MetS 42
1.8 Conclusions 51
1.9 References 52

Chapter 2. Reproducibility and levels of blood lactate transition thresholds in persons with metabolic syndrome 75

2.1 Abstract 75
2.2 Introduction 76
2.3 Methods 78
2.3.1 Participants and definition of MetS 78
2.3.2 Measurements 78
2.3.3 Blood lactate transition threshold test 79
2.3.4 Determination of the BLTT 80
2.4 Statistical analysis 82
2.5 Results 83
2.5.1 Participants 83
2.5.2 Comparison of the Mader and modified ADAPT method 85
2.5.3 Determinants of VO_2 peak and the AT 87
2.6 Discussion 88
2.7 Conclusions 93
2.8 References 94

Chapter 3. Effects of exercise intervention programs on physical physiological and biochemical parameters of persons with and without metabolic syndrome 98
3.1 Abstract 98
3.2 Introduction 99
3.3 Methods 101
3.3.1 Participants and groups 101
3.3.2 Measurements 102
3.3.3 Training programs 103
3.3.4 Medication and Nutrition 106
3.4 Statistical analysis 107
3.5 Results 109
3.5.1 Participants 109
3.5.2 Intra-group comparisons 110
3.5.3 Absolute changes in body mass 116

3.5.4 Inter-group comparison of the % change in variables from week 0 to week 12 116
3.5.5 Inter-group comparison of the % change in variables from week 0 to week 20 118
3.5.6 Determinants of the % change in VO_2 peak and velocity at AT 122
3.5.7 Exercise energy expenditure 123
3.5.8 Nutritional intake 124
3.5.9 Incidence of metabolic syndrome 124
3.6 Discussion 126
3.7 Conclusions 137
3.8 References 138

Chapter 4. Factors that influence VO_2 peak, blood lactate transition threshold and the components of metabolic syndrome 145
4.1 Abstract 145
4.2 Introduction 146
4.3 Methods 147
4.3.1 Participants and definition of MetS 147
4.3.2 Measurements 148
4.3.3 The blood lactate transition threshold test 149
4.3.4 Determination of anaerobic threshold 150
4.4 Statistical analysis 150
4.5 Results 152
4.5.1 Participants 152
4.5.2 Univariate correlation and multiple regression analysis for VO_2 peak and AT 155
4.5.3 Univariate correlation and multiple regression analyses for components of MetS and HOMA 158
4.6 Discussion 163
4.7 Conclusions 170
4.8 References 170

Chapter 5 Conclusion 175
5.1 Conclusions 175
5.2 Limitations of the thesis 177
5.3 Future research 179

Appendix
A: Standardized nutrition programme 181
B: Willett food frequency questionnaire 186
C: 24 hour eating record 191
D: Copy of the paper that was published 192

LIST OF FIGURES **Page Number**

Fig 1 The modified ADAPT method. 82

Fig 2 Bland Altman comparison between the Mader method and the modified ADAPT technique. 86

Fig 3 Change in components of metabolic syndrome and incidence of metabolic syndrome in the MetSV group. 124

Fig 4 Change in components of metabolic syndrome and incidence of metabolic syndrome in the MetSL group. 125

LIST OF TABLES **Page Number**

Table 1 Particulars of studies investigating exercise effects on Metabolic Syndrome. 43

Table 2 Mean ± SD levels of the physical characteristics of study participants. 84

Table 3 Mean ± SD and coefficient of variation for velocity at anaerobic threshold. 85

Table 4 Results of backward, stepwise multiple regression analyses for isolating principle determinants of VO_2 Peak and AT. 88

Table 5 Protocol of the 20 week treadmill walking program. 104

Table 6 The training program for groups using AT to set intensity. 105

Table 7 Physical and biochemical characteristics of study participants. 110

Table 8 Changes in physical and physiological parameters at weeks 4, 8, 12, 16 and 20 for Non-MetSV group. 111

Table 9 Changes in metabolic parameters at weeks 12 and 20 for Non-MetSV group. 112

Table 10 Changes in physical and physiological parameters at weeks 4, 8, 12, 16 and 20 for MetSV group. 113

Table 11 Changes in metabolic parameters at weeks 12 and 20 for the MetSV group. 114

Table 12 Changes in physical and physiological parameters at weeks 4, 8, 12, 16 and 20 for MetSL group. 115

Table 13 Changes in metabolic parameters at weeks 12 and 20 for the MetSL group. 115

Table 14 Absolute changes in body mass. 116

Table 15 ANOVA and ANCOVA results for comparison of % change in data from week 0 to week 12 across the 3 subject groups. 117

Table 16 Comparison of week 0 vs week 12 % change data across the 3 subject groups. 118

Table 17 ANOVA and ANCOVA results for comparison of % change in data from week 0 to week 20 across the 3 subject groups. 120

Table 18 Comparison of week 0 vs week 20 % change data across the 3 subject groups. 121

Table 19 Determinants of the % change in VO_2 peak and velocity at AT. 122

Table 20 Weekly exercise energy expenditure over 12 weeks. 123

Table 21 Energy expenditure per kilogram mass-loss over 12 weeks. 123

Table 22 Nutritional intake for all groups during the training period. 124

Table 23 Physical and biochemical characteristics of study participants. 152

Table 24 ANOVA and ANCOVA results for comparison of data between the MetS and Non-MetS groups. 153

Table 25 Univariate correlations between VO_2 peak and selected variables. 155

Table 26 Univariate correlations between AT and selected variables. 156

Table 27 Results of backward, stepwise multiple regression analyses for isolating principle determinants of VO_2 peak and AT. 157

Table 28 Univariate correlations between fasting blood glucose levels and selected variables. 158

Table 29 Univariate correlations between HDL-cholesterol and selected variables. 159

Table 30 Univariate correlations between plasma triglycerides and selected variables. 160

Table 31 Univariate correlations between systolic and and diastolic blood pressures and selected variables. 161

Table 32 Univariate correlations between HOMA and selected variables 162

Table 33 Results of backward stepwise multiple regression analyses for isolating principle determinants of components of MetS and HOMA 163

ABBREVIATIONS

ACSM- American college of sports medicine

ADAPT – Automatic data analysis for progressive tests

AE - Aerobic exercise

AIT – Aerobic interval training

ANCOVA – Analysis of covariance

ANOVA – Analysis of variance

AT- Anaerobic threshold

BLTT – Blood lactate transition threshold

BMI – Body mass index

CT – Circuit training

CVD – Cardiovascular disease

D - Diet

DHSSPS – Department of health, social sciences and public safety

ECG – Electro-cardiogram

EX – Exercise

EX + D – Exercise + diet

FFA – Free fatty acids

GC - Glucocorticoids

HDL – High density lipoproteins

HOMA – Homeostatic model assessment

HOMA-IR – Insulin resistance index as determined by HOMA

HRR – Heart rate reserve

IAT – Individual anaerobic threshold

IDF – International diabetes federation

IL-6 – Interleukin-6

LDL – Low density lipoproteins

LT – Lactate threshold

MetS – Metabolic syndrome

MetSL – Group with metabolic syndrome exercising using the Leon et al. (1979) program

MetSV - Group with metabolic syndrome exercising using the AT

MHR – Maximal heart rate

MLSS – Maximal lactate steady state

NCEP – The national cholesterol education program

Non-MetSV - Group without metabolic syndrome exercising using the AT

OBLA – Onset of blood lactate accumulation

OGTT – Oral glucose tolerance test

PAI-1 – Plasminogen activator inhibitor 1

SBP – Systolic blood pressure

ST – Resistance / strength training

STRRIDE – Studies of targeted risk reduction interventions through defined exercise

T2D – Type 2 Diabetes

TEM – Technical error of measurement

TNF_{α} – Tumor necrosis factor alpha

VIF – Variance inflation factors

VLDL – Very low density lipoproteins

VO_2 – Oxygen consumption

VO_2 max – Maximal oxygen consumption

VO_2 peak – Peak oxygen consumption

W – Walking

BM - Body mass - loss program

yrs - Years

CHAPTER 1

INTRODUCTION AND AIMS

Metabolic syndrome (MetS) or Syndrome X is a complex of interrelated risk factors for cardiovascular disease (CVD) and diabetes. The National Cholesterol Education Program (NCEP) Expert Panel in 2002 (NCEP, ATP III, 2002) defined it as a cluster of three or more of the following:

a) fasting plasma glucose concentration $\geq$ 6.1 mmol.L^{-1};

b) serum triglyceride concentration $\geq$ 1.69 mmol.L^{-1};

c) serum high-density lipoprotein (HDL) cholesterol concentration lower than 1.04 mmol.L^{-1};

d) blood pressure $\geq$ 130/85 mmHg or controlled with medication

e) waist circumference of more than 88 cm in women and 102 cm in men.

In April 2005, the International Diabetes Federation (IDF) introduced an alternative definition (Alberti et al. 2005) which stated that patients must have central obesity (defined as waist circumference $\geq$ 94 cm for Europid men and $\geq$ 80 cm for Europid women , >90 cm for Asian men and >80cm for Asian women); with any two of the following:

a) serum triglyceride concentration $\geq$ 1.7 mmol.L^{-1}

b) high-density lipoprotein (HDL) concentration < 1.03 mmol.L^{-1} for men, and < 1.29 mmol.L^{-1} for women

c) blood pressure: $\geq$ 130/85 mmHg

d) previously diagnosed Type 2 diabetes or a raised fasting plasma glucose concentration $\geq$ 5.6 mmol.L^{-1}

Recently an attempt was made to resolve the differences between definitions of MetS. It was agreed that abdominal obesity (waist circumference) should not be a prerequisite for diagnosis but that it is one of the five criteria. When an individual has any three of the five risk factors, a diagnosis of MetS can be made (Alberti et al. 2009). This definition agrees with the NCEP ATP III (2002) definition stated above. According to the American College of Sports Medicine (ACSM) guidelines, the NCEP ATP III definition is the most commonly used for diagnosis (ACSM, 2013).

Physical activity has been identified as a therapeutic goal and is recommended for the management of MetS (Carroll et al. 2004; Eckel, 2005; Hafidh et al. 2005; Liberopoulos et al. 2005; Stone et al. 2005). Currently exercise guidelines for MetS are the same as those for obesity with consideration given to the presence of any CVD risk factors (ACSM, 2013). Yet, MetS is a multi-faceted disease and the effect of specific exercise protocols on the different components of MetS has not been investigated. Therefore, the main aim of this PhD study was to design an exercise program to optimize exercise responses and improve metabolic characteristics in individuals with metabolic syndrome.

The blood lactate transition threshold (BLTT) referred to as the anaerobic threshold (AT), was used to optimize the exercise response. The AT was used since it is a point of optimal exercise overload. Overload is a critical principle of physical training in exercise.

In order to determine this point, the AT needs to be measured. Therefore, the first part of this PhD (Study 1) aimed to investigate the reproducibility of blood lactate testing and the determination of AT via the Mader (Mader et al. 1986) and ADAPT (Cheng et al. 1992) methods in patients with MetS. Furthermore, since the BLTTs of patients with MetS have not been described by previous studies, Study 1 also aimed to describe the BLTT of such patients.

The hypotheses tested in Study 1 were:

a) Blood lactate transition thresholds are reproducible in patients with Met S.

b) The ADAPT method of determining blood lactate transition thresholds is comparable to the Mader (4 $mmol.L^{-1}$) method of determining blood lactate transition thresholds.

The second part of the PhD (Study 2) compared how individuals with MetS respond to two different exercise programs. One exercise program has been validated in a previous study (Leon et al. 1979) using obese participants and does not use AT to set exercise intensity. The other exercise program used AT to set exercise intensity. The Leon et al. (1979) study was chosen since obesity is a component of MetS and the study showed improved metabolic profiles at high exercise volumes. The exercise program using AT

uses a moderate exercise volume. The intention of using AT was to individualize the exercise program and optimize the improvements in metabolic characteristics at lower exercise volumes. In addition, previous studies had not investigated the metabolic improvements that could result by training at AT. The aim of Study 2 was to show that patients will achieve greater responsiveness in their MetS profile (i.e. improve the "cluster" of MetS risk factors) when exercise intensity is set using velocity at AT.

The third part of the thesis focused on the relationship between cardio-respiratory fitness and the components of the metabolic syndrome. The role of cardio-respiratory fitness in the attenuation of MetS has been noted in the literature (Carroll et al. 2004; Katzmarzyk et al. 2003; Katzmarzyk et al. 2004). However, the determinants of cardio-respiratory fitness measurements such as VO_2 peak and anaerobic threshold (AT) have not been identified in persons with MetS. This study developed multiple regression models to find variables that correlate with VO_2 peak and AT, in persons with MetS. Regression models were also developed to investigate whether cardio-respiratory fitness measurements were associated with the individual metabolic and cardiovascular components of the metabolic syndrome. The hypothesis tested in study 3 was that cardio-respiratory fitness measurements are correlated to the individual components of MetS and thus physical activity may be the mechanism for reversing the syndrome.

The aims of this thesis can therefore be summarised as:
(a) to assess the reproducibility and levels of blood lactate transition thresholds in persons with MetS.

(b) to assess the effectiveness of an exercise program using BLTT in persons with MetS.

(c) to find the variables that correlate with cardio-respiratory fitness in persons with MetS and investigate the association of components of the MetS with cardio-respiratory fitness measurements.

LITERATURE REVIEW

1.1 Association of Metabolic Syndrome with Diabetes and Cardiovascular Disease

MetS has been identified as a major health challenge of the 21st century (Alberti et al. 2009; Chan et al. 2005; Wilson et al. 2003) and is currently used extensively as a significant predictor of CVD and type 2 diabetes mellitus (Carroll et al. 2004; Chan et al. 2005; Eckel et al. 2005; Malik et al. 2004; Meigs 2004; Reaven, 1995; Wannamethee et al. 2005; Wilson et al. 2003).

Nesto (2005) cites the Kuopio study which found the risk of cardiovascular death with MetS to be 10% at 10 years after the diagnosis of MetS and correspondingly the risk of nonfatal MI, stroke, or all-cause death was 18%. Ninomiya et al. (2004) also reported an association between metabolic syndrome and myocardial infarction and stroke. Meigs (2002), showed that individuals exhibiting metabolic clustering related to insulin resistance have a 4 - 11 fold increased relative risk for type 2 diabetes and a 2 – 4 fold increased risk of cardiac mortality compared with individuals without this syndrome. In addition, Girman et al. (2004) showed that patients with metabolic syndrome had increased risk of CVS events regardless of Framingham risk category.

In contrast, data from the San Antonio Heart Study showed that the MetS was inferior to established prediction models for prediction of either type 2 diabetes or cardiovascular disease (Stern et al. 2004). The American Diabetes Association have also identified eight major concerns regarding the clinical value of the diagnosis of MetS (Kahn et al. 2005).

Furthermore, Sattar et al. (2008) showed that fasting plasma glucose is as good as a diagnosis of MetS for predicting diabetes. Their analysis also showed that a diagnosis of the MetS has negligible association with risk of cardiovascular disease. However, Kahn (2008) comments that the syndrome's greatest strength is that its identification will improve patients' outcomes. Also, that people with MetS are at an increased risk of cardiovascular disease does not mean that the construct is useful for risk prediction. Kahn (2008) concludes that more research is needed to understand risk factor clustering and the pathogenesis of insulin resistance rather than seeking a diagnosis of the metabolic syndrome.

1.2 The Pathophysiology of Metabolic Syndrome

Researchers have acknowledged insulin resistance as the central component of MetS (De Fronzo et al. 1991; Eckel, 2005; Nesto, 2005). In this regard, Eckel (2005) have proposed the following model for the pathophysiology of MetS: free fatty acids (FFA) are released from an enlarged adipose tissue mass. In the liver, these FFAs cause hepatic insulin resistance that in turn causes an increased production of glucose, triglycerides and secretion of very low density lipoproteins (VLDL). Associated abnormalities include reductions in HDL cholesterol and an increased density of low density lipoproteins (LDL). In muscle, FFAs also reduce insulin sensitivity by inhibiting insulin-mediated glucose uptake (Eckel, 2005). Associated problems with this include a reduction in glucose partitioning to glycogen and increased lipid accumulation as triglyceride. Increases in circulating glucose and to some extent FFA increase pancreatic insulin secretion resulting in hyperinsulinaemia. Hyperinsulinaemia may result in increased

sodium reabsorption and increased sympathetic nervous system activity (Eckel, 2005). This may contribute to the hypertension, as might increased levels of circulating FFAs.

In addition, contributory to the insulin resistance produced by excessive FFAs is the paracrine and endocrine effect of the proinflammatory state. A variety of adipose tissue cells (eg. adipocytes and monocyte-derived macrophages) increase secretion of interleukin-6 (IL -6) and tumor necrosis factor alpha (TNF-α) (and others), which result in increased insulin resistance and lipolysis of triglyceride stores to circulating FFAs. The increased circulating IL-6 and other cytokines enhance hepatic glucose and VLDL production and insulin resistance in muscle (Eckel, 2005). Cytokines and FFAs also increase the production of hepatic fibrinogen and plasminogen activator inhibitor-1 (PAI-1) that complements the overproduction of PAI-1 by adipose tissue. Furthermore, the production of the insulin - sensitizing and anti-inflammatory cytokine, adiponectin, is reduced. Finally, IL-6 has also been shown to promote synthesis of C-reactive protein (CRP) (Reaven, 2005) and high CRP levels have been associated with a state of chronic inflammation (Alberti et al. 1998). All the above-mentioned factors contribute to the pro-thrombotic/ inflammatory state associated with MetS.

The pathogenesis of insulin resistance as a linking factor for MetS though remains unclear (Alberti et al. 2005; Eckel, 2005). An alternative concept has been suggested by Unger (2003) citing leptin resistance as the linking factor. Recently though Peterson et al. (2007) investigated the hypothesis that insulin resistance in skeletal muscle promotes the development of artherogenic dyslipidemia associated with MetS, by changing post-

prandial energy storage. These researchers showed that insulin resistance in skeletal muscle promotes dyslipidemia by changing the pattern of the metabolism of ingested carbohydrates away from skeletal muscle glycogen synthesis toward hepatic lipogenesis which results in an increase in plasma triglyceride levels and a decrease in plasma high-density lipoproteins levels. This study also showed that insulin resistance was independent of changes in plasma TNF-α; IL-6 (and other plasma adipocytokine) levels or intra-abdominal obesity, suggesting that these factors are not influential in the development of insulin resistance during the early stages of MetS. The researchers suggested that abdominal obesity and non-alcoholic fatty liver disease appears later in the course of MetS and is more likely a consequence of skeletal muscle insulin resistance rather than a primary cause of insulin resistance and dyslipidemia.

Although it has been suggested that insulin resistance is the central etiological factor for the MetS, epidemiological data do not support the idea that this can account for all of the cluster abnormalities. Studies have suggested that hyperleptinemia (leptin resistance) rather than hyperinsulinemia may play a central role in the genesis of the risk factor cluster that constitutes MetS (Zimmet et al. 1999). Hyperleptinaemia and leptin resistance may contribute to hypertension, impaired glucose metabolism, and pro-atherogenic state in MetS (Marcelo et al. 2006). Furthermore, leptin-resistance has been associated with elevated neuropeptide Y levels (Marcelo et al. 2006) and elevated neuropeptide Y levels have been shown to lead to obesity and the MetS (Kuo et al. 2008).

Furthermore, glucocorticoid (GC) excess has also been associated with the MetS (Wang, 2005). A good correlation was observed between total urinary GC metabolites and the number of features of the MetS in an elderly cohort of patients (Andrew et al. 2002). Additional studies have also suggested correlation of increased GC activity with insulin resistance, hyperglycemia and hypertension (Filipovsky et al. 1996; Walker et al. 1998). The following have been cited as mechanisms for the metabolic effects of glucocorticoids on features of MetS:

- In the liver, GCs increase the activities of enzymes involved in fatty acid synthesis and promote the secretion of lipoproteins (Diamant et al. 1975; Itoh et al. 1977). Liver fat also appears to be involved in the negative regulation of hepatic insulin sensitivity (Samuel et al. 2004) and is associated with certain features of the MetS (Seppala-Lindrood et al. 2002). Therefore, liver fat accumulation promoted by GCs is likely to contribute to the pathophysiology of the MetS.
- GCs also induce the hepatic gluconeogenic pathway via the activation of the rate-limiting enzymes in gluconeogenesis, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (Friedman et al. 1993), which results in increased hepatic glucose output and hyperglycemia.
- In adipose tissue, GCs promote the differentiation of pre-adipocytes to adipocytes, which leads to increased body fat mass (Hauner et al. 1989). Furthermore, once differentiated, the adipocytes develop insulin resistance in the presence of GCs (Olefsky, 1975).

- GCs may also induce insulin resistance in skeletal muscle (Dimitriadis et al. 1997).
- In addition, GCs reduce GLUT4 translocation in adipose and skeletal muscle tissue that contribute to peripheral insulin resistance (Wang, 2005).
- Furthermore, GCs are agonists of the mineralocorticoid receptor (MR), which upon activation may lead to renal salt retention and elevated blood pressure (Lloyd-MacGlip et al. 1999).

Tooke (1998) has suggested that vascular changes occur prior to the emergence of Type 2 diabetes and act to increase vascular resistance at the arteriolar level. All of the individual components of the MetS appear to have an adverse effect on the endothelium and its capacity to vasodilate or may be caused by endothelial dysfunction. Endothelial dysfunction is manifested by impaired vasodilatation in response to stimulators of endothelium-derived nitric oxide synthesis. Evidence that insulin's vasodilating effect is mediated by nitric oxide (Steinberg et al. 1994) has led to research suggesting that insulin resistance may be caused by inadequate blood flow to skeletal muscle and resulting diminished glucose extraction.

Endothelin-1 (ET-1), a potent vasoconstrictor peptide, may also contribute to endothelial dysfunction through its inhibitory effects on nitric oxide (NO) production (Kalani, 2008). Furthermore, ET-1 reduces insulin sensitivity and may take part in the development of the metabolic syndrome (Kalani, 2008).

Evidence also exists to support a genetic basis of the syndrome including single gene defects in lamin A/C, 1-acylglycerol-3-phosphate, O-acyltransferase, and seipen (Hegele, 2003). Genome-wide scan analysis has shown strong signals linked to all traits of MetS on chromosomes 1, 2 and 16, also suggesting possible harbouring of major genes for this syndrome (Chan et al. 2005). In addition, these researchers proposed that a central neuro-hormonal dysregulation is characterised by activation of stress–related hormones such as cortisol and catecholamines and an age-associated decline in sex hormones and growth hormone. These changes might lead to increased deposition of visceral adiposity associated with insulin resistance and MetS.

MetS can also be accompanied by other alterations not included in the diagnostic criteria. These include increases in apolipoprotein B and Apolipoprotein C-111, uric acid, prothrombotic factors, serum viscosity, homocysteine, white blood cell count; the presence of microalbuminuria, non-alcoholic fatty liver disease, obstructive sleep apnoea and polycystic ovarian disease (Eckel, 2005).

It can therefore be seen that the aetiology of MetS is still not fully understood and is an area of intensive research. Furthermore, MetS is related to other areas of metabolic dysfunction other than those used in its diagnosis. It is possible that future research will lead to the extension of the criteria for MetS diagnosis to these other metabolic variables.

The National Cholesterol Education Program have suggested increased physical activity as the basis of therapy for MetS (NCEP, 2002). Yet protocols for an effective training program for this syndrome have not been devised. Furthermore, MetS is a multi-faceted disease and the effect of specific exercise protocols on the different components of MetS have also not been investigated. Study 2 of this thesis investigated an exercise program that uses blood lactate transition thresholds (BLTT, specifically the anaerobic threshold (AT)) to optimize exercise responses and thus improve metabolic characteristics in individuals with MetS. The review will thus now focus on research involving BLTT testing and then the use of BLTT in the design of training programs.

1.3 Blood Lactate Transition Threshold Testing

Measurement of BLTTs in conjunction with heart rate, oxygen consumption (VO_2), and workload have been used in athletes:

a) as more sensitive indicators of training adaptations (Denis et al. 1982; Edwards et al. 2003; Gollnick et al. 1986; Karlsson et al. 1982; Kohrt et al. 1989; Sjodin et al. 1982; Tanaka et al. 1986).

b) as better indicators of endurance performance (Bishop et al. 1998; Coyle et al. 1991; Farrell et al. 1979; Faude et al. 2009; Heck et al. 1985; Karlsson et al. 1982; Sjodin et al. 1982; Sjodin et al. 1985; Tanaka et al. 1983; Weltman et al. 1987; Weltman 1995; Yoshida et al. 1987); and of prolonged, high intensity, intermittent running performance in team sports (Sirotic et al. 2007). There is also evidence to suggest that any point used consistently in the lactate curve during exercise can be used as an index of performance (Tokmakidis et al. 1998).

c) as best indices for setting the exercise intensities of training programs (Coen et al. 1991; Sjodin et al. 1982; Stegmann et al. 1982; Weltman et al. 1992; Weltman 1995; Yoshida et al. 1982).

The AT has been used in prescribing exercise intensity among healthy, non-athletes (Weltman et al. 1992) and among adults with cardiac disease (Coyle et al. 1983). Blood lactate measurement, integrated with the objectives above, has not been investigated and applied to exercise programming for MetS.

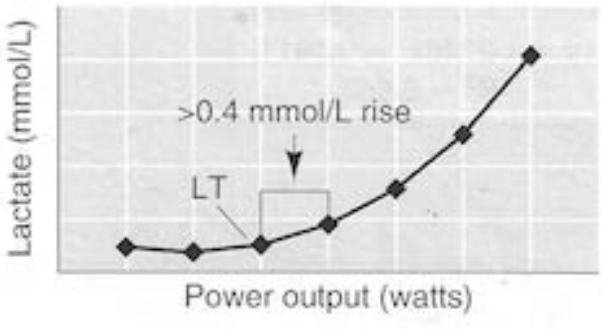
Furthermore, automated blood lactate analysers have made lactate measurement uncomplicated and accessible, whilst many individuals find the VO_2 peak tests uncomfortable and difficult. Many are claustrophobic and cannot perform a VO_2 peak test easily (i.e. the maximal exercise criteria of the test cannot be attained). In addition, VO_2 peak tests require exercising to exhaustion. In a clinical setting this is not desirable due to risk and is difficult to attain (Faude et al. 2009). Lactate measurements are easier to administer because they can be performed during sub-peak exercise, are cheaper to administer and do not need highly specialized staff.

Shifts in the blood lactate – work intensity curves of BLTTs can also be used to assess exercise adaptations on a more regular basis than that of peak VO_2 testing (Weltman, 1995). It is generally accepted that a down- and rightward shift of the lactate curve denotes an improved endurance capacity (Acevedo et al. 1989; Bosquet et al. 2002; Yoshida et al. 1990); is a marker of cellular adaptations to exercise; and reflects training adaptations with greater sensitivity than VO_2 max or VO_2 peak (Coen et al. 1991). This

allows for regular feedback to patients, which in turn helps adherence and exercise program adjustment. An even more practical option could be to perform a single bout of exercise at a constant speed/pace/power output and monitor the blood lactate concentration at the end of the bout. The blood lactate concentration at the end of an exercise bout should decrease with each testing session (Costill et al. 1985).

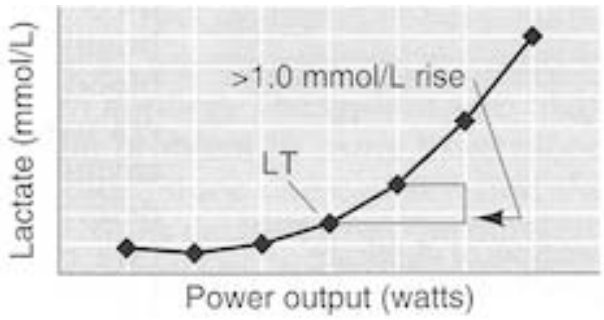
One problem in interpreting literature about BLTT that many terms have been used to describe the thresholds. This research will utilise the following two terms to describe the two thresholds that have been found in the blood lactate response during incremental exercise:

1) **The Lactate Threshold (LT):** The lactate threshold is defined as the first workload at which there is a sustained increase in blood lactate levels above resting levels. This point generally occurs at blood lactate levels below 2 $mmol.L^{-1}$. Other descriptions given to this threshold include:
    - Aerobic Threshold - fixed at 2$mmol.L^{-1}$ (Bourdon, 2000; Faude et al. 2009).
    - The workload preceding a nonlinear rise in blood lactate during progressive work (Bourdon, 2000; Weltman, 1995)
    - The workload preceding a 0.4$mmol.L^{-1}$ rise in blood lactate above the baseline (ADAPT method) (Bourdon, 2000).



(Figure taken from Bourdon, 2000)

- Maximal Steady State – fixed 2.2 mmol.L^{-1} value (Bourdon, 2000).
- Onset of Plasma Lactate Accumulation – Exercise intensity that elicited a blood lactate concentration 1.0 mmol.L^{-1} greater than baseline (i.e. lactate at low intensity corresponding to 40-60% VO_2 max) (Bourdon, 2000; Faude et al. 2009).

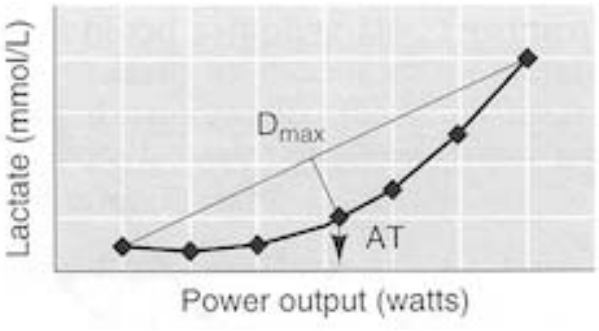


(Figure taken from Bourdon, 2000)

- The workload 0.2mmol.L^{-1} (the error of lactate analysers), above the lowest exercise lactate value (Faude et al. 2009).
- The workload at which blood lactate increases 0.5 mmol.L^{-1} above resting concentration (Faude et al. 2009).

- The workload at which there is a rise in the relationship of blood lactate between two consecutive workloads and the work intensities of those workloads (Farrell et al. 1979).

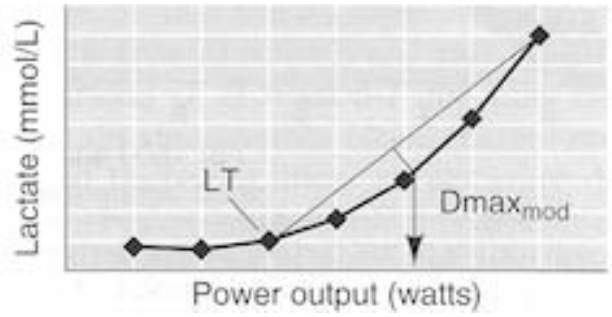
2) **The Anaerobic Threshold (AT):** The workload marked by a rapid rise in blood lactate denoting the upper limit of equilibrium between lactate production and clearance. This point occurs at blood lactate levels between 3 and 5.5 mmol.L^{-1} (Heck et al. 1985). Other descriptions given to this point are:
   - Aerobic-Anaerobic threshold; Onset of Blood Lactate Accumulation (OBLA); 4 mmo/L threshold. All these terms are used to describe the workload causing a fixed 4 mmol.L^{-1} blood lactate level (Heck et al. 1985; Mader et al. 1986; Sjodin et al. 1985). OBLA has been shown to be related to average power output during time-trials (Bishop et al. 1998; Sjodin et al. 1981). In contrast, Bentley et al. (2001) showed that OBLA was not related to the average power output during a 20 minute or 90 minute cycle time-trial. Some studies have used 3.5 mmol.L^{-1} instead of 4 mmol.L^{-1} (Denadai et al. 2005).
   - Dmax (Cheng et al. 1992) – The point on the lactate curve at maximal distance from the line connecting starting and finishing lactate levels.



(Figure taken from Bourdon, 2000)

McGehee et al. (2005) showed that running velocity and other parameters at AT determined via this method were significantly lower than those determined using the 4 mmol.L^{-1} threshold method. Yet Bishop et al. (1998; 2000), found that Dmax and OBLA were the two variables that were most related to the average power output achieved during 60 minutes of cycle exercise in female cyclists. Also, Bentley et al. (2001) found that 90 minute time-trial performance is highly related to this Dmax. To eliminate the influence of the start point of the test on the Dmax method, Bishop et al. (1998) connected the LT (i.e. workload preceding a 0.4mmol.L^{-1} rise in blood lactate above the baseline) with the end-point of the lactate curve (i.e. the finishing lactate level).

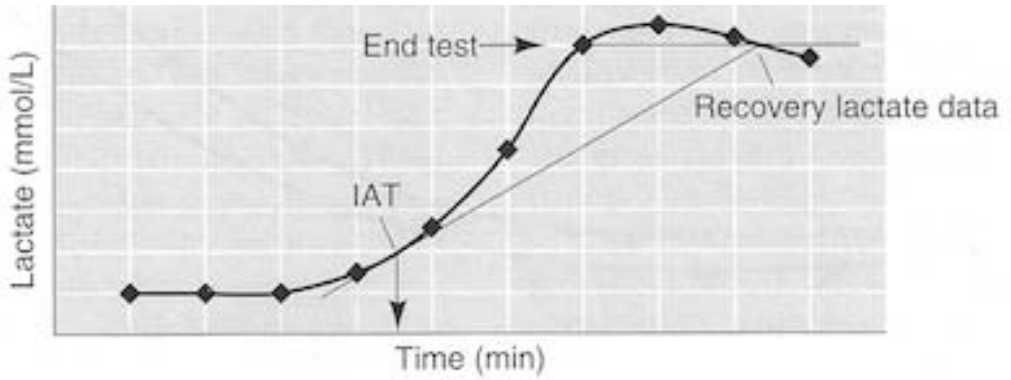
- Anaerobic Threshold (ADAPT method) (Bourdon, 2000) – Modified Dmax utilizing LT instead of the first workload as the start point.



(Figure taken from Bourdon, 2000)

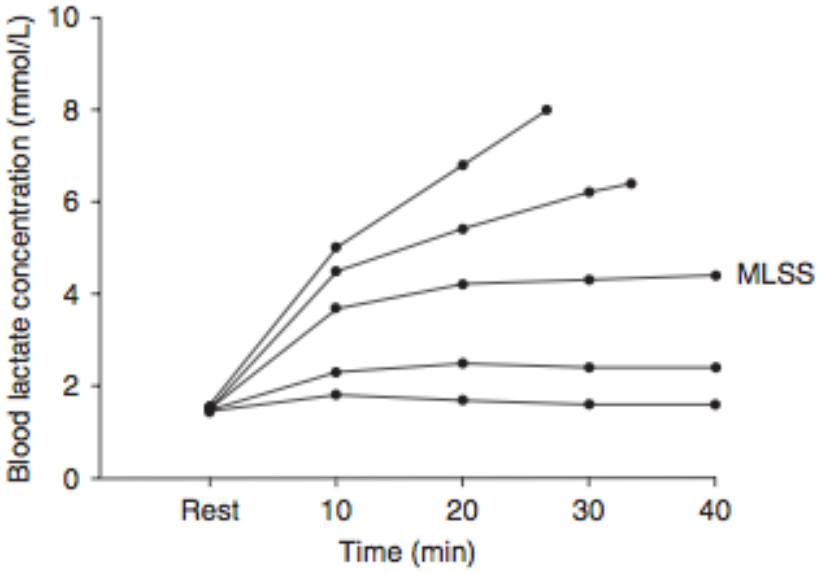
- Anaerobic Threshold (Kindermann et al. 1979) - Part of exponential increase in lactate concentration, approximately 4 mmol.L^{-1}.

- The individual anaerobic threshold – Calculated as the tangent to the blood lactate curve from recovery curve where blood lactate is equal to the value at the end of the test (Stegmann et al. 1981; McLellan et al. 1992)



(Figure from Bourdon, 2000)

- Maximal Steady State Workload – Workload at fixed 3 mmol.L^{-1} blood lactate level (Bourdon, 2000).
- Lactate Minimum test (Tegtbur et al. 1993): Starts with a short supramaximal bout of exercise and is followed by an incremental exercise test. The lactate minimum speed is the lowest point on the lactate curve.
- Maximal Lactate Steady State (MLSS): The highest constant workload that still leads to equilibrium between lactate production and elimination (Faude et al. 2009). This is determined by performing several constant load trials, at least 30 minutes long, on different days, at various intensities (50-90% VO_2 max). An increase in blood lactate of not more than 1 mmol.L^{-1} between the 10^{th} and 30^{th} minute of the trial determines the MLSS workload. MLSS has also been termed as the individual anaerobic threshold (IAT) (Weltman, 1995).



(Figure from Weltman, 1995)

The disadvantage of this determination is that the athlete has to come to the laboratory for several days. Some studies have shown that the MLSS corresponds to a concentration of 4 mmol.L^{-1} (Jones et al. 1998; Poole et al. 1988), yet wide individual variability has been observed (Denadai et al. 2005). Denadai et al. (2005) also found no significant difference between OBLA and MLSS and between OBLA and determination of critical velocity.

In addition to the terminology debate, there is the debate of the best fitting procedure for the determining of these BLTTs. Bishop et al. (1998), describes the most commonly used methods for the determination of the above-mentioned BLTTs. Exponential and 3rd - degree polynomial fitting procedures are the most commonly used fitting procedures. The best fitting procedure for obtained blood lactate data has not yet been established (Faude

et al. 2009). Therefore, the data fitting procedures in research should be reported, since they influence interpretation of results.

This study will compare two of the methods used in the determination of BLTTs:

a) The MADER model (Mader et al. 1986): Identifies only the AT. This is the workload associated with the fixed blood lactate concentration of 4 mmol.L^{-1}. This is the most frequently used method (Faude et al. 2009).
b) The ADAPT method (Bourdon, 2000): Uses both LT and AT. LT is the workload preceding a 0.4mmol.L^{-1} rise in blood lactate above the baseline; and AT is determined using the modified Dmax method as described above.

The Mader method was chosen for this study since it is the most extensively used method and the Lactate Scout blood lactate analyser software that was used in this study utilises the Mader method of determining AT.

Heitkamp et al. (1991) investigated the reproducibility of the Mader model. These researchers found a good reproducibility of the AT for untrained women and an even higher reproducibility for trained women. However, no studies have investigated the reproducibility of the 4 mmol.L^{-1} AT in MetS patients. Furthermore, the 4 mmol.L^{-1} determination method has been shown to have large individual variation (Weltman, 1995); and to underestimate (in anaerobically trained individuals) or overestimate (in aerobically trained athletes) endurance capacity (Stegmann et al. 1981;1982). Fixed blood lactate concentrations, such as those used by the Mader model, are also strongly influenced by nutritional and training/recovery state (Dotan et al. 1989; Hughes et al.

1982). Therefore, individually based methods of determining BLTT have been developed.

The ADAPT method of BLTT determination uses one such individually based threshold method calculated from the shape of the lactate – work intensity curve. Frohlich et al. (1989) found that nutritional factors (glycogen depletion as a result of dietary or training manipulations) did not alter the shape nor the slope of the lactate - work intensity curve. Therefore, BLTT determined via fixed blood lactate levels in a glycogen depleted state will overestimate endurance capacity, while individually based thresholds determined from the shape of the lactate-work intensity curve are hardly changed. This may be the reason for this thesis choosing to also investigate the ADAPT method of BLTT determination.

The technical error of measurement (TEM: also called the standard error of measurement) for BLTT determination using the ADAPT method has been shown to have good precision for athletes tested at the South Australian Sports Institute (Bourdon, 2000). No study has investigated the applicability of this method in the clinical environment.

It has been argued that blood lactate concentrations increase continuously rather than show a clear threshold. Similarly, the contribution of oxygen independent (anerobic) and dependent (aerobic) pathways to energy production show a continuous transition, not a sudden change. The processes of these energy pathways, simultaneously contribute to energy production during both low and high intensity exercise. Therefore, the term

"threshold" might be misleading (Faude et al. 2009). However, the review of Faude et al. (2009) aimed to integrate all the different BLTT concepts into a framework that was originally called the aerobic-anaerobic transition (i.e the intensity range between LT and AT (MLSS)) (Kindermann et al. 1979; McLellan, 1981). These researchers noted that the model is valuable from a practical and didactical point of view and that it illustrates the physiological relevance of the blood lactate transition thresholds (Faude et al. 2009).

In setting up protocols for BLTT determination, the following factors should be noted:

- Sampling site

  BLTT determined from differing sample sites (i.e. blood vessel types) or differing automated lactate analysers, are not comparable. Samples taken from the earlobe have been shown to result in lower blood lactate values than those taken from the fingertip (Faude et al. 2009). Whole blood lactate concentrations are between 10 – 30% lower than plasma values (Bourdon, 2000; Faude et al. 2009). Sweat contains lactate therefore the sampling site must be cleaned with water first before the blood sample is taken.

- Test protocol workload and rest duration

  A number of studies have noted that exercise periods of at least 4 –7 minutes are required to attain steady-state blood lactate concentrations and a more consistent indication of the relationship between muscle and blood lactate concentrations (Bourdon, 2000; McNaughton et al. 2006; Weltman, 1995). Also, Weltman et al. (1990a) found no differences in the determination of LT and AT when using a continuous, 3 minute stage treadmill protocol compared to a discontinuous 10

minute stage protocol. Thus, there seems to be disagreement on the optimal workload time. Therefore, this PhD study used a 4 minute workload test protocol to make sure that the workload was longer than the minimum research period. The periods in between work-bouts to allow for blood sampling, must also be kept to a minimum, with 1 minute as a maximum (Bourdon, 2000). Work intensity increments should be small and 6 – 8 workloads are sufficient (Bourdon, 2000).

- Ergometer type

The choice of test ergometer should be dictated by the principle of training specificity.

- Substrate availability

AT can be altered by changes in substrate availability. Ivy et al. (1981) determined AT on a cycle ergometer under 3 conditions: control; glucose trial (ingesting 75g of glucose 30 minutes before the exercise test); elevated free fatty acids state (by administration of heparin). No differences existed in AT between the control and glucose trial when adjusted for baseline blood lactate concentrations. A significant reduction in blood lactate occurred in the elevated free fatty acid trial and AT occurred at a higher % VO_2 max in this condition. Hughes et al. (1982) found that AT occurs at a lesser workload in a glycogen-depleted state. Yoshida (1984), observed that the workload at AT was significantly reduced after a high compared to a low carbohydrate diet. In contrast, Quirion et al. (1988) reported that changing the diet had no effect on AT.

- Environmental factors

Altitude and external temperature can also affect the blood lactate response to exercise. Blood lactate transition threshold values are reduced with increasing altitude or temperature (Weltman, 1995).

- Training Status

There is a decrease in blood lactate concentration at a given workload following endurance training. It has been suggested that this may be related to the finding that training reduces carbohydrate utilization and muscle lactate accumulation during exercise (Saltin et al. 1976). Increases in skeletal muscle mitochondrial density (Holloszy, 1967; Holloszy et al. 1984) and improved fatty acid oxidation (Hickson et al. 1997; Rennie et al. 1976) after endurance training have been identified as mechanisms in explaining the reduced carbohydrate utilization during exercise after training. Increases in mitochondrial density and mitochondrial enzyme activity, allows for greater ATP production via oxidative processes and thus would decrease glycolytic flux and lactate formation. Also, the improvement in fat oxidation as an adaptation to endurance training would decrease the need for ATP formation via glycolysis and thus decrease the rate of lactate production. In addition, Holden et al. (1992) showed that the reduced blood lactate concentration after training is the combined result of the reduced rate of lactate appearance and improvement in the rate of lactate clearance. This factor is influential in this study and will be further investigated.

BLTT tests are influenced by many factors, yet if standardized they are reproducible. The first study of this thesis hypothesized that reproducibility could be attained in patients with MetS.

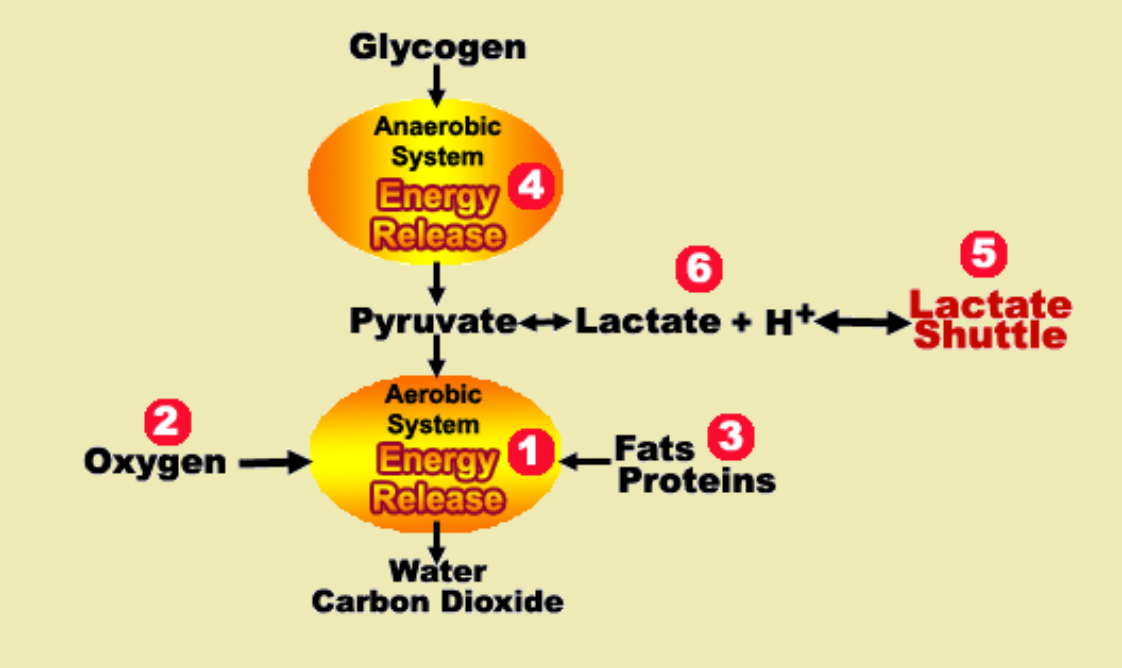
1.4 The Effects of Endurance Training on Blood Lactate Transition Thresholds

Endurance training substantially reduced blood lactate concentrations at any given VO_2 (MacRae et al. 1992; Stanley et al. 1985). These researchers suggested that training results in a diminished blood lactate response during exercise by decreasing the rate of lactate production or increasing the rate of lactate clearance or both. The decrease in blood lactate production may be related to the reduced carbohydrate utilization during exercise after endurance training (Saltin et al. 1976). Coggan et al. (1992) investigated the glucose and glycogen metabolism at a given intensity after training and concluded that the individuals with a higher LT (more metabolically fit) used less muscle glycogen during an exercise bout and had more favourable glucose turnover during exercise. This supports the concept that the skeletal muscle capacity is related to the blood lactate response to exercise and is a major determinant of the metabolic response to exercise (Weltman, 1995).

Many studies have also reported that the workload and VO_2 associated with blood lactate parameters improve to a greater degree with training than does VO_2 max (Denis et al. 1982; Hurley et al. 1984; Yoshida et al. 1982; Sjodin et al. 1982; Weltman et al. 1992). These data also provide evidence that the blood lactate response to exercise and VO_2 max are affected by differing mechanisms. It is suggested that VO_2 max is dependent on

cardiovascular (central) factors such as 1) maximal cardiac output; 2) pulmonary diffusing capacity; 3) oxygen carrying capacity of the blood (Basset et al. 2000); and that the blood lactate response to exercise is dependent on muscle (peripheral) factors such as number and size of mitochondria or muscle fiber type (Weltman, 1995).

The blood lactate threshold will change with training primarily for three reasons: 1) lactate utilization increases, 2) lactate production declines and/or 3) lactate clearance increases (Olbrecht, 2000). The flow diagram below will be used to explain the adaptations:



1) Lactate utilization increases:

Training can affect lactate utilization in two different ways:

a) Oxygen utilization – Training adaptations within the muscle fiber allow it to utilize more of the available oxygen. These adaptations include an increase in number and size of mitochondria and an increase of oxidative enzyme

concentration in the mitochondria. This higher utilization of oxygen means more of the pyruvate will be used for aerobic energy, thus less of the pyruvate will be converted to lactate and the blood lactate threshold will occur at a higher work output. ("1" in the diagram above refers to the processes discussed).

b) Better oxygen delivery – Training adaptations allow the cardiovascular system to deliver more oxygen to the muscle, at a faster rate. The greater the amount of oxygen delivered, the greater the amount of pyruvate that will be used in the aerobic process and thus less will be converted to lactate. (These processes are represented in "2" in the diagram above). Some training adaptations that improve oxygen delivery are an increase in skeletal muscle capillarization; increase in the proportion of red blood cells to plasma in the blood and an increased cardiac output.

2) Lactate production declines:

a) Improved fat oxidation - The higher utilization of fat means there is less need for glycolysis and consequently less pyruvate and less lactate is produced. The increase of oxidative enzyme concentration in the mitochondria of the muscle fiber is a training adaptation that promotes this shift of energy source during exercise. (These processes are represented in "3" in the diagram above).

b) Lower anaerobic capacity – Endurance training may change the anaerobic capacity. This may be the main reason for short term changes in the lactate threshold (Olbrecht, 2000). The lactate threshold will automatically change because pyruvate production is changed. When the anaerobic capacity is lowered less pyruvate is produced for a given effort level. Thus, the lactate threshold will

increase without any change in the ability of the body to process aerobic energy or to shuttle lactate. The lactate threshold is always an equilibrium between lactate production and lactate elimination. ("4" on diagram above).

3) Lactate clearance increases:

Training allows the body to become more efficient at removing lactate from the producing muscles and shuttling it to other parts of the body where it can be used. This eases the acid levels in the producing muscles and thus lets them operate at a higher energy level before producing the acidosis levels that slow down energy production. (Process "5" in the diagram above). Also training can help the lactate shuttle as the increased capillary system will help clear the lactate out of producing muscles and into the blood stream. The same adaptation facilitates the transfer of lactate from the blood to other muscles for elimination.

Buffering:

The muscles can be trained to buffer some of the acid accumulating in the lactate producing muscles. The hydrogen ions causing the problems with contraction are neutralized and this allows even more lactate to be produced before there are problems with contraction. However, it probably does not affect the threshold since it does not slow down lactate production (Olbrecht, 2000). (Process "6" in diagram above).

1.5 Blood Lactate Threshold Testing and the Prescription of Exercise

Studies have suggested that training intensity be based on the VO_2 at AT (determined by a BLTT test); or the velocity of movement at AT (Coen et al. 1991; Coyle et al. 1983; Heck et al. 1985; Karlsson et al. 1982; Kindermann et al. 1979; Stegmann et al. 1982;

Sjodin et al. 1982; Tanaka et al. 1986; Weltman et al. 1992; Weltman 1995; Yoshida et al. 1982). These studies have also suggested that improvement in such blood lactate parameters are more important than elevating VO_2 peak for enhancing endurance performance. A major underlying mechanism for this is the strong association between muscle respiratory capacity and VO_2 at AT (Ivy et al. 1980; Sjodin et al. 1982).
The review by Jacobs (1986), notes that prescribing exercise intensity as a function of lactate concentration may prove to be a means of obtaining a homogeneous training adaptation in a group of participants. In addition, this review also noted that lactate response to supramaximal exercise is a sensitive indicator to "sprint training" adaptation and is correlated with supramaximal exercise performance.

Blood lactate levels have also been associated with exercise durations for different exercise intensities. Exercise intensities only slightly above the LT result in elevated but constant blood lactate levels during steady-state exercise and can be maintained for ~ 4 hours (Faude et al. 2009). At exercise intensities corresponding to AT (MLSS), exercise can be maintained for 45- 60 minutes (Urhausen et al. 1993).

Significant correlation exists between the response of plasma lactate during a running training program and the percentages of speed at the AT determined on a treadmill (Coen et al. 1991). This forms the basis for using BLTT treadmill tests to set exercise intensities. Coen et al. (1991) showed that AT determined during a treadmill BLTT test allows for precise setting of training recommendations for both endurance runs

performed at different intensities and for 1000m interval training programs (external conditions must also be considered).

Another reason for using blood lactate to set exercise intensity is that exercise with no significant accumulation of lactate results in only a slight increase in sympathetic activity and to moderate adaptation of regulatory hormones. At intensity close to 100% of AT, sympathetic activity increases (Coen et al. 1991). High correlations between catecholamine concentrations and blood lactate concentrations during exercise have been reported (Podolin et al. 1991). It should be noted that it is speculation that training at AT increases sympathetic activity, but no links between lactate, glucose metabolism and sympathetic activity have been found. It has also been suggested that a training intensity which approximates AT would be optimal in eliciting the local training adaptation changes in muscle metabolism (Kindermann, 1979). Sjodin et al. (1982) investigated this area with trained runners. The trained runners incorporated training at an exercise intensity corresponding to AT (4 $mmol.L^{-1}$ blood lactate) once a week for 20 minutes. These researchers found that the rate of glycogenolysis during exercise was slower post-training and that the potential to oxidize pyruvate and lactate increased. Improved intracellular oxidative capacity was also indicated by measurement of muscle enzymes in the vastus lateralis. Velocity and VO_2 at AT also increased significantly after this type of training.

Tanaka et al. (1986) also showed that the addition of a run lasting longer than 60 minutes at, or slightly above AT to other training may be effective in improving both endurance

performance and AT for middle-distance runners. The mechanism for such alterations, proposed by these researchers, is supported by the findings of Sjodin et al. (1982) i.e. an increased activation of relatively more slow-twitch fibers at AT and /or improved oxygen extraction in skeletal muscle.

The study of Lucia et al. (1999) also supports the concept of a transitional exercise intensity that is required to produce exercise adaptations. These researchers showed that changes in electro-myographical activity of the rectus femoris and vastus lateralis muscles were coincidental with the aerobic (LT) - anaerobic (AT) transition in elite cyclists.

Weltman et al. (1992) showed that training using BLTT is effective in improving VO_2 and velocity at LT and at fixed blood lactate concentrations of 2, 2.5 and 4 $mmol.L^{-1}$. For the first 4 months, training at LT (approximately 55% of VO_2 max) or training at above LT (approximately 81% of VO_2 max) resulted in similar training adaptations in the previously untrained women. However, for continued training adaptations (after the 4 months), some exercise was required at an intensity above the LT. Participants in this study trained 6 times per week. These researchers concluded that the increase in physical activity associated with the onset of endurance training is sufficient to elicit a training effect provided the initial training intensity is at or above LT. However this data also suggests that training above LT is more effective than training at LT for longer term improvements. It is speculated that such intensities may induce an increase in the oxidative metabolism of muscle cells (Kindermann et al. 1979).

Yoshida et al. (1982) monitored untrained males that trained 15 minutes a day, 3 days a week, for 8 weeks at an intensity corresponding to AT (Mader method). The change in VO_2 at LT after training compared to the change in VO_2 max led the authors to conclude that training at an intensity corresponding to AT may be one of the most effective methods for endurance training.

Keith et al. (1992) investigated two groups of athletes. One group trained at AT for 30 minutes. The other group divided the 30 minute workout into four intervals, each seven and a half minutes long. Two of the intervals were performed above AT, while the other two were carried out below AT. Each group trained four times a week. Both groups showed similar increases in VO_2 max and velocity at AT. It must be noted though, that the AT group had 120 weekly minutes of quality exertion and the non-AT group had 60 weekly minutes of quality work. Thus, BLTT determination may be important for exercise prescription if long-term exercise adaptations are desired. Hollman et al. (1981) also showed that training at AT for 30 min, 5 times weekly will significantly increase velocity at AT, yet training at a higher exercise intensity results in no changes after 6 weeks of training.

In addition, exercising above the MLSS (AT) has been associated with an excess excretion of stress hormones (e.g. plasma epinephrine and plasma cortisol) (Urhausen et al. 1994) and of immunological markers (e.g. monocytes, lymphocytes, neutrophils)

(Gabriel et al. 1997). Therefore, establishing the AT from blood lactate testing may be important in preventing over-reaching during endurance exercise.

Weltman et al. (1989), found that for sedentary women, heart rates of 75% MHR and 55% of HRR were required for most to be above LT. For blood lactate concentrations of 4mmol.L^{-1} (AT), heart rates in excess of 95% MHR were required.

The work of Alois Mader and Jan Olbrecht (Mader et al. 1986; Mader, 1991; Olbrecht, 2000), introduced a technique that has been used to train world champion athletes. This theory considers the contributions of both the aerobic and anaerobic systems separately, instead of focusing on the AT. This concept emphasizes the importance of the lactate production process (glycolysis) and how it can be modified in athletes ranging from 50m freestyle sprinters to Ironman triathletes. This system aims to fine-tune the innate anaerobic capacity level to a desired level at race time. Blood lactate testing is used to monitor anaerobic capacity level. This training concept however, views blood lactate testing in a different light. It notes that raising anaerobic capacity will lower the AT for traditional endurance testing. Lowering anaerobic capacity will raise the AT of endurance tests because there is less lactate to deal with at the same effort level. In each case, the aerobic capacity may not have changed but traditional analysis may assume that there is a decrease in aerobic endurance in the first situation and an increase in the second one. In both situations the wrong training may then be prescribed. Thus, this concept cautions that the aerobic system may seem improved in traditional lactate testing, by temporarily suppressing the anaerobic capacity.

In summary, Weltman (1995) notes that there exists a lack of scientific consensus about the best way to use blood lactate levels for designing and altering training programs. One of the questions that this PhD study attempts to answer is whether training based on the blood lactate response to exercise is more effective than one other training techniques. Furthermore, this training methodology has not been investigated in a clinical setting. The second study of this PhD examines this question in persons with MetS.

1.6 Exercise Intervention Programs for the Reduction of Progressive Disease Risk Factors and Effects on Components of the Metabolic Syndrome

Many studies have shown that low levels of physical activity and low cardiorespiratory fitness are associated with increased risk of CVD, cancer and all cause mortalities (Blair et al. 1989; Blair et al. 2009; Lakka et al. 1994; Lee et al. 1995; Mark et al. 2003; Paffenbarger et al. 1983). Regular physical activity has also been shown to lead to a reduced risk of cardiovascular disease in men (Bassuk et al. 2005; Katzmarzyk et al. 2004; Sesso et al. 2000). In addition, a dose-response relationship exists between physical activity and coronary heart disease and type 2 diabetes (DHSSPS, 2011).

Impaired glucose tolerance is a component of the MetS, and is associated with a high risk of developing type 2 diabetes. Studies have investigated the effect of exercise and/or diet in preventing type 2 diabetes in this at risk population. Such studies include the Diabetes Prevention Program (Knowler et al. 2002), that showed modest increases in physical activity can reduce the incidence of diabetes by 58%. The intervention, (diet counselling

and 150 minutes of moderate intensity exercise per week) - was nearly twice as effective as metformin therapy in preventing the progression to diabetes in an at-risk population. The DA Qing IGT and Diabetes Study (Pan et al. 1997), randomised participants into a control group, diet only group, exercise only group and a diet + exercise group. The exercise program was based on increasing the amount of leisure physical activity (30 minutes of mild exercise or 20 minutes of moderate exercise or 5 - 10 minutes of vigorous exercise per day), rather than using a formal exercise prescription. The incidence of diabetes in this study decreased by 33% and 47% in the diet only and exercise only groups respectively, when compared to the control group. The incidence reduced by 38% in the diet + exercise group. This study noted that the efficacy of diet was similar to that of exercise and that no additional benefit was gained from combining the two interventions.

Laaksonen et al. (2005) found that increasing total leisure time physical activity (> 4 hours/wk of moderate exercise) and modifying diet, reduced risk of developing diabetes by 58% (even after adjusting for confounding parameters). McAuley et al. 2002 showed that 5 weekly, 20 minute exercise sessions at 80 – 90% maximal heart rate attained a greater improvement in insulin sensitivity than modest lifestyle changes among overweight insulin-resistant normoglycaemic adults.

A Cochrane review (Oronzo et al. 2009) on preventing type 2 diabetes showed that physical activity interventions (on average, at least 150 minutes each week of brisk walking, cycling, jogging) with diet modification reduced incidence of diabetes by 37%

in high-risk groups such as people with MetS. Favourable effects were also shown on body mass, waist circumference and blood pressure. The review did conclude that more evidence is required on the effects of exercise alone.

Leon et al. (1979) used a 16-week walking program to train obese men aged 19 – 31 years (without MetS). These researchers showed that the walking program reduced body mass (4.9 – 6kg), increased the high-density lipoprotein (HDL),/ low density lipoprotein (LDL) ratio; reduced fasting blood glucose and reduced the ratio of plasma insulin / glucose concentrations. These effects indicate an increase in tissue sensitivity to insulin, which should aid in the prevention of type 2 diabetes and reduce the risk of vascular disease. Thus, exercising 5 times per week, 7.5h/wk, at an intensity eliciting 1100 kcal/session (4603 kJ/session), suggests a reversal of metabolic disease. A limitation of this study is that no control group was investigated. Study 2 of this PhD, applied the Leon et al. (1979) exercise program to persons with MetS, in comparison to an exercise programme using less volume and using AT to set intensity.

Contradictory evidence exists regarding the optimal amount and intensity of exercise needed for health benefits. Some international organisations suggest 30 minutes of moderate intensity exercise (in minimum bouts of 10 minutes), 5 days/wk or 75 minutes of vigorous intensity exercise. These organisations also suggest minimizing sitting time (American College of Sports Medicine, 2006; DHSSPS, 2011). Other organisations suggest 60 minutes of exercise per day. Some studies showed that vigorous activity is required to achieve a reduction in cardiovascular events (Lakka et al. 1994; Lee et al.

1995). Other studies have indicated that only moderate activities are sufficient (Shaper et al. 1991; Slattery et al. 1989). Some researchers have shown that for metabolic benefits, regular exercise should be performed more frequently (3 -5 day/wk) and for a longer duration (60 minutes) at a lower intensity (40 – 60% VO2 max) than typically prescribed for improvements in cardiorespiratory fitness (Buemann et al. 1996; Despres et al. 1997).

Few, randomized, controlled studies exist in this area of optimal amount and intensity of exercise. The STRRIDE study (Slentz et al. 2005; Slentz et al. 2007a) is one such study. The study investigated the effect of different exercise amounts and intensities. Four groups were used in the STRRIDE study. 1) A control group; 2) A low amount, moderate intensity exercise group, (40 -55% of peak VO_2 , exercise energy expenditure of 14 kcal.kg body mass^{-1}.wk^{-1}); 3) A low amount, vigorous intensity exercise group, (65 - 80% of peak VO_2, exercise energy expenditure of 14 kcal.kg body mass^{-1}.wk^{-1}); 4) A high amount, vigorous intensity exercise group, (65 – 80% of peak VO_2, 23kcal.kg body mass^{-1}.wk^{-1}). Central obesity (determined from abdominal fat measurements) was used since it has been linked to risk of disease (Kissebah et al. 1994; Lemieux et al. 2000). The STTRIDE study showed that body mass and visceral fat responded in a dose-response manner. Thus the greater the amount of exercise (23 kcal.kg^{-1}.wk^{-1}), the greater the decrease in these parameters. Body mass decreased by 2.31 kg and peak VO_2 increased by 17.9% with the above exercise prescription. An exercise expenditure of 14 kcal.kg^{-1}.wk^{-1}or 1200 kcal.wk^{-1} (19.2 km.wk^{-1}) maintained body mass and visceral fat. This study also noted that exercise intensity did not appear to have any effect on body mass or

abdominal fat responses. However, other studies have found that exercise intensity is important in determining training adaptations (Gibala et al. 2012; Rynders et al. 2014).

Duscha et al. (2005) analysed the STRRIDE study with respect to the exercise effect on VO_2 peak. The researchers found that VO_2 peak also responded in a dose-response manner. Other published findings from this cohort also showed improvements in lipids, lipoproteins, and insulin sensitivity (Houmard et al. 2004; Kraus et al. 2002; Slentz et al. 2004; 2007a). The relative improvement in the insulin sensitivity index was greater in the low exercise volume/moderate intensity (40-50% VO_2 peak) and in the high volume/high intensity (65-80% VO_2 peak) groups than in the low volume/high intensity group (Houmard et al. 2004). The improvements on the lipoprotein profiles were influenced by amount and intensity of exercise (Slentz et al. 2007b). Therefore, the above-mentioned exercise programme suggests a prescription for reversing metabolic disease.

Commenting on the STRRIDE studies, Slentz et al. (2007a) noted that the theoretical minimal physical activity level for body mass maintenance occurs at around 12.8 $km.wk^{-1}$ (or 14 $kcal.kg^{-1}.wk^{-1}$). At 17.6 - 27.2 $km.wk^{-1}$, a beneficial effect occurs on lipoproteins and lipoprotein particle size and number (Slentz et al. 2007b). The article also highlighted that the theoretical minimal amount of exercise is different for each individual – i.e. some proportion of individuals would still gain body mass when doing the minimal amount (12.8 $km.wk^{-1}$) of exercise. This PhD study used BLTT to individualize the exercise response.

Both the STRRIDE and the Leon et al. (1979) studies did not influence caloric intake of the participants. The participants were asked not to diet and not to change their eating habits for, and during the duration of the exercise period. A limited number of randomised, controlled trials have investigated exercise-induced reductions in visceral fat among groups that did not change dietary habits. One such study, Ross et al. (2000), showed that an exercise program designed to increase energy expenditure by 700kcal/day (2928J/day) in men for 12 weeks, resulted in a decrease of visceral fat of 6.9cm^2 per kilogram of body mass loss (28% decrease). The diet–only group in this study had a similar decrease (5.9 cm^2 per kg mass loss).

A review of the treatment of obesity (McQueen, 2009), suggested that exercise at 55 - 69% of MHR, 5-7 days per week, 45 - 60 min duration is needed. A dosage of 250 - 300 minutes per week was suggested for long-term body mass-loss and for prevention of body mass regain. This review also states that the value of intermittent exercise bouts is as yet inconclusive and that resistance training in the obese subject does not influence energy expenditure or absolute mass loss.

The above-mentioned exercise prescriptions rely on peak VO_2 testing to set exercise intensity. Peak VO_2 tests (and equipment) are expensive and the former are difficult to conduct, especially in the clinical environment. Furthermore, two tests were required to set the exercise intensity. A maximal and sub-maximal test to determine the work rate that required a particular oxygen consumption (Slentz, 2007b). Therefore, this PhD study aimed to utilise a cheaper, easier test of setting exercise intensity – BLTT. In addition,

the studies described above used exercise programs that were not periodized. A ramp period was used and thereafter participants exercised at a constant intensity and volume for 6 -8 months. Furthermore, the participants used in the studies mentioned above were not diagnosed with MetS – the participants were overweight, yet healthy. The presence of the components of the syndrome may influence the effect of exercise.

This review has focused only on studies that used cardio-pulmonary exercise. The Canadian and American Diabetes Associations recommend combined cardio-pulmonary and resistance exercises for at-risk individuals (Sigal et al. 2004). Studies that have investigated combined cardio-pulmonary and resistance exercises and type 2 diabetes have shown increases in aerobic capacity and an increase in muscular strength (Maiorana et al. 2002; Oberbach et al. 2006; Tokmakidis et al. 2004). Mathieu et al. (2008) further added flexibility and balance to a cardio-pulmonary and resistance program for type 2 diabetics. The combined 10 week program showed a 1.1kg body mass - loss, decreases in waist circumference (2.5cm) and increases in cardiovascular capacity and HDL-C. No changes were shown in total cholesterol, triglycerides or LDL-C. The study however had the limitations of an absence of a control group, a small number of participants, heterogeneity of participants and the absence of food intake monitoring.

In summary, the beneficial effect of regular exercise on CVD, type 2 diabetes and cardiovascular risk factors is evident. The effect of exercise alone on the simultaneous reduction of multiple, clustered risk factors (as they appear in persons with MetS) will now be discussed.

1.7 Exercise Intervention Programs for Persons with Metabolic Syndrome

The National Cholesterol Education Program suggested body mass loss and increased physical activity as the basis of therapy for MetS (Haffner et al. 2003). The Kuoppio Study (Laaksonen et al. 2002), showed that men who engaged in moderate intensity (>4.5 METs) leisure time physical activity of < 1 $h.wk^{-1}$ were 60% more likely to have MetS than those engaging in > 3 $h.wk^{-1}$ even after adjustment for confounding variables. In addition, men with a VO2 max < 29.1 $ml.kg^{-1}.min^{-1}$ were almost 3-4 times more likely to have MetS than those with a VO2 max $\geq$35.5 $ml.kg^{-1}.min^{-1}$ (Lakka et al. 2003).

Rennie et al. (2003) also found an indirect association between moderate and vigorous physical leisure-time activity and risk of being classified with MetS. Reduced body mass index and increased cardio-vascular fitness were cited as important mediators of this association.

Other researchers have also shown an inverse relationship between cardio-respiratory fitness and the incidence of MetS (Carroll et al. 2000; Irwin et al. 2002; Kullo et al. 2002; LaMonte et al. 2005; Whaley et al. 1999). Katzmarzyk et al. (2004) showed that cardiorespiratory fitness has a strong protective effect against all-cause and cardiovascular disease mortality in healthy men and in men with MetS.

As discussed in section 1.6 and 1.7, physical exercise has been shown to reduce individual cardiac risk factors, yet few controlled studies have reported the effect of exercise alone on the reduction of several risk factors simultaneously, as is the case in individuals with MetS. The table below summarises some of the research studies within this field.

Table 1 Particulars of studies investigating exercise effects on Metabolic Syndrome

STUDY	**PARTICIPANT**	**GROUPS**	**EX.PROGRAM DURATION**	**EX. INTENSITY**	**EX. DURATION**	**EX. FREQUENCY**	**EX. MODE**	**RESULTS**	**TYPE OF STUDY/ LIMITATIONS**
The Heritage Family Study (Katzmarzyk et al. 2003)	17-65 yrs healthy, sedentary n=621	105 with MetS; 516 without MetS No change in life-style or diet levels	20weeks Endurance program	55% VO_2 max. Increase every 2 weeks Up to 75% VO_2 max. for final 6 weeks	30 min. Increase to 50 min for final 6 weeks	Three times per week	Cycle Ergo	30.5% decrease in persons with MetS. Exercise improved "cluster" of risk factors simultaneously. VO_2 max increased by 16.3%	No control group

STUDY	PARTICIPANT	GROUPS	EX.PROGRAM DURATION	EX. INTENSITY	EX. DURATION	EX. FREQUENCY	EX. MODE	RESULTS	TYPE OF STUDY/ LIMITATIONS
Smutok et al. 1993	50yrs(±9yrs), sedentary males n=37	Strength training (ST); aerobic training (AE)& control. No change in diet.	20 weeks	ST: 12-15 RM max; 11 exercises AT: 50% MHR reserve increased to 75-85%	AT: 30 min	Three times per week	Tread-mill	ST and AE improved glucose tolerance and insulin response to OGTT. AE: 19% increase in VO_2 max. Body fat decreased. No significant changes in body mass, lipoprotein profile or blood pressure	Randomised, controlled
Katzel et al. 1997	Obese, sedentary 46 -80yrs men n=67	One exercising group, given a diet	Nine months, then a nine month body mass intervention program included	Start at 50-60% HR Reserve-increased to 70 – 80%	45 min	Three times per week	Tread-mill, cycle ergo	Exercise alone: No change in OGTT, blood pressure, lipid profile. Vo2 max increased 14%. Post ex. Program body mass intervention: improved OGTT response, lipoprotein profile and body mass.	No control group

STUDY	PARTICIPANT	GROUPS	EX.PROGRAM DURATION	EX. INTENSITY	EX. DURATION	EX. FREQUENCY	EX. MODE	RESULTS	TYPE OF STUDY/ LIMITATIONS
Dengel et al. 1998	50 -70yrs. Obese, hypertensive sedentary, insulin-resistant men with MetS n=17	MetS group and a control group. Given a diet	Six months aerobic ex. + mass-loss	Started 50-60 % HR reserve-increased to 75-85% HR reserve	40 minutes	3 – 4 times per week	Tread-mill, Cycle ergo	Decrease in body mass, waist girth, blood pressure, cholesterol, TG. Increase in VO2 max, HDL Improved GTT response	Small sample size
Katriina et al. 2005	Middle-aged, obese men. n= 90	Walking (W) resistance (ST) and control	Six months with dietary advice	W: 60-70% VO2 max ST: 60-80%1RM; 6 ex. eight reps; three sets	45 minutes	Three times per week	Walk	Modest changes in the components of metabolic syndrome. Improved OGTT response, HDL, Exercise did not add any additional effect to that of diet counsel alone.	Randomized , controlled
Watkins et al. 2003	Men and women, older than 29yrs with MetS n=53	Ex only (EX), EX + body mass-loss program (BM) control group	26 weeks	70-85% HR reserve	10 min cool-down and warm-up and 35 minute in target zone	3 -4 times per week	Tread-mill walk/ Jog Cycle ergo	EX and EX+WT: Improved insulin response to OGTT. EX+WT: Decrease in DBP. No changes in lipoprotein profile	Randomized, controlled

STUDY	PARTICIPANT	GROUPS	EX.PROGRAM DURATION	EX. INTENSITY	EX. DURATION	EX. FREQUENCY	EX. MODE	RESULTS	TYPE OF STUDY/ LIMITATIONS
Anderssen et al. 1995 The Oslo Diet and Exercise Study	Males and females, 40 yrs, sedentary, overweight, dyslipidemic, hypertensive n=92	Exercise (EX); Exercise+ diet(EX+ D); Diet(D); Control	One year	60-80%MHR	60 minutes	Three times per week	Aerobics, circuit, brisk walk, jogging	Diet and exercise affected lipid profile and blood pressure markedly; affected hemostasis and fibrinolytic components moderately. EX+D often superior in effect.	Randomised, controlled
Kraus et al. 2002 STRRIDE study	Male and female, aged 40-65yrs, sedentary, overweight, dyslipidemic n=84	Three exercise groups(1,2 ,3) ; control group	Six months	1) High amount/ High int:65-80% VO2 max; 174min/wk 2) Low amount/ High int:65-80% VO2 max; 117min/wk 3) Low amount/mod int: 40-55% VO2 max;	1) 45.8 min 2) 39 min 3) 52 min 176 min per week	3.8 times per week Three times per week 3.4 times per week	Treadmill cycle ergo; elliptical	Exercise group 1) had the greatest influence on lipoprotein profile (with the least body mass loss) Improvements to lipoprotein profile were related to amount and not intensity of exercise. Effect on body mass and fat was dose related.	Randomised, controlled

STUDY	PARTICIPANTS	GROUPS	EX.PROGRAM DURATION	EX. INTENSITY	EX. DURATION	EX. FREQUENCY	EX. MODE	RESULTS	TYPE OF STUDY/ LIMITATIONS
Juneau et al. 1987	Men and women; middle-aged; healthy; sedentary n=57	Control; exercise	Six months 235-345 kcal expenditure per session	60-80% MHR	40 – 50 min	Three times per week	Home-based, walk, slow jog	VO2 max increased by 9-15%. Body mass decreased in men only. No changes in lipoprotein profile.	Randomised, controlled
Eriksson et al. 1998	Male and female. Mean age: 60yrs; Impaired glucose tolerance n=14	Aerobic ex(AE); Circuit train.(CT) Control	Six months	60%MHR	60-90min	Three times per week	Walk, jog, swim, cycle	AE: Increased VO2 max, HDL. No change in insulin sensitivity, CT: Increased insulin sensitivity	Randomised, controlled (small sample size)

STUDY	PARTICIPANTS	GROUPS	EX.PROGRAM DURATION	EX. INTENSITY	EX. DURATION	EX. FREQUENCY	EX. MODE	RESULTS	TYPE OF STUDY/ LIMITATIONS
Wing et al. 1998	Male and female 40-55yrs, overweight, family history of T2D n=57	Diet(D); Exercise (EX); D+EX; Comtrol	24 months	Moderate	50-60 min (4.8km) 1500kcal/wk energy expenditure	Five times per week	Brisk walk	Initial: Wt loss; decrease in glucose, insulin, cholesterol, trigs, LDL, SBP; increase in HDL greatest in D and D+EX. At 2 yrs no between group differences were maintained. Wt loss of 4.5kg in 2 yrs decreased risk of T2D by 30%	Randomised, controlled
Lavrencic et al. 2000	Male and female, 40-65yrs, sedentary, with MetS n=29	Exercise (EX); control	12 weeks	80% MHR	20 min w/up; 30 min ex.	Three times per week	Cycle Ergo	18% increase in fitness in EX group; enhanced flow-mediated dilation (endothelial function); no change in body mass index; blood pressure, lipid profile; insulin resistance	Randomised controlled

STUDY	PARTICIPANTS	GROUPS	EX.PROGRAM DURATION	EX. INTENSITY	EX. DURATION	EX. FREQUENCY	EX. MODE	RESULTS	TYPE OF STUDY/ LIMITATIONS
Nieman et al. 2002	Female, overweight, 25-75yrs; n=43	Exercise (EX); Exercise+ diet(EX+ D); Diet(D); Control	12 weeks	60-80% MHR	45 minutes	Five times per week	Walk	(D) and (EX+D): Decrease in mass, triglycerides, cholesterol. No changes in the (EX)	Randomised, controlled
Stenvold et al. 2012	Men and women, sedentary with MetS n=31	Aerobic interval training (AIT); strength (ST); control	12 weeks	AIT: 4x4 min @ 90%MHR; 3 min rest @ 70%MHR; ST: 80%1RM;	AIT: 43 min total with w/up + cool/down ST: 40 min	Three times per week	Treadmill, cycle	AIT and ST: decrease in fat mass; AIT associated with a more favorable inflammatory status.	Small sample size, randomized, controlled

The studies appearing in the tables above show the efficacy of exercise in improving a cluster of risk factors simultaneously and the metabolic profile of individuals with metabolic syndrome. Yet, there seems to be contradictory evidence with some studies showing exercise alone to having an effect on components of MetS and others showing no effect.

Carroll et al. (2004), in their review of metabolic abnormalities and exercise, applied meta-analyses and a fixed-effects model to analyse randomised controlled trials. The review concluded that there is now more evidence that long-term exercise, without body mass reduction, modestly decreases abdominal adipose tissue and improves insulin action among overweight/obese adults. In addition, exercise alone is effective in improving impaired glucose control and reducing the incidence of type 2 diabetes in both sexes. Furthermore, exercise alone was associated with modest but clinically relevant lipoprotein profile improvements in raising HDL-C and lowering triglycerides. More often than not, though, exercise did not alter total cholesterol and LDL-C concentrations. The review also found that exercise alone modestly reduces blood pressure with greatest changes evident in overweight individuals with hypertension. The majority of the randomised controlled studies that Carroll et al. (2004) analysed have suggested aerobic endurance activity, 3-5 days per week, 30-60 minutes per session at moderate to moderately vigorous intensity (40-80% VO_2 max; median weekly energy expenditure of 1600 $kcal.wk^{-1}$). The authors did however state that more trials are needed to establish the lower threshold for exercise amount and intensity for metabolic outcomes.

Yamaoka et al. (2012) also performed a systematic review and meta-analysis of lifestyle modification interventions (LMI) effects on individuals with MetS. Their analysis however included "diet only" and "diet and exercise" randomised, controlled trials as opposed to the Carroll et al. (2004) review that analysed "exercise only" interventions. Like the Carroll et al. (2004) review, the Yamaoka et al. (2012) review also showed that LMI decreases the prevalence of MetS and associated abnormalities of MetS. Yamaoka et al. (2012) though suggested that their review (when compared to the Carroll et al. (2004) review) indicates that "dietary modifications" may be more effective than "exercise interventions".

1.8 Conclusion

The reliability and use of BLTT has been extensively investigated with athletes, yet the use of BLTT in exercise prescription for individuals with MetS has not been researched. The first study of this PhD investigated this topic. Furthermore, there is a lack of research data on the effect of exercise programs on the diagnosis of MetS. The second study of this thesis thus investigated an exercise program that used BLTT to optimize the effects of exercise on the metabolic profile of persons with MetS.

There is concensus that long-term lifestyle modifications (diet alone, exercise alone or diet and exercise combined) are effective in reducing the prevalence of MetS, the risk of type 2 diabetes and simultaneously improving the cluster of risk factors associated with MetS. The review by Yamaoka et al. (2012) indicated that dietary interventions may be more effective than exercise interventions in the outcomes needed to influence MetS.

However, there is a large individual variation to the response to exercise programs. There is a lack of data with respect to individualizing exercise programs for persons with MetS in order to optimize the improvements in metabolic characteristics at lower exercise volumes. This PhD will aim to add knowledge to this area by using AT to individualize the exercise program. Furthermore, since improving cardio-respiratory fitness is an important part of the lifestyle modifications for MetS, this study will try identify the variables that are strongly related to cardio-respiratory fitness parameters.

1.9 References

1) Acevedo EO. Goldfarb AH. Increased training intensity effects on plasma lactate, ventilatory threshold, and endurance. Med Sci Sports Exerc. 1989, 21:563-568.
2) Alberti KG. Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998, 15:539-553.
3) Alberti KG. Zimmet P. Shaw J. IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. Lancet 2005, 366:1059-1062.
4) Alberti KG. Eckel RH. Grundy SM et al. Harmonizing the Metabolic Syndrome. Circulation 2009, 120:1640-1645.
5) American College of Sports Medicine (ACSM). Other clinical conditions influencing exercise prescription. In: ACSM's guidelines for exercise testing and prescription. 7th edition, Lippincott Williams and Wilkins, Maryland, 2006:205-236.

6) American College of Sports Medicine (ACSM). Exercise prescription for other clinical populations. In: ACSM's guidelines for exercise testing and prescription. 9th edition, Lippincott Williams and Wilkins, Maryland, 2013:309-311.

7) Anderssen SA. Haaland A. Hjermann I. et al. Oslo Diet and Exercise Study: a one-year randomised intervention trial: effect on hemostatic and other coronary risk factors. Nutr Metab Cardiovasc Dis 1995, 5:189-200.

8) Andrew R. Gale CR. Walker BR. et al. Glucocorticoid metabolism and the Metabolic Syndrome: associations in an elderly cohort. Exp Clin Endocrinol Diabetes 2002, 110(6):284-290.

9) Bassett DR. Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc 2000, 32(1):70-84.

10) Bassuk SS. Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J Appl Physiol 2005, 99:1193-1204.

11) Bentley DJ. McNaughton LR. Thompson D et al. Peak power output, the lactate threshold, and time trial performance in cyclists. Med Sci Sports Exerc 2001, 33:2077-2081.

12) Bishop D. Jenkins DG. Mackinnon LT. The relationship between plasma lactate parameters, Wpeak and 1-h cycling performance in women. Med Sci Sports Exerc 1998, 30:1270-1275.

13) Bishop D. Jenkins DG. McEniery M et al. Relationship between plasma lactate parameters and muscle characteristics in female cyclists. Med Sci Sports Exerc 2000, 32:1088-1093.

14) Blair S. Kohl HI. Paffenbarger Jr. RJ et al. Physical Fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989, 262: 2395-2401.

15) Blair SN. Physical inactivity: the biggest public health problem of the 21st century. Br J Sports Med 2009, 43:1-2.

16) Bosquet L. Leger L. Legros P. Methods to determine aerobic endurance. Sports Med 2002, 32:675-700.

17) Bourdon P. Blood Lactate Transition Thresholds: Concepts and Controversies. In: Gore CJ, Physiological Tests for Elite Athletes. Human Kinetics, Illinois, 2000:50-65.

18) Buemann B. Tremblay A. Effects of exercise training on abdominal obesity and related metabolic complications. Sports Med 1996; 2:191-212.

19) Carroll S. Dudfield M. What is the relationship between exercise and Metabolic Abnormalities? A review of Metabolic Syndrome. Sports Med 2004, 34:371-418.

20) Carroll S. Cooke CB. Butterly RJ. Metabolic risk factor clustering , associations of both physical activity and cardiorespiratory fitness in middle-aged men. Med Sci Sports Exerc 2000, 32:2079-2086.

21) Chan NN. Kong APS. Chan JCN. Metabolic Syndrome and Type 2 Diabetes: The Hong Kong Perspective. Clin Biochem Rev 2005, 26:51–57.

22) Cheng B. Kuipers H. Snyder A. A new approach for the determination of ventilatory and lactate thresholds. Int J Sports Med 1992, 13:518–522.

23) Coen B. Schwarz L. Urhausen A et al. Control of training in middle and long-distance running by means of the individual anaerobic threshold. Int J Sports Med 1991, 12:519–524.

24) Coggan AR. Kohrt WM. Spina RJ et al. Plasma glucose kinetics during exercise in subjects with high and low lactate thresholds. J Appl Physiol 1992, 73:1873-1880.

25) Costill DL. Fink WJ. Hargreaves M et al. Metabolic characteristics of skeletal muscle during detraining from competitive swimming. Med Sci Sports Exer 1985, 17:339-343.

26) Coyle EF. Feltner M. Kautz SA. Physiological and biomechanical factors associated with elite endurance cycling performance. Med Sci Sports Exerc 1991, 23:93-107.

27) Coyle EF. Martin WH. Ehsani AA. Blood lactate threshold in some well-trained ischemic heart disease patients. J Appl Physiol 1983, 54:18–23.

28) De Fronzo RA. Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for non-insulin dependent diabetes, obesity, hypertension, dyslipidemia, and artherosclerotic cardiovascular disease. Diabetes Care 1991, 14: 173-194.

29) Denadai BS. Gomide EBG. Greco CC. The relationship between onset of blood lactate accumulation, critical velocity, and maximal lactate steady state in soccer players. J Str Cond Res 2005, 19:364-368.

30) Dengel DR. Hagberg JM. Pratley RE et al. Improvements in blood pressure, glucose metabolism, and lipoprotein lipids after aerobic exercise plus weight loss in obese, hypertensive middle-aged men. Metabolism 1998, 47:1075-1082.

31) Denis C. Fouquet R. Poty P et al. Effect of 40 weeks of endurance training on the anaerobic threshold. Int J Sports Med 1982, 3:208-214.

32) DHSSPS: Department of Health, Social Services and Public Safety (UK gov.) Start active, stay active: A report on physical activity from the four home countries' chief medical officers. July 2011. London.

33) Despres JP. Visceral obesity, insulin resistance, and dyslipidemia: contribution of endurance exercise training to the treatment of the plurimetabolic syndrome. Exerc Sport Sci Rev 1997, 25:271-300.

34) Diamant S. Shafrir E. Modulation of the activity of insulin-dependent enzymes of lipogenesis by glucocorticoids. Eur J Biochem 1975, 53(2):541-546.

35) Dimitriadis G. Leighton B. Parry-Billings M. et al. Effects of glucocorticoid excess on the sensitivity of glucose transport and metabolism to insulin in rat skeletal muscle. Biochem J 1997, 321(3):707-712.

36) Dotan R. Rotstein A. Grodjinovsky A. Effect of training load on OBLA determination. Int J Sports Med 1989, 10:346–351.

37) Duscha BD. Slentz CA. Johnson JL et al. Effects of exercise training amount and intensity on Peak Oxygen Consumption in middle-age men and women at risk for cardiovascular disease. Chest 2005, 128:2788-2793.

38) Eckel RH. The metabolic syndrome. Lancet 2005, 365:1415-1428.

39) Edwards AM. Clark N. Macfadyen AM. Lactate and ventilatory thresholds reflect the training status of professional soccer players where maximum aerobic power is unchanged. J Sports Sci Med 2003, 2:23-29.

40) Eriksson J. Tuominen J. Valle T et al. Aerobic endurance exercise or circuit-type resistance training for individuals with impaired glucose tolerance. Horm Metab Res 1998, 30:37-41.

41) Farrell PA. Wilmore J.H. Coyle EF et al. Plasma lactate accumulation and distance running performance. Med Sci Sports Exerc 1979, 11:338-349.

42) Faude O. Kindermann W. Meyer T. Lactate Threshold Concepts. How valid are they? Sports Med 2009, 39:469-490.

43) Filipovsky J. Dicimetiere P. Eschwege E. et al. The relationship of blood pressure with glucose, insulin, heart rate, free fatty acids and plasma cortisol levels according to degree of obesity in middle-aged men. J Hypertens 1996, 14(2):229-235.

44) Friedman JE. Yun JS. Patel YM. et al. Glucocorticoids regulate the induction of phosphonolpyruvate carboxykinase gene transcription during diabetes. J Biol Chem 1993, 268(17): 12952-12957.

45) Frohlich L. Urhausen A. Seul U. The influence of low- carbohydrate and high carbohydrate diets on the individual anaerobic threshold. Leistungs sport 1989, 19:18–20.

46) Gabriel H. Kindermann W. The acute immune response to exercise: what does it mean? Int J Sports Med 1997, 18:S28-45.

47) Gibala MJ. Little JP. Macdonald MJ et al. Physiological adaptations to low-volume, high-intensity interval training in health and disease. J Physiol 2012, 590(5):1077-1084.

48) Girman CJ. Rhodes T. Mercuri M. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Artherosclerosis Prevention Study. Am J Cardiol 2004, 93:136-141.

49) Gollnick PD. Bayly WM. And Hodgson DR. Exercise intensity, training, diet and lactate concentration in muscle and blood. Med Sci Sports Ex 1986, 18:334-340.

50) Haffner S. Taegtmeyer H. Epidemic obesity and the Metabolic Syndrome. Circulation 2003, 108:1541–1545.

51) Hafidh S. Senkottaiyan N. Villarreal D et al. Management of the Metabolic Syndrome. Am J Med Sci 2005, 330:343-351.

52) Hauner H. Entenmann G. Wabitsch M. et al. Promoting effect of glucocorticoids on the differentiation of human adipocyte precursor cells cultured in a chemically defined medium. J Clin Invest 1989, 84(5):1663-1670.

53) Heck H. Mader A. Hess G. Justification of the 4 mmol.L^{-1} lactate threshold. Int J Sports Med 1985, 6:117–130.

54) Heitkamp HC. Holdt M Scheib K. The reproducibility of the 4 mmol.L^{-1} lactate threshold in trained and untrained women. Int J Sports Med 1991, 12:363– 369.

55) Hegele RA. Monogenic forms of insulin resistance: apertures that expose the common metabolic syndrome. Trends Endocrinol Metab 2003, 14:371-377.

56) Hickson RC. Rennie MJ. Conlee RK. Effects of plasma fatty acids on glycogen utilization and endurance. J Appl Physiol 1997, 43:829-833.

57) Holden S. MacRae H. Dennid SC. et al. Effects of training on lactate production and removal during progressive exercise in humans. J Appl Physiol 1992, 75(5):1649-1656.

58) Hollmann W. Rost R. Liesen H et al. Assessment of different forms of physical activity with respect to preventive and rehabilitative cardiology. Int J Sports Med 1981, 2:67-80.

59) Holloszy JO. Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. J Appl Physiol 1984, 56:831-835.

60) Holloszy JO. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. J Biol Chem 1967, 242:2278-2282.

61) Houmard JA. Tanner CJ. Slentz CA et al. The effect of the volume and intensity of exercise training on insulin sensitivity. J Appl Physiol 2004, 96:101-106.

62) Hughes EF. Turner SC. Brooks GA. Effects of glycogen depletion and pedalling speed on anaerobic threshold. J Appl Physiol: Respirat Environ Ex Physiol 1982, 52:1598-1607.

63) Hurley BF. Hagberg JM. Allen WK et al. Effect of training on blood lactate levels during submaximal exercise. J Appl Physiol 1984, 56:1260-1264.

64) Irwin ML. Ainsworth BE. Mayer-Davis EJ. Physical activity and the multiple metabolic Syndrome in a tri-ethnic sample of women. Obes Res 2002, 10:1030-1037.

65) Itoh S. Igarashi M. Tsukada Y. et al. Nonalcoholic fatty liver with alcoholic hyalin after long-term glucocorticoid therapy. Acta Hepatogastroenterol 1977, 24(6):415-418.

66) Ivy JL. Withers RT. Van Handel PJ et al. Muscle respiratory capacity and fiber type as determinants of the lactate threshold. J Appl Physiol 1980, 48:523-527.

67) Ivy JL. Costill DL. Van Handel PJ et al. Alteration in the lactate threshold with changes in substrate availability. Int J Sports Med 1981, 2:139-142.

68) Jacobs I. Blood lactate. Implications for training and Sports Performance. Sports Med 1986, 3:10–25.

69) Jones AM. Doust JH. The validity of the lactate minimum test for determination of the maximal of the maximal lactate steady state. Med Sci Sports Ex 1998, 30:1304-1313.

70) Juneau M. Rogers F. De Santos V et al. Effectiveness of self-monitored, home-based, moderate-intensity exercise training in middle-aged men and women. Am J Cardiol 1987, 60:66-70.

71) Kahn R. Buse J. Ferrannini E et al. The metabolic syndrome: time for a critical appraisal. Joint statement form the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005; 28:2289-2304.

72) Kahn R. Metabolic syndrome-what is the clinical usefulness? Lancet 2008, 371:1892-1893.

73) Kalani M. The importance of endothelin-1 for microvascular dysfunction in diabetes. Vasc Health Risk Manag 2008, 4(5):1061-1068.

74) Karlsson J. Jacobs I. Onset of blood lactate accumulation during muscular exercise as a threshold concept. Int J Sports Med 1982, 3:190-201.

75) Katriina T. Kukkonen-Hurjula D. Borg PT. Effect of a weight maintenance program with or without exercise on the metabolic syndrome: A randomized trial in obese men. Preventitive Medicine 2005, 41:784-790.

76) Katzel LI. Bleecker ER. Rogus EM. Sequential effects of aerobic exercise training and weight loss on risk factors for coronary disease in healthy, obese middle-aged and older men. Metabolism 1997, 46:1441-1447.

77) Katzmarzyk PT. Leon AS. Wilmore JH et al. Targeting the metabolic syndrome with exercise: Evidence from the HERITAGE Family Study. Med Sci Sports Ex 2003, 35:1703-1709.

78) Katzmarzyk PT. Church T. Blair S. Cardiorespiratory fitness attenuates the effects of metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004, 164:1092-1097.

79) Keith S. Jacobs I. McLellan TM. Adaptations to Training at the Individual Anaerobic Threshold. Eur J Appl Physiol Occup Physiol 1992, 65:316-323.

80) Kindermann W. Simon G. and Keul J. The significance of the aerobic-anaerobic transition for the determination of workload intensities during endurance training. Eur J Appl Physiol 1979, 42:25–34.

81) Kissebah AH. Krakower ER. Regional adiposity and morbidity. Physiol Rev 1994, 74:761-811.

82) Knowler WC. Barrett-Connor E. Fowler SE et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002, 346:393-403.

83) Kohrt WM. O'Connor JS. Skinner JS. Longitudinal assessment of responses by triathletes to swimming, cycling, and running. Med Sci Sports Ex 1989, 21:569-575.

84) Kraus W. Houmard J. Duscha B et al. Exercise training amount and intensity effects on plasma lipoproteins: a randomised, controlled trial. N Engl J Med 2002, 347:1483-1492.

85) Kullo IJ. Hensrud DD. Allison TG. Relation of low cardiorespiratory fitness to the metabolic syndrome in middle-aged men. Am J Cardiol 2002, 90:795-797.

86) Kuo LE. Czarnecka M. Zukowska Z et al. Chronic stress, combined with a high fat/high-sugar diet, shifts sympathetic signaling toward Neuropeptide Y and leads to obesity and the Metabolic Syndrome. Ann N Y Acad Sci 2008, 1148:232-237.

87) Laaksonen DE. Lakka H-M. Salonen JT. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. Diabetes Care 2002, 25:1612-1618.

88) Laaksonen DE. Lindstrom J. Lakka TA et al. Physical activity in the prevention of type 2 diabetes. The Finnish diabetes prevention study. Diabetes 2005, 54:158-165.

89) Lakka TA. Venalainen JM. Rauramaa R et al. Relation of leisure- time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. N Engl J Med 1994, 330:1549-1554.

90) Lakka TA. Laaksonen DE. Lakka H-M et al. Sedentary life-style, poor cardiorespiratory fitness and the metabolic syndrome. Med Sci Sports Ex 2003, 35:1279-1286.

91) LaMonte MJ. Barlow CE. Jurca R et al. Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome. A prospective study of men and women. Circulation 2005, 112:505-512.

92) Lavrencic A. Salobir BG. Keber I. Physical training improves flow-mediated dilation in patients with the polymetabolic syndrome. Arterioscler Thromb Vasc Biol 2000, 20:551-560.

93) Lee I-M. Hsieh CC. and Paffenbarger Jr. RS. Exercise intensity and Longevity in men: The Harvard Alumni Study. JAMA 1995, 273:1179-1184.

94) Lemieux I. Pascot A. Coillard C et al. Hypertriglyceridemic waist- a marker of the artherogenic metabolic triad in men? Circulation 2000, 102:179-184.

95) Leon AS. Conrad J. Hunninghake DB et al. Effects of a vigorous walking program on body composition, and carbohydrate and lipid metabolism of obese young men. Am J Clin Nutr 1979, 33:1776-1787.

96) Liberopoulos EN. Mikhailidis DP. Elisaf MS. Diagnosis and management of the metabolic syndrome in obesity. Obesity reviews 2005, 6:283-296.

97) Lloyd-MacGlip SA. Nelson SM. Florin M. et al. 11β-hydroxysteroid dehydrogenase and corticosteroid action in lyon hypertensive rats. Hypertension 1999, 34(5):1123-1128.

98) Lucia A. Sanchez O. Carvajal A. Analysis of the aerobic-anaerobic transition in elite cyclists during incremental exercise with the use of electromyography. Br J Sports Med 1999, 33:178-185.

99) MacRae HS. Dennis S. Bosch AN et al. Effects of training on lactate production and removal during progressive exercise in humans. J Appl Physiol 1992, 72:1649-1656.

100) Mader A. Evaluation of the endurance performance of marathon runners and theoretical analysis of test results. J Sports Med Phys Fitness 1991, 31:1-19.

101) Mader A. Heck H. A theory of the metabolic origin of anaerobic threshold. Int J Sports Med 1986, 7:45–65.

102) Maiorana A. O'Driscoll G. Goodman C. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabetes Res Clin Pract 2002, 56:115-123.

103) Malik S. Wong ND. Franklin SS. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004, 110:1245-1250.

104) Marcelo L. Correia G. Rahmouni K. Role of leptin in the cardiovascular and endocrine complications of metabolic syndrome. Diab Obes Metab 2006, 8:603-610.

105) Mark DB. Lauer MS. Exercise capacity: the prognostic variable that doesn't get enough respect. Circulation 2003, 108:1534-1536.

106) Mathieu M. Brochu M. Beliveau L. DiabetAction: Changes in physical activity practice, fitness, and metabolic syndrome in type 2 diabetic and at risk individuals. Clin J Sport Med 2008, 18:70-75.

107) McAuley KA. Williams SM. Mann JL et al. Intensive lifestyle changes are necessary to improve insulin sensitivity: a randomised controlled trial. Diabetes Care 2002, 25:445-452.

108) McGehee JC. Tanner CJ. Houmard JA. A comparison of methods for estimating the lactate threshold. J Str Cond Res 2005, 19:553-558.

109) McLellan TM. Skinner JS. The use of the aerobic threshold as a basis for training. Can J Appl Sport Sci 1981, 6:197-201.

110) McLellan TM. Cheung KSY. A comparative evaluation of the individual anaerobic threshold and the critical power. Med Sci Sports Ex 1992, 24:543-550.

111) McNaughton LR. Roberts S. Bentley DJ. The relationship among peak power output, Lactate Threshold, and Short-distance Cycling Performance: Effects of Incremental Exercise Test Design. J Str Cond Res 2006, 20;157-161.

112) McQueen MA. Exercise aspects of obesity treatment. The Ochsner J 2009, 9: 140-143.

113) Meigs JB. Epidemiology of the metabolic syndrome. Am J Manag Care 2002, 11: S283-292.

114) Meigs JB Metabolic syndrome: In search of a clinical role. Diabetes Care 2004, 227:2761–2763.

115) National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). Third report of the (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults - final report. Circulation 2002, 106:3143-3421.

116) Nesto RW. Obesity- A major component of the Metabolic Syndrome. Texas Heart Inst J 2005, 32:387–389.

117) Nieman DC. Brock DW. Butterworth D et al. Reducing diet and/or exercise training decreases the lipid and lipoprotein risk factors of moderately obese women. J Am Coll Nutr 2002, 21:344-350.

118) Ninomiya JK. L'Italien G. Criqui MH et al. Association of the metabolic syndrome with history of myocardial infarction and stroke in third national health and nutrition examination survey. Circulation 2004, 109:42-46.

119) Oberbach A. Tonjes A. Klonting N. Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. Eur J Endocrinol 2006, 154:577-585.

120) Olbrecht J. The Science of Winning. Planning, Periodizing and optimizing swim training. Swimshop, Luton, England, 2000.

121) Olefsky JM. Effect of dexamethasone on insulin binding, glucose transport, and glucose oxidation of oxidation of isolated rat adipocytes. J Clin Invest 1975, 56(6):1499-1508.

122) Oronzo LJ. Buchleitner AM. Gimenez-Perez G. et al. Exercise or exercise and diet for preventing type 2 diabetes mellitus (Review). The Cochrane Library 2009, (1).

123) Paffenbarger Jr RS. Wing AL. Hyde RT et al. Physical activity and incidence of hypertension in college alumni. Am J Epidemiol 1983, 117:245-257.

124) Pan X. Li G. Hu Y-H et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997, 20:537-544.

125) Peterson KF. Dufour S. Savage DB et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. PNAS 2007, 104(31):12587-12594.

126) Podolin DA. Munger PA. Mazzeo RS. Plasma catecholamine and lactate response during graded exercise with varied glycogen conditions. J Appl Physiol 1991, 71:427-433.

127) Poole DC. Ward SA. Gardner GW et al. A metabolic and respiratory profile of the upper limit for prolonged exercise in man. Ergonomics 1988, 31:1265-1279.

128) Quirion A. Brisson GR. Laurencelle L et al. Lactate threshold and onset of blood lactate accumulation after dietary modifications. Eur J Appl Physiol 1988, 57:192-197.

129) Reaven GM. Pathophysiology of insulin resistance in human disease. Physiol Rev 1995, 75:473-486.

130) Reaven GM. The metabolic syndrome: requiescat in pace. Clin Chem 2005, 51:931-938.

131) Rennie MJ. Winder WW. Holloszy JO. A sparing effect of increased plasma fatty acids on muscle and liver glycogen content in the exercising rat. Biochem J 1976, 156:647-655.

132) Rennie KL. McCarthy N. Yazdgerdi S et al. Association of the metabolic syndrome with both vigorous and moderate physical activity. Int J Epidem 2003, 32:600-606.

133) Ross R. Dugnone D. Jones PJH et al. Reduction in Obesity and related comorbid conditions after diet-induced weightloss or exercise-induced weightloss in men. Ann Intern Med 2000, 133:92-103.

134) Rynders CA. Weltman A. High-intensity exercise training for the prevention of type 2 diabetes mellitus. Phys Sportsmed 2014, 42(1):7-14.

135) Saltin B. Nazar K. Costill DL et al. The nature of the training response : peripheral and central adaptations to one-legged exercise. Acta Physiol Scand 1976, 96:289-305.

136) Samuel VT. Liu ZX. Qu X. et al. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J Biol Chem 2004, 279(31):32345-32353.

137) Sattar N. McConnachie A. Shaper G et al. Can metabolic syndromes usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 2008, 371:1927-1935.

138) Seppala-Lindroos A. Vehkavaara S. Hakkinen AM. et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 2002, 87(7):3023-3028.

139) Sesso HD. Paffenbarger Jr RS. Lee IM. Physical activity and CHD in men: the Harvard alumni Health Study. Circulation 2000, 102:975-980.

140) Shaper AG. Wannemethee G. Weatherall R. Physical activity and ischaemic heart disease death in middle-aged British men. Br Heart J 1991, 66:384-394.

141) Sigal RJ. Kenny GP. Wasserman DH. Physical activity/exercise and type 2 diabetes. Diabetes Care 2004, 27:2518-2539.

142) Sirotic AC. Coutts AJ. Physiological and performance correlates of prolonged, high intensity, intermittent running performance in moderately trained women team sport athletes. J Str Cond Res 2007, 21:138–144.

143) Sjodin B. Jacobs I. Onset of blood lactate accumulation and marathon running performance. Int J Sports Med 1981, 2:23-26.

144) Sjodin B. Jacobs I. Svedenhag J. Changes in onset of blood lactate accumulation and muscle enzymes after training at OBLA. Eur J Appl Physiol 1982, 49:45–57.

145) Sjodin B. Svendenhag J. Applied physiology of marathon running. Sports Medicine 1985, 2:83–99.

146) Slattery ML. Jacobs Jr DR. Leisure time physical activity and CHD death: the US Railroad Study. Circulation 1989, 79:304-311.

147) Slentz C. Duscha B. Johnson J et al. Effects of the amount of exercise on body weight, body composition and measures of central obesity. STRIDDE – A randomised controlled study. Arch Intern Med 2004, 164:31-39.

148) Slentz CA. Aiken LB. Houmard JA et al. Inactivity, exercise, and visceral fat. STRRIDE: a randomized, controlled study of exercise intensity and amount. J Appl Physiol 2005, 99:1613–1618.

149) Slentz CA. Houmard JA. Kraus WE. Modest exercise prevents the progressive disease associated with physical inactivity. Ex Sport Sci Rev 2007a, 35:18-23.

150) Slentz CA. Houmard JA. Johnson JL et al. Inactivity, exercise training and detraining, and plasma lipoproteins . STRRIDE: a randomized, controlled study of exercise intensity and amount. J Appl Physiol 2007b, 103:432-442.

151) Smutock MA. Reece PF. Kokkinos PF. Aerobic versus strength training for risk factor intervention in middle-aged men at high risk for coronary heart disease. Metabolism 1993, 42:177-184.

152) Stanley WC. Gertz EW. Wisneski JA et al. Systematic lactate kinetics during graded exercise in man. Am J Physiol Endocrinol Metab 1985, 249:E595-E602.

153) Stegmann H. Kindermann W. Schnabel A. Lactate kinetics and individual anerobic threshold. Int J Sports Med 1981, 2:160-165.

154) Stegmann H. Kindermann W. Comparison of prolonged exercise tests at the individual anaerobic threshold and the fixed anaerobic threshold of 4 mmol.L^{-1} lactate. Int J Sports Med 1982, 3:105–110.

155) Steinberg HO. Brechtel G. Johnson A et al. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. J Clin Invest 1994, 94(3):1172-1179.

156) Stenvold D. Slordahl SA. Wisloff U. Effect of exercise training on inflammatory status among people with metabolic syndrome. Metab Syndr Relat Disord 2012, 10:267-272.

157) Stern MP. Williams K. Gonzalez-Villalpando C et al. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 2004, 27:2676-2681.

158) Stone NJ. Saxon D. Approach to treatment of the patient with metabolic syndrome: Lifestyle Therapy. Am J Cardiol 2005, 96:15E-21E.

159) Tanaka K. Matsuura Y. Sumagai S et al. Relationships of anaerobic threshold and onset of blood lactate accumulation with endurance performance Eur J Appl Physiol 1983, 52:51-56.

160) Tanaka K. Watanabe H. Konishi Yet al. Longitudinal associations between anaerobic threshold and distance running performance. Eur J Appl Physiol 1986, 55:248-252.

161) Tegtbur U. Busse MW. Braumann KM. Estimation of an individual equilibrium between lactate production and catabolism during exercise. Med Sci Sports Ex 1993, 25:620-627.

162) Tokmakidis SP. Leger L. Pilianidis JC. Failure to obtain a unique threshold on the blood lactate concentration curve during exercise. Eur J Appl Physiol 1998, 77:333-342.

163) Tokmakidis SP. Zois CE. Volaklis KA. The effects of a combined strength and aerobic exercise program on glucose control and insulin action in women with type 2 diabetes. Eur J Appl Physiol 2004, 92:437-442.

164) Tooke JE. Endotheliopathy precedes Type 2 diabetes. Diabetes Care 1998, 21:2047–2048.

165) Unger RH. Lipid overload and overflow: metabolic trauma and the metabolic syndrome. Trends Endocrinol Metab 2003, 14:398-403.

166) Urhausen A. Weiler B. Coen B. Plasma catecholamines during endurance exercise of different intensities as related to the individual anaerobic threshold. Eur J Appl Physiol 1994, 69:16-20.

167) Urhausen A. Coen B. Weiler B. Individual anaerobic threshold and maximum lactate steady state. Int J Sports Med 1993, 14:134-139.

168) Walker BR. Phillips DI. Noon JP. et al. Increased glucocorticoid activity in men with cardiovascular risk factors. Hypertension 1998, 31(4):891-895.

169) Wang M. The role of glucocortoid action in the pathophysiology of the Metabolic Syndrome. Nutri & Metab 2005, 2:3.

170) Wannamethee SG. Sharper G. Lennon L et al. Metabolic Syndrome vs Framingham Risk Score for prediction of Coronary Heart Disease, Stroke, and Type 2 Diabetes Mellitus. Arch Intern Med 2005, 165:2644–2650.

171) Watkins LL. Sherwood A. Feinglos M et al. Effects of exercise and weight loss on cardiac risk factors associated with syndrome X. Arch Intern Med 2003, 163:1889-1895.

172) Weltman A. Weltman J. Rutt R et al. Percentages of maximal heart rate, heart rate reserve and VO2 peak for determining endurance training intensity in sedentary women. Int J Sports Med 1989, 10:212-216.

173) Weltman A. The blood lactate response to Exercise. Current issues in exercise science: monograph no.4. Human Kinetics, Illinois, 1995.

174) Weltman A. Seip RL. Snead D. Exercise training at and above the lactate threshold in previously untrained women. Int J Sports Med 1992, 13:257–263.

175) Weltman A. Snead D. Stein P et al. Reliability and validity of a continuous incremental treadmill protocol for the determination of lactate threshold, fixed blood lactate concentrations and VO2 max. Int J Sports Med 1990a, 11:26-32.

176) Weltman A. Snead D. Seip R. Prediction of lactate threshold and fixed blood lactate concentrations from 3200m running performance in male runners. Int J Sports Med 1987, 8:401–406.

177) Whaley MH. Kampert JB. Kohl HW. Physical fitness and clustering of risk factors associated with the metabolic syndrome. Med Sci Sports Ex 1999, 31:287-293.

178) Wilson PWF. Grundy SM. The metabolic Syndrome: Practical guide to origins and treatment: Part 1. Circulation 2003, 108:1422–1424.

179) Wing RR. Venditti EV. Jakicic JM et al. Lifestyle intervention in overweight individuals with a family history of diabetes. Diabetes Care 1998, 21:350-359.

180) Yamaoka K. Tango T. Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. BMC Medicine 2012, 10:138-149.

181) Yoshida T. Suda Y. Takeuchi N. Endurance training regimen based upon arterial blood lactate: Effects on anaerobic threshold. Eur J Appl Physiol 1982, 49:223–230.

182) Yoshida T. Effect of dietary modifications on lactate threshold and onset of blood lactate accumulation during incremental exercise. Eur J Appl Physiol 1984, 53:200-205.

183) Yoshida T. Chida M. Ichioka M et al. Blood lactate parameters related to aerobic capacity and endurance performance. Eur J Appl Physiol 1987, 56:7-11.

184) Yoshida T. Udo M. Chida M. Specificity of physiological adaptation to endurance training in distance runners and competitive walkers. Eur J Appl Physiol Occup Physiol 1990, 61:197-201.

185) Zimmet P. Boyko EJ. Collier GR. et al. Etiology of the Metabolic Syndrome: Potential role of insulin resistance, leptin resistance and other players. Ann N Y Acad Sci 1999, 892:25-44.

CHAPTER 2

REPRODUCIBILITY AND LEVELS OF BLOOD LACTATE TRANSITION THRESHOLDS IN PERSONS WITH METABOLIC SYNDROME

2.1 Abstract

Background

The optimal exercise load/intensity for exercise programs for individuals with metabolic syndrome (MetS) has not been investigated. One method of determining optimal exercise load is to measure the blood lactate transition threshold (BLTT), referred to as the anaerobic threshold (AT). This study investigated the reproducibility of BLTT testing and the consequent determination of AT via the Mader method and a modified form of the ADAPT method in patients with MetS.

Methods

Fifteen, male patients diagnosed with MetS and fifteen healthy, male participants each performed BLTT measurements on a treadmill at the same daily times on three different days. Peak oxygen consumption was also determined during testing.

Results

There was no significant difference in treadmill velocity at AT determined by the Mader method or the Modified ADAPT method within both groups ($p > 0.05$). Both methods yielded good coefficients of variation. When combining both groups, the typical error also demonstrated good reproducibility. The mean treadmill velocity at AT was higher in the healthy compared to the MetS group using both the Mader and the ADAPT method.

Regression analysis and ANCOVA demonstrated that this difference was largely due to a higher VO_2 peak in the healthy group. The study also found an association between VO_2 peak and waist circumference.

Conclusion

This study demonstrated that BLTT tests are reproducible in persons with MetS. The Modified ADAPT method may be the preferred method of determining treadmill velocity at AT since fewer factors are known to influence its determination.

2.2 Introduction

The metabolic syndrome has been identified as a major health challenge (Alberti et al. 2009; Chan et al. 2005; Wilson et al. 2003) and has been shown to be a significant predictor of cardiovascular disease (CVD) and type 2 diabetes mellitus (Meigs. 2004; Wannamethee et al. 2005; Wilson et al. 2003). In addition, the syndrome confers additional risk to those accounted for by traditional CVD scoring paradigms (Carroll et al. 2004).

Lifestyle changes, most especially following a controlled exercise program have been shown to play a major role in the therapeutic management of MetS (Carroll et al. 2004). To maximise the exercise response for any person involved with a training program (including persons with MetS), one needs to identify an individual's optimal exercise load (exercise intensity), duration of exercise and exercise frequency. While standards have been set for the last two (Wallace, 2006), it is more difficult to determine the first. Blood lactate transition thresholds have been shown to be the best indices for setting

exercise intensity (Coen et al. 1991; Coyle et al. 1983; Stegmann et al. 1982; Weltman et al. 1992; Weltman, 1995; Yoshida et al. 1982). It has been shown that an increase in physical activity is sufficient to elicit a training effect provided that the initial training intensity is at or above the anaerobic threshold (Weltman et al. 1992). It is speculated that at intensities close to100% of AT, sympathetic activity increases to a level that results in adaptive changes of regulatory hormones and muscle metabolism (Coen et al. 1991; Kindermann et al. 1979). This method of exercise intensity determination has not been applied to training programs for individuals with MetS. Optimizing exercise results for MetS patients may also be important in improving exercise adherence levels, which are low in individuals with this syndrome (Magkos et al. 2009).

Therefore, the main aim of this study was to investigate the most appropriate method of determining BLTT in persons with MetS. Most BLTT methods can be broadly classified into two categories: those using fixed blood lactate concentrations (e.g. the Mader method); and those using individualized lactate and anaerobic thresholds (e.g. the Automatic Data Analysis for Progressive Tests (ADAPT) method). In order to use BLTT for determining the appropriate exercise intensity to be used in participants with MetS it is necessary to determine the best method for measuring BLTT in such participants, as this has not previously been attempted. In addition, since the BLTT of patients with MetS has not been measured in other studies, this investigation aimed to determine the BLTT of such patients. Furthermore, the study aimed to assess the variables that most strongly correlate with VO_2 peak and AT.

2.3 Methods

The Human Ethics Committee of the University of the Witwatersrand, Gauteng, accepted the study protocol (MO61104).

2.3.1 Participants and definition of metabolic syndrome

Fifteen male patients diagnosed with MetS and fifteen healthy participants each performed three BLTT tests. All healthy participants were age-matched with the patient group and had one or no components of MetS. Patients were diagnosed with MetS by clinicians using the harmonised guidelines (Alberti, 2009). The presence of any 3 of the 5 criteria denoted below constituted a diagnosis of MetS: waist circumference ($\geq$94 cm); triglycerides ($\geq$1.7 mmol.L^{-1}) or drug treatment for high triglycerides; HDL-cholesterol (<1.0 mmol.L^{-1}) or drug treatment for reduced HDL-cholesterol; elevated blood pressure ($\geq$ 130/85) or on anti-hypertensive drug treatment; elevated fasting glucose ($\geq$ 5.6 mmol.L^{-1}) or drug treatment for glucose intolerance.

2.3.2 Measurements

All participants underwent an oral glucose tolerance test (OGTT) for the detection of undiagnosed diabetes. Fasting and two hour plasma glucose levels were measured using a glucose oxidase method (Roche Diagnostics, Mannheim, Germany) whilst fasting serum triglyceride, total cholesterol and HDL-cholesterol levels were assayed using enzymatic assay methods (Roche Diagnostics, Mannheim, Germany).

The following were determined on the first day of laboratory testing: height (measured to the nearest millimetre by a Seca Stadiometer [Hamburg, Germany]); body mass (measured to the nearest gram by a Charder electronic scale [Taiwan, China]); waist circumference (taken as the greatest reading around the girth, midway between lateral lower ribs and the iliac crests); blood pressure (measured by a Honsun sphygmomanometer [Shanghai, China]; sitting; average of two readings) and a BLTT test was performed and the time of day was noted.

2.3.3 Blood lactate transition threshold (BLTT) test

The BLTT test was repeated at the same time of day a total of three times, with one day rest in between tests. As in the study of Heitcamp et al. (1991), participants did not vary their usual dietary habits, exercise or leisure time activities between the three tests. All participants did not exercise for 12 hours before the testing sessions. The BLTT test used an initial treadmill speed of 2.5 kph at a 5% gradient with speed increments of 0.5 kph every 4 minutes. (This was within the recommended 4-7 minute period for steady state to be attained). The treadmill speed was modified depending on the response of a participant to ensure the collection of at least six blood samples for lactate analysis (i.e. if the blood lactate value remained low after 3 workloads, the speed was increased by 1 kph). After signalling impending exhaustion, participants were encouraged to continue to complete the 30 seconds period already begun.

Electrocardiographic responses and oxygen consumption (VO_2) were measured at the same time (Cortex Biophysik Metalyzer 3b CPX system, Leipzig, Germany). The

electrocardiogram (ECG) was used to monitor electrocardiographic responses during testing of the participants. Testing was stopped if any ECG abnormalities were observed. VO_2 at exhaustion was recorded as the VO_2 peak. No abnormalities in ECG readings were observed. This protocol was designed taking into consideration the low level of physical conditioning of patients with MetS.

Lactate concentration was measured from whole-blood samples taken from the fingertip using the Lactate Scout automated analyser (Lactate Scout, SensLab, Leipzig). The error of measurement for repeated measures on the same blood sample using the Lactate Scout is 0.5 $mmol.L^{-1}$ (Tanner et al. 2010). Blood samples (collected from finger capillary vessels using a lancet) were taken at the end of each 4 minute exercise period within 30 – 40 seconds of the participants standing still on the treadmill. The fingertip was first wiped with water to remove the sweat and then it was dried before the blood sample was collected. The participant continued exercising within one minute of standing.

2.3.4 Determination of the BLTT

The BLTT that was determined for each participant will be defined in this study, for purposes of terminology, as Anaerobic Threshold (AT). AT, in this study, will be defined as the workload (treadmill velocity given as $km.h^{-1}$) marked by a rapid rise in blood lactate denoting the upper limit of equilibrium between lactate production and clearance (Bourdon, 2000). The treadmill velocity at AT for each BLTT test was determined using two methods: the Mader method and the ADAPT method, as these are the two most frequently used and recognised methods for assessing AT.

The Mader method determines AT as the workload that corresponds to the fixed blood lactate level of 4 mmol.L^{-1} (Mader et al. 1986). This was calculated using the Lactate Scout software. The software fits the data with a third degree polynomial regression curve and then determines the velocity at 4 mmol.L^{-1} blood lactate

The ADAPT method determines AT from the individual shape of the velocity – blood lactate curve (not from a fixed blood lactate concentration). The ADAPT method is based on the Dmax $_{mod}$ method (Cheng et al. 1992). It determines AT by calculating the workload corresponding to the greatest perpendicular distance from a regression curve relating workload to blood lactate and a straight line formed by the first and last points of the curve. When using the ADAPT method the Australian Sports Commission modified the Dmax $_{mod}$ analysis by defining the first point as the workload preceding a 0.4mmol.L^{-1} rise in blood lactate above the baseline (Bourdon, 2000). However the use of a particular data point on the curve to determine the first point is artificial and arbitrary, and this study re-defined this point as the lowest point on the curve. This point was then connected to the last point of the curve which was defined as the lactate concentration measured at VO_2 peak (Fig.1). The modified ADAPT method used in this study allows for a consistent and reproducible first and last point of the curve. A two phase exponential regression was fitted to the data points in our modification of the ADAPT method (GraphPad Prism Version 3.02) (Fig.1). The regression curves fitted to our data yielded high correlations (R^2 = 0.9691 to 0.9995).

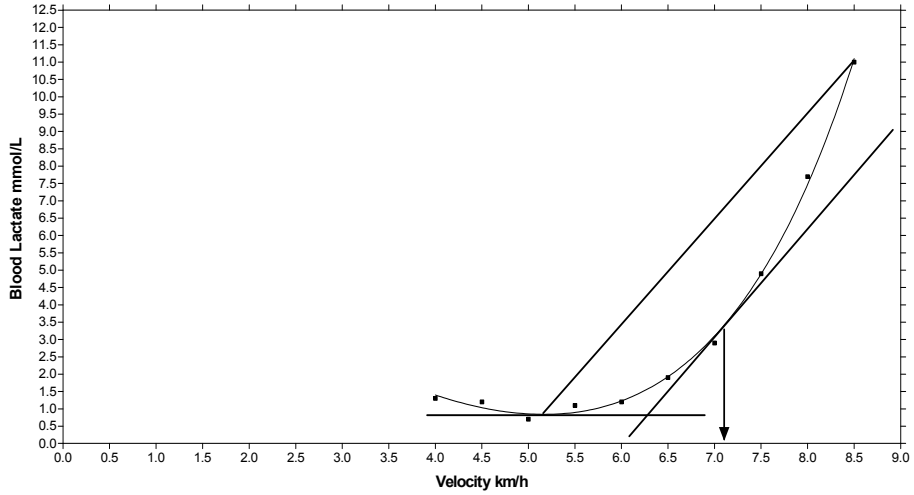


Figure 1. The modified ADAPT method, using the lactate value at VO_2 peak as the end point and the lowest point on the curve as the first point, to measure AT. The vertical line (with arrow) indicates the velocity at the point that is the greatest perpendicular distance from the curve and a straight line formed by the end and the lowest points of the curve.

The % VO_2 peak at AT was calculated by first determining the VO_2 at AT. This was determined in the same way described above (ADAPT method), but with VO_2 on the x-axis as opposed to velocity. The VO_2 at AT was then expressed as a percentage of VO_2 peak. The % VO_2 peak was calculated using the ADAPT method, since no significant difference was found between the two methods and and the ADAPT method was going to be used in study 2 of the thesis.

2.4 Statistical analysis

Data distribution was analysed using Shapiro-Wilk's W test, and any variables that were found to be significantly skewed were log transformed to normality i.e. $p>0.05$ by Shapiro-Wilk's W test. Coefficients of variation [CV = (SD / MEAN) x 100] were

calculated between testing sessions for the two groups. We confirmed our findings by also using the typical error technique as reported by Hopkins (Hopkins, 2000).

The Bland – Altman method was used to assess agreement between the Mader and modified ADAPT methods. The average values of the two groups were compared using the independent t statistic. Pearson correlation analyses were used to determine the principal correlates of the VO_2 peak and the AT. Variables that gave a $p<0.10$ in the univariate analyses were then used as independent variables in two separate multiple regression models in which VO_2 peak and AT were the dependent variables. Collinearity was assessed by calculating the variance inflation factors (VIFs) and variables with a VIF>10 were excluded from the initial regression models. Backward, stepwise regression analysis was then performed until only variables with $p<0.05$ remained in the model. One-way ANOVA and ANCOVA were then used to confirm the data from the regression models. The results of the multiple regression models were the same for AT measured using the ADAPT or Mader methods.

2.5 Results

2.5.1 Participants

Table 2 depicts the physical characteristics of the participants. There were significant differences between the groups in waist circumference, high-density lipoprotein, triglycerides, systolic blood pressure and VO_2 peak. Fasting and 2 hour glucose levels, total cholesterol, diastolic blood pressure, body mass and age were not significantly different between the groups. No undiagnosed diabetic participants were detected.

The percentage of VO_2 peak associated with AT was 73.4 ± 7.8% in the group with MetS, and 75.8 ± 8.8% in the group without MetS. This difference was not significant ($p > 0.05$).

Table 2 Mean ± SD levels of the physical characteristics of study participants

PARAMETER	**METABOLIC SYNDROME (N=15)**	**HEALTHY (N=15)**
Age (Yrs)	43.5 ± 7.52	44.1 ± 6.08
Body Mass (kg)	103.3 ± 13.93	94.2 ± 15.22
Body Mass Index ($kg.m^{-2}$)	32.1 ± 3.2	29.2 ± 4.5
Waist Circumference (cm)	112.4 ± 8.43	102.3 ± 12.37*
Serum High Density Lipoprotein ($mmol.L^{-1}$)	0.9 ± 0.19	1.1 ± 0.18*
Serum Triglycerides ($mmol.L^{-1}$)	1.87 ± 0.45	1.38 ± 0.55*
Serum Total Cholesterol ($mmol.L^{-1}$)	5.72 ± 1.41	5.63 ± 1.07
Systolic Blood Pressure (mmHg)	135.8 ± 12.02	122 ± 10.34*
Diastolic Blood Pressure (mmHg)	86.7 ± 5.34	82.7 ± 7.06
Fasting Plasma Glucose ($mmol.L^{-1}$)	5.2 ± 0.6	5.0 ± 0.3
Two Hour Plasma Glucose ($mmol.L^{-1}$)	5.3 ± 1.5	5.2 ± 1.1
VO_2 Peak ($ml.min^{-1}.kg^{-1}$)	30.3 ± 6.6	42.7 ± 11.3*

*$p < 0.05$ versus metabolic syndrome

2.5.2 Comparison of the Mader and modified ADAPT method

There was no significant difference ($p > 0.05$) in velocity at AT determined by the Mader method or the modified ADAPT method, in both participant groups. Both methods of determining velocity at AT yielded good (< 4%) coefficients of variation (CV). There was no statistical difference between the coefficients of variation of the two groups (Table 3).

Table 3 Mean ± SD and coefficient of variation (CV) for velocity at anaerobic threshold (AT)

	METABOLIC SYNDROME (N=15)		**HEALTHY (N=15)**	
	Mader Method	***Modified Adapt Method***	***Mader Method***	***Modified Adapt Method***
Coefficient of Variation (%)	2.61	3.52	2.97	3.44
Mean of Velocity at AT (km.h^{-1})	6.78 ± 0.19*	5.87 ± 0.21*	8.62 ± 0.26	7.89 ± 0.26

*p<0.05 versus healthy males

The healthy males attained a significantly higher velocity at AT than that attained by the males with MetS for both the Mader method ($P < 0.05$) and the modified ADAPT method ($P < 0.05$) (Table 3).

Our findings of good reproducibility were confirmed when we used an alternate method of calculating reproducibility i.e. the typical error technique reported by Hopkins (Hopkins, 2000), which gave values of 3.1%; 0.29km.h^{-1} and 4%; 0.27km.h^{-1} for the Mader and modified ADAPT methods respectively. The Bland-Altman plot was used for determining the level of agreement between the 2 methods (Fig. 2) and demonstrated that the Mader method gave a higher value than ADAPT, with a mean difference of 0.82 ± 0.37 km.h^{-1} (p=0.03).

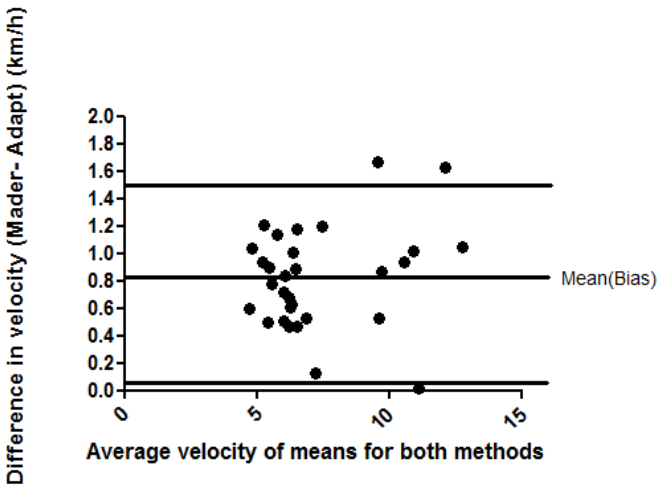


Figure 2. Bland Altman comparison between the Mader method and the modified ADAPT technique (data for the two groups of participants have been combined). The two horizontal lines depict the 95% limits of agreement (from 0.09 to 1.55), with a mean difference of 0.82 ± 0.37 km.h^{-1} (p=0.03).

In addition, this study found a close exponential relationship between treadmill speed and plasma lactate concentration using a two-phase exponential regression fit to the blood lactate values (R^2 = 0.96 to 0.99).

2.5.3 Determinants of VO_2 peak and the AT

Pearson correlation analysis demonstrated that the VO_2 peak and the AT both correlated with each other and with the following variables: BMI, body mass, waist circumference, diastolic and systolic blood pressure and 2 hour plasma glucose levels. These variables, as well as coding variables for the presence/absence of metabolic syndrome, were then included as independent variables in two separate backward, stepwise regression models in which VO_2 peak and AT were the dependent variables. In both models, BMI and waist had a VIF>10 and therefore BMI was excluded from each of the initial regression models. In the first regression model, waist circumference and metabolic syndrome were found to correlate with VO_2 peak (see Table 4). These data suggest that the lower VO_2 peak of participants with metabolic syndrome is associated with their higher waist circumference. This was confirmed in an ANCOVA comparing VO_2 peak between the 2 participant groups, where waist circumference was added as a covariate. This attenuated the F-value from 11.4 to 4.34 and the p-value from 0.002 to 0.05. In the second regression model, body mass and VO_2 peak were found to correlate with AT (see Table 4). This suggests that the lower AT of participants with the metabolic syndrome may be due to differences in body mass and/or VO_2 peak. This hypothesis was tested by comparing AT in control and metabolic syndrome patients using ANCOVA adjusted for either mass or VO_2 peak. Adjusting for body mass attenuated the F value from 7.49 to 4.46 and the p-value from 0.01 to 0.04, whereas adjusting for VO_2 peak attenuated the F-value to 0.0006 and the p-value to 0.98. This demonstrates that the lower AT values in participants with the metabolic syndrome is largely associated with their lower VO_2 peak levels.

Table 4 Results of backward, stepwise multiple regression analyses for isolating principle determinants of VO_2 peak and anaerobic threshold (AT)

REGRESSION MODEL NUMBER	DEPENDENT VARIABLE	INDEPENDENT VARIABLES WITH STANDARDISED BETA COEFFICIENT (P-VALUE)	R^2 FOR FULL MODEL (P-VALUE)
1	VO_2 peak (log)	Waist: -0.82 (<0.0001) Metabolic syndrome†: -0.22 (0.02)	0.85 (<0.0001)
2	Anaerobic threshold (log)	Mass: -0.61 (<0.0001) VO_2 peak (log): 0.38 (0.007)	0.84 (<0.0001)

†Presence of the metabolic syndrome was coded as 1 and absence was coded as 0

2.6 Discussion

The MetS group in this study had higher waist circumference; higher triglyceride levels and lower HDL-cholesterol levels when compared to the healthy group. These results agree with the definition used in this study to classify MetS.

Considering body mass and age were not different between the two groups, the lower VO_2 peak found in the MetS group agrees with the Kuoppio study (Lakka et al. 2003) that found directly determined VO_2 max to be lower in persons with MetS. Also, Laaksonen et al. (2002) showed that men with a VO_2 max of < 29.1 $ml.min^{-1}.kg^{-1}$ were 3 – 4 times more likely to have MetS than those with VO_2 max of ≥ 35.5$ml.min^{-1}.kg^{-1}$. The difference in VO_2 peak between the 2 groups cannot be due to the healthy group

training more than the MetS group, because all participants in the study had not exercised regularly for a minimum of 4 weeks prior to the testing.

Multiple regression analysis suggested that the lower VO_2 peak of MetS participants is associated with their higher waist circumference. This is an original finding and it highlights the importance of reducing waist circumference in individuals with MetS, in order to improve energy production and health. It is interesting to note that both longitudinal (Eisenmann et al. 2005) and cross sectional studies (Jago et al. 2010) have shown that, of all anthropometric variables measured, only waist circumference was negatively correlated with level of fitness. It is not known why waist circumference specifically influences VO_2 peak. However, waist circumference is a proxy indicator of visceral fat mass (Pouliot et al. 1994) and this body fat depot is a negative regulator of whole body insulin sensitivity (Ross, 2002) and may therefore limit glucose metabolism in skeletal muscle.

To our knowledge, no other study has shown that the velocity at AT is lower in patients with MetS and that this was largely associated with their lower VO_2 peak. This finding supports the notion of a lower level of aerobic fitness in patients with MetS, as has been demonstrated in other studies (Church, 2009; Eisenmann, 2007). Also, the higher velocity attained at AT by the healthy participants when compared to the participants with MetS, confirms the observation that persons with MetS exhibit a lower level of physical conditioning than their healthier counterparts (Lakka et al. 2003).

The percentage of VO_2 peak associated with AT (% VO_2 peak @ AT) is not significantly different in the group with MetS when compared to the group without MetS. It is believed that the % VO_2 peak @ AT and VO_2 peak are determined by different factors, with VO_2 peak being dependent on cardiovascular factors, such as cardiac output, stroke volume and the % VO_2 peak @ AT being dependent on peripheral factors such as number of mitochondria and muscle fiber type (Weltman et al. 1992; Weltman, 1995). This suggests that the MetS group had a lower performance in an index of central, cardiovascular function yet similar characteristics in peripheral muscle morphology when compared to individuals without MetS.

The Mader method of determining AT yielded good reproducibility in this study (see Table 3). Heitkamp et al. (1991) used correlation coefficients for treadmill speed, and also found good reproducibility of AT at 4 $mmol.L^{-1}$ for the Mader method. Coefficients of variation for velocity at AT determined by the modified ADAPT method in our study were not different to those yielded by the Mader method (Table 3).

The advantage of the ADAPT method is that it calculates AT from the shape of the lactate-work intensity curve. Frohlich et al. (1989) found that nutritional factors (glycogen depletion as a result of dietary or training manipulations) did not alter the shape nor the slope of the lactate- work intensity curve. In contrast, nutritional and training/recovery factors will influence the calculation of AT when fixed blood lactate levels are used, as is the case with the Mader method (Bourdon, 2000). Urhausen et al. (1992) also showed that AT determined via fixed blood lactate levels in a glycogen

depleted state will overestimate endurance capacity, while this threshold determined from the shape of the lactate-workload curve is hardly changed. Furthermore, some individuals with very low levels of conditioning do not reach 4 mmol.L^{-1} lactate but one can still use the shape of their curve to determine AT. Furthermore, the Bland-Altman analysis showed that when data from the two subject groups was combined the Mader method gave a higher value for the AT compared to the ADAPT method, with a mean difference of 0.82 ± 0.37 km.h^{-1}. The Mader method uses a fixed blood lactate level of 4 mmol.L^{-1} yet mean maximal steady state exercise blood lactate values range from 3.0 to 5.5 mmol.L^{-1} (Weltman, 1995). In view of our results, it is possible that a fixed lactate level of 4 mmol.L^{-1} is too high and more studies need to be performed to determine if this fixed level of lactate is appropriate for determining AT.

The technical error of measurement (TEM: also called the standard error of measurement: $\sqrt{\Sigma di^2 / 2n}$) for AT determination using the ADAPT method has been shown to have good precision for athletes tested at the South Australian Sports Institute (TEM%= 1.5%) (Bourdon, 2000). No study has investigated the applicability of this method in the clinical environment. This study found that the modified ADAPT method can be used in the clinical environment with good reproducibility. This finding was also confirmed by the method that Hopkins (Hopkins, 2000) has set up to test reliability of data. The typical error obtained via this method also shows good reproducibility of velocity at AT using both the Mader and the modified ADAPT methods.

Swart et al. (2004) reviewed the reliability and accuracy of the Accusport and Lactate Pro portable blood lactate analysers. These researchers stated that the changes in blood lactate concentration at threshold that occur with training (approximately 0.7 mmol.L^{-1}), might be of a smaller magnitude than the level of error inherent in the portable blood lactate analysers (up to 0.35 mmol.L^{-1} at 5mmol.L^{-1} or 0.7 mmol.L^{-1} at 10 mmol.L^{-1}). This study used the ADAPT method and velocity at AT in determining BLTT, and found the level of error inherent in the Lactate Scout (0.27-0.29 km.h^{-1}) is smaller than the changes that can occur with training (0.5 – 1.6 km.h^{-1}) (Bourdon, 2000). Thus, the use of treadmill speed (work load), rather than blood lactate concentration to denote the threshold has improved the reliability of the BLTT.

The AT has been used in prescribing exercise intensity among healthy, non-athletes (Weltman et al. 1992) and among adults with cardiac disease (Coyle, 1983). As far as the authors are aware, this is the first study to investigate AT among adults with MetS. Measuring AT on a regular basis in such individuals is straight forward. The test takes only 20-30 minutes to complete and automated blood lactate analysers have made lactate measurement simple and accessible. Most patients find the VO_2 peak tests uncomfortable and difficult to perform. Lactate measurements are easier to administer because they can be performed during sub-peak exercise, and do not require highly specialized staff. In addition, regular monitoring of changes in AT motivates individuals by showing their improvement in endurance capacity as their BLTT curve shifts to the right.

Typical changes in blood lactate levels during exercise range from 1.2 mmol.L^{-1} to 11 mmol.L^{-1} for athletes (Bourdon, 2000); 5 mmol.L^{-1} in heart disease patients (Coyle et al. 1983); 8 mmol.L^{-1} in healthy subjects (Coyle et al. 1983; Weltman et al. 1992; Weltman, 1995). The changes are similar across different modes of activity (running, cycling, arm ergometer) (Weltman, 1995).

The current study shows that AT measurements can be used to establish an exercise prescription for persons with MetS. This can be accomplished by firstly asking the subject to exercise for 20 minutes at 85% of the treadmill velocity at which AT occurred. This would slowly be increased over 12 weeks to 45 minutes at 100% of the treadmill velocity at which AT occurred (if a cycle is used, watts will be used instead of velocity). The intention of using AT to prescribe exercise is to prevent an exercise load that is too small or too strenuous.

2.7 Conclusions

- This study showed that the BLTT is reproducible in persons with metabolic syndrome, and that BLTT tests can be used to set the exercise load for persons with MetS.
- The Mader and ADAPT methods of determining the AT were similarly reproducible. The ADAPT method may be preferable because fewer factors influence its determination. In addition, our modifications to the ADAPT method yielded acceptable reproducibility.

- In addition, this study found that the lower VO_2 peak and velocity at AT in individuals with MetS was associated with a greater waist circumference and a lower VO_2 peak respectively.

2.8 References

1) Alberti KG. Eckel RH. Grundy SM et al. Harmonizing the Metabolic Syndrome. Circulation 2009, 120:1640-1645.
2) Bourdon P. Blood Lactate Transition Thresholds: Concepts and Controversies. In: Gore CJ, Physiological Tests for Elite Athletes. Human Kinetics, Illinois, 2000:50-65.
3) Carroll S. Dudfield M. What is the relationship between exercise and Metabolic Abnormalities? A review of Metabolic Syndrome. Sports Med 2004, 34:371 – 418.
4) Chan NN. Kong APS. Chan JCN. Metabolic Syndrome and Type 2 Diabetes: The Hong Kong Perspective. Clin Biochem Rev 2005, 26:51–57.
5) Cheng B. Kuipers H. Snyder A. A new approach for the determination of ventilatory and lactate thresholds. Int J Sports Med 1992, 13:518–522.
6) Church T. The low-fitness phenotype as a risk factor: more than just being sedentary? Obesity 2009, 17:S39–42.
7) Coen B. Schwarz L. Urhausen A et al. Control of training in middle and long-distance running by means of the individual anaerobic threshold. Int J Sports Med 1991, 12:519–524.

8) Coyle EF. Martin WH. Ehsani AA. Blood lactate threshold in some well-trained ischemic heart disease patients. J Appl Physiol 1983, 54:18–23.

9) Eisenmann JC Wickel EE Welk GJ et al. Relationship between adolescent fitness and fatness and cardiovascular disease risk factors in adulthood: the Aerobics Center Longitudinal Study (ACLS). Am Heart J 2005, 149:46–53.

10) Eisenmann JC. Aerobic fitness, fatness and the metabolic syndrome in children and adolescents. Acta Paediatr 2007, 96:1723–1729.

11) Frohlich L. Urhausen A. Seul U. The influence of low- carbohydrate and high carbohydrate diets on the individual anaerobic threshold. Leistungs sport 1989, 19:18–20.

12) Heitkamp HC Holdt M Scheib K. The reproducibility of the 4 mmol.L^{-1} lactate threshold in trained and untrained women. Int J Sports Med 1991, 12:363–369.

13) Hopkins WG. Measures of reliability in sports medicine and science. Sports Med 2000, 30:1-15.

14) Jago R. Drews KL. McMurray RG et al. Fatness, fitness, and cardiometabolic risk factors among sixth-grade youth. Med Sci Sports Exerc 2010, 42:1502–1510.

15) Kindermann W. Simon G. Keul J. The significance of the aerobic-anaerobic transition for the determination of workload intensities during endurance training. Eur J Appl Physiol 1979, 42:25–34.

16) Laaksonen DE. Lakka HM. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of metabolic syndrome. Diabetes Care 2002, 25:1612-1618.

17) Lakka TA. Laaksonen DE. Sedentary life-style, poor cardiorespiratory fitness and metabolic syndrome. Med Sci Sports Exerc 2003, 35:1279–1286.

18) Mader A. Heck H. A theory of the metabolic origin of anaerobic threshold. Int J Sports Med 1986, 7:45–65.

19) Magkos F. Yannakoulia M. Chan JL et al. Management of metabolic syndrome and type 2 diabetes through lifestyle modification. Annu Rev Nutr 2009, 29:223-256.

20) Meigs J. Metabolic syndrome: In search of a clinical role. Diabetes Care 2004, 227:2761–2763.

21) Pouliot MC. Despres JP. Lemieux S et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994, 73:460–468.

22) Ross R. Aru J. Freeman J et al. Abdominal adiposity and insulin resistance in obese men. Am J Physiol Endocrinol Metab 2002, 282:E657–663.

23) Stegmann H. Kindermann W. Comparison of prolonged exercise tests at the individual anaerobic threshold and the fixed anaerobic threshold of 4 mmol.L^{-1} lactate. Int J Sports Med 1982, 3:105–110.

24) Swart J. Jennings C. Use of blood lactate concentration as a marker of training status. SA J Sports Med 2004, 16:3-7.

25) Tanner RK. Fuller KL. Ross MLR . Evaluation of three portable lactate analyzers: Lactate Pro, Lactate Scout and Lactate Plus. Eur J Appl Physiol 2010, 109:551-559.

26) Urhausen A. Kindermann W. Exercise Physiology: Performance diagnostics and training control. In: Haag H, Grupe O, Kirsch A. Sports Science in Germany. Springer, Berlin, 1992.

27) Wallace J. Principles of cardiorespiratory endurance programming. In: American College of Sports Medicine (ACSM), Resource Manual for guidelines for exercise testing and prescription, 5th edition, Lippincott Williams and Wilkins, Philadelphia, 2006:336-349.

28) Wannamethee SG. Sharper G. Lennon L et al. Metabolic Syndrome vs Framingham Risk Score for prediction of Coronary Heart Disease, Stroke, and Type 2 Diabetes Mellitus. Arch Intern Med 2005, 165:2644–2650.

29) Weltman A. Seip RL. Snead D. Exercise training at and above the lactate threshold in previously untrained women. Int J Sports Med 1992, 13:257–263.

30) Weltman A. The blood lactate response to Exercise. Current issues in exercise science: monograph no.4. Human Kinetics, Illinois, 1995.

31) Wilson PWF. Grundy SM. The metabolic Syndrome: Practical guide to origins and treatment: Part 1. Circulation 2003, 108:1422–1424.

32) Yoshida T. Suda Y. Takeuchi N. Endurance training regimen based upon arterial blood lactate: Effects on anaerobic threshold. European J Appl Physiol 1982, 49: 223–230.

CHAPTER 3

EFFECT OF EXERCISE INTERVENTION PROGRAMS ON PHYSICAL, PHYSIOLOGICAL AND BIOCHEMICAL PARAMETERS OF PERSONS WITH AND WITHOUT METABOLIC SYNDROME

3.1 Abstract

Background

Protocols for an effective exercise program for treating metabolic syndrome (MetS) have not been devised. Furthermore, MetS is a multi-faceted disease and the effect of specific exercise protocols on the different components of MetS has also not been investigated. Therefore, this study compared the effects on the components of the MetS of an exercise program that uses blood lactate transition thresholds (specifically, the anaerobic threshold (AT)) to the same measurements obtained in an exercise program (not using AT) appearing in the literature. The main aim of the study was to design an exercise program that optimized exercise responses and may thus improve metabolic characteristics in individuals with MetS.

Methods

Ten participants with MetS exercised using the walking program of Leon et al. (1979) (MetSL). Ten participants with MetS exercised using velocity at AT to set training intensities (MetSV). Ten participants without MetS also exercised using velocity at AT to set training intensities (Non-MetSV). Physical, physiological and metabolic parameters were measured in all groups before, during and after twenty weeks of exercise. Nutritional records were collected at week 0, 8 and 20 of training.

Results

BMI and waist circumference decreased significantly in all training groups with the training program using AT and the program not using AT showing similar outcomes in these variables among persons with MetS. Body mass, Velocity at AT also improved in all training groups yet body mass and VO_2 peak did not change significantly in the group without MetS. Similarly, the blood pressure response was favourable in the groups with MetS yet absent in the group without MetS. The training group with MetS that used AT was the only group to show significant, positive changes in any of the metabolic parameters (fasting serum insulin and HOMA). In addition, the training program using AT had a greater effect on the incidence of MetS than the training program not using AT.

Conclusion

An endurance exercise program using AT to set intensity is effective in eliciting favourable responses in individuals diagnosed with MetS and in reducing the incidence of MetS. The training program using AT elicited the responses with a reduced exercise frequency and intensity. It also improved insulin sensitivity which was not affected by the walking program of Leon et al. (1979). The response to the exercise program that used AT was similar in persons with MetS and in persons without MetS, except in the central cardiovascular adaptations of VO_2 peak and in the metabolic parameters of fasting insulin and the HOMA index.

3.2 Introduction

The National Cholesterol Education Program suggested body mass - loss and increased physical activity as the basis of therapy for MetS (NCEP, 2001). Yet protocols for an

effective training program for this syndrome have not been devised. Furthermore, MetS is a multi-faceted disease and the effect of specific exercise protocols on the different components of MetS have also not been investigated. Therefore, the main aim of this study is to design an exercise program that uses blood lactate transition thresholds (BLTT, specifically the anaerobic threshold (AT)) to optimize exercise responses and thus improve metabolic characteristics in individuals with MetS.

The intention of using AT is to individualize the exercise program and optimize the improvements in metabolic characteristics. The AT has been suggested as a point of optimal exercise overload (Coen et al. 1991; Sjodin et al. 1982; Yoshida et al. 1982). However, it should be noted that other studies have suggested this may not be the case (Gibala et al. 2012; Rynders et al. 2014). Exercise overload refers to exercising at a level of intensity higher than is normally performed in order to induce training adaptations. Overload is a critical principle of physical training and may need to be determined in individuals with MetS in order to influence their metabolic profile. This study will use the AT as the point of optimal exercise overload. Previous studies have not investigated the metabolic improvements that could result in persons with MetS by training at AT.

In addition, this study will ascertain how individuals with MetS respond to an exercise program that has been validated in a previous study that used obese participants (Leon et al. 1979). The responses of this group will be compared to the response of individuals with MetS using an exercise program incorporating the AT.

The hypothesis that will be tested in this investigation is that persons using AT to individualize exercise intensity will show greater beneficial changes in their MetS profile compared to individuals not using AT in their exercise program.

3.3 Methods

The Human Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa, approved the study protocol (MO61104).

3.3.1 Subject groups and definition of MetS

The study investigated three groups:

a) Ten participants with MetS exercised using the walking program of Leon et al. (1979) (Group: MetSL).

b) Ten participants with MetS exercised using velocity at AT to set training intensities (Group: MetSV).

c) Ten participants without MetS exercised using velocity at AT to set training intensities (Group: Non-MetSV).

Subjects were diagnosed with MetS by using the harmonised guidelines (Alberti, 2009). The presence of any 3 of the 5 criteria denoted below constituted a diagnosis of MetS: waist circumference ($\geq$94 cm); triglycerides ($\geq$1.7 mmol.L^{-1}) or drug treatment for high triglycerides; HDL-cholesterol (<1.0 mmol.L^{-1}) or drug treatment for reduced HDL-cholesterol; elevated blood pressure ($\geq$130/85) or on anti-hypertensive drug treatment; elevated fasting glucose ($\geq$5.6mmol.L^{-1}) or drug treatment for glucose intolerance.

Participants were recruited from a physician's (Dr. F. Fleming) medical practice and from advertisements placed in a local newspaper.

3.3.2 Measurements

Fasting blood samples were analysed by a pathology laboratory (Lancet Laboratories, Richmond, Johannesburg) as part of the diagnosis. The following baseline measurements were made on every subject before the training program commenced:

a) Blood serum concentrations of: triglycerides; HDL and total cholesterol were assayed using enzymatic assay methods (Roche Diagnostics, Mannheim, Germany), measured on the Architect i2000 Abbott autoanalyser. The LDL levels were calculated using the method of Friedewald et al. (1972).

b) An oral glucose tolerance test (OGTT) was performed in a fasting state after administering a 75 g glucose load. Fasting, 30 minute and two-hour plasma glucose levels were measured on the Architect i2000 Abbott instrument, using a glucose oxidase method (Roche Diagnostics, Mannheim, Germany). Serum insulin levels (measured on the Architect i2000 Abbott instrument using the Chemiluminescent Microparticle Immunoassay) were also measured at each time point. The HOMA-IR (Matthews et al. 1985) and insulinogenic index (Utzschneider et al. 2009) were calculated to assess insulin sensitivity and insulin secretory response, respectively.

c) Anthropometric variables: height (measured to the nearest millimetre by a Seca Stadiometer [Hamburg, Germany]); body mass (measured to the nearest gram by a Charder electronic scale [Taiwan, China]); waist circumference (taken as the greatest reading around the girth, midway between lateral lower ribs and the iliac crests).

d) Blood pressure was measured with a Honsun sphygmomanometer (Shanghai, China) in the sitting position and an average taken of two readings.

e) Peak VO_2 and heart rate were measured using the Cortex, Biophysik, Metalyzer 3b CPX on-line system (Leipzig, Germany).

The treadmill protocol was the same as the protocol reported in Chapter 2.

f) A BLTT test using the modified ADAPT method, was performed at the same time as the peak VO_2 test. The protocol was the same as that described in Chapter 2.

3.3.3 Training programs

The subjects in Group MetSL followed the walking program of Leon et al. (1979) outlined below. The program was modified to allow a five-week, instead of a two-week adaptation period. Also, the gradient was modified due to the older age-group of the participants in this study. Consequently, the training period was extended to 20 weeks instead of 16 weeks. The Leon et al. (1979) training program was chosen since it was periodized and measured outcomes of components of the metabolic syndrome that this study was also measuring.

Table 5 Protocol of the 20-week treadmill walking program (Leon et al. 1979).

Week	Day	Speed (Kph)	Duration (Min)	Elevation (% grade)
1	M	2.4	10 + 5 rest + 5	0
1	T	2.4	10 + 5 rest + 5	2
1	W	2.4	10 + 5 rest + 10	2
1	Th	2.4	10 + 5 rest +10 + 5 rest + 5	*4*
1	F	2.6	10 + 5 rest +10 + 5 rest + 5	4
2	M	2.6	10 + 5 rest +10	2
2	T	2.8	10 + 5 rest +10 + 5rest + 5	2
2	W	3.0	10 + 5 rest +10 + 5 rest +10	*4*
2	Th	3.2	15 + 5 rest +10 + 5 rest +10	4
2	F	3.4	15 + 5 rest +15 + 5 rest +15	6
3	M	3.4	15 + 5 rest +10 + 5 rest +10	4
3	T	3.6	15 + 5 rest + 15 + 5rest +15	4
3	W	3.8	20 + 5 rest + 15 + 5 rest +15	6
3	Th	4.0	20 + 5 rest + 20 + 5 rest +15	6
3	F	4.2	20 + 5 rest + 20 + 5 rest +20	6.5
4	M	4.2	20 + 5 rest + 20 + 5 rest +15	6
4	T	4.4	20 + 5 rest + 20 + 5 rest +20	6
4	W	4.6	25 + 5 rest + 20 + 5 rest +20	6.5
4	Th	4.8	25 + 5 rest + 25 + 5 rest +20	6.5
4	F	5.0	25 + 5 rest + 25 + 5 rest +25	7
5	M	5.0	25 + 5 rest + 25 + 5 rest +20	6.5
5	T	5.0	25 + 5 rest + 25 + 5 rest +25	6.5
5	W	5.1	30 + 5 rest + 25 + 5 rest +25	7
5	Th	5.1	30 + 5 rest + 30 + 5 rest +25	7
5	F	5.1	30 + 5 rest + 30 + 5 rest +30	7.5
6	M,T,W,Th,F	5.1	30 + 5 rest + 30 + 5 rest +30	7.5
7	M	5.1	30 + 5 rest + 30 + 5 rest +30	7.5
7	T	5.1	30 + 5 rest + 30 + 5 rest +30	8
7	W	5.1	30 + 5 rest + 30 + 5 rest +30	7.5
7	Th	5.1	30 + 5 rest + 30 + 5 rest +30	7.5
7	F	5.1	30 + 5 rest + 30 + 5 rest +30	8
8 - 20	M,T,W,Th,F	5.1	30 + 5 rest + 30 + 5 rest +30	8

The MetSV and Non-MetSV groups followed the 20 week program outlined below:

Table 6 The training program for groups using AT to set intensity

Week	**Duration** (min/session)	**Frequency** (sessions/week)	**Intensity** (% AnaerobicThreshold)
1	20	3	90
2	25	3	90
3	25	3	95
4	20	3	95
5	25	3	100
6	30	3	100
7	35	4	100
8	25	3	100
9	35	4	100
10	40	4	100
11	45	4	100
12	35	3	100
13	45	4	100
14	50	4	100
15	55	4	100
16	40	3	100
17	55	4	100
18	60	4	100

(Week 19)			
Day	**Duration** (min/session)	**Sessions**	**Intensity** (% Anaerobic Threshold)
1	40	1	100
2	35	1	100
3	30	1	100
(Week 20)			
Day	**Duration** (min/session)	**Sessions**	**Intensity** (% Anaerobic Threshold)
1	25	1	100
2	20	1	100
3	15	1	100

A tapering phase was used in the training program using AT to prevent fatigue from affecting post-training results and to adhere to periodization principles of exercise

prescription. Heart rate was monitored during training sessions with Polar Heart rate monitors.

Training was performed and controlled at the Technogym Wellness Centre, Bryanston, using the Technogym key system that records all training sessions. These sessions were accessed using the Technogym Wellness System Software (V7) (Technogym,Italy). Participants who had downloadable Polar heart rate monitors were able to exercise at their own training facility. Their training information was accessed from the Polar web-site (www.polarmypersonaltrainer.com).

Participants warmed-up and cooled-down at a lower exercise intensity than that set for each session for 5 minutes. The training duration and frequency of the program using AT was less than the training program not using AT. This is because training at AT is considered as quality training and needs to be limited in frequency and duration. It will be beneficial for clinical practice to have a training protocol that achieves results with a relatively low training duration and frequency.

3.3.4 Medication and Nutrition

All medications taken by the participants were recorded. No participants used any confounding medications (eg. Statins; Glucophage). All participants were given a standardised nutrition programme (Document A in Appendix). The nutrition plan was given in an attempt to get a similar energy intake across the 3 groups. The Willett food frequency questionnaire (Lee, 1996) (Document B in Appendix) in combination with a 24 hour eating record for 3 days (Document C in Appendix) were used to monitor the

energy intake of all participants. These nutritional records were taken at week 0, 8 and 20 of training. Nutritional records were analysed for caloric content using the site www.nal.usda.gov/fnic/foodcomp/search.

All baseline measurements were re-tested in all groups during weeks 12 and 20, with the BLTT, VO_2 peak test, waist circumference and body mass being measured every 4 weeks.

Exclusion criteria for the study were:

- Women
- Men younger than 25 and older than 55 years of age
- Any individuals with known cardiovascular or pulmonary disease.
- Type 1 diabetes
- Use of confounding medications

3.4 Statistical Analysis

The n per group for this study was chosen as 10. This was based on convenience and was the upper n as determined by infrastructural limitations. A *post hoc* sample size calculation based on the data shown in Table 18 (percentage change in variables for each group after 20 weeks of exercise) for waist circumference, assuming a power of 0.80 and an α of 0.05 gave an n for each group of 18. If BMI was used, the n per group was 8.

Data distribution was analysed using Shapiro-Wilk's W test, and any variables that were found to be significantly skewed were log transformed to normality. Student's t-test for paired values obtained at week 0 and week 12; and at week 0 and week 20 were used to analyse intra-group responses. Inter-group comparisons were made using an ANOVA. If the ANOVA analysis found significant differences for confounding variables, an ANCOVA analysis was performed adjusting for the confounding variable and a *post hoc* analysis was performed using a Tukey HSD test. Dunnett's test was used for comparing mean values obtained at weeks 4, 8, 12, 16 and 20 with the mean value at week 0. A level of $P< 0.05$ was set as statistically significant.

Pearson correlation analyses were used to determine the principal correlates of the % changes in VO_2 peak and AT. Variables that gave significant correlations in the univariate analyses ($p<0.1$) were then used as independent variables in two separate multiple regression models in which % change in VO_2 peak and % change in AT were the dependent variables. Backward, stepwise regression analysis was then performed until only variables with $p<0.10$ remained in the model.

The statistics package Statistica version 11 (StatSoft, Tulsa, OK, USA) was used for the statistical analysis and sample size calculations.

3.5 Results

3.5.1 Subjects

Table 7 describes the study's subject baseline characteristics. Significant intra-group differences between the Non-MetSV and MetSL groups were found for waist circumference, VO_2 peak (p=0.15 between the MetS groups), systolic blood pressure, fasting insulin, OGTT insulin level at 30 minutes and HOMA index. Fasting glucose and OGTT glucose levels at 2 hours differed between the MetSV and MetSL groups. (Table 7).

Twelve (12) participants were originally recruited in the MetSL and in the MetSV groups and 15 participants were originally recruited in the Non-MetSV group. These numbers were recruited based on an original sample size of 10 per group, to allow for drop outs. By week 12, five (5) participants dropped out of the MetSL group (n=7); 3 from the MetSV group (n=9) and 6 from the Non-MetSV group (n=9). At week 20, a further 1 dropped out from the MetSL group (n=6); 4 from the MetSV group (n=5) and 1 from the Non-MetSV group (n= 8). The reasons for drop-out were duration of sessions for MetSL group were very long (90 minutes); colds and flu; work commitments (≥4 times/week exercise could not be maintained) and birth of a child. There were participants who did not have high "readiness to change" level and dropped-out early on in the study. This highlights the need to assess psychological aspects and offer support in this area during an exercise intervention. This is a limitation of this study.

Table 7 Physical and biochemical characteristics of study participants

Parameter	Non-MetS V (n=9)	MetS V (n=9)	MetS L (n=7)
Age (years)	40.2 ± 7.90	40.8 ± 8.21	48.3 ± 7.32
Body mass (kg)	101 (15.2)	99.8 (29.6)	114 (35.1)
BMI (kg.m $^{-2}$)	31.0 (6.10)	31.8 (4.80)	33.9 (11.1)
Waist circumference (cm)	104 (13.0)	111 (11.9)	116 (27.2)*
Triglycerides (mmol.L^{-1})	1.21 (0.45)	1.70 (1.00)	1.28 (0.69)
Total cholesterol (mmol.L^{-1})	5.27 ± 1.18	5.48 ± 1.23	5.41 ±1.61
LDL (mmol.L^{-1})	3.65 ± 1.19	3.76 ± 0.95	3.65 ± 1.48
HDL (mmol.L^{-1})	1.06 (0.20)	0.90 (0.01)	1.00 (0.49)
Systolic blood pressure (mmHg)	120 ± 11.1	134 ± 14.2	144 ± 8.52**
Diastolic blood pressure (mmHg)	80.0 ± 6.61	88.3 ± 6.61	89.3 ± 9.32
Fasting glucose (mmol.L^{-1})	5.10 (0.40)	4.80 (0.60)	5.90 (0.61)†
30 min glucose (mmol.L^{-1})	7.42 ± 1.64	6.76 ± 2.38	9.16 ± 1.92
2 hour glucose (mmol.L^{-1})	6.20 (2.20)	3.80 (2.00)	7.40 (3.30)†
Fasting insulin (µU.ml^{-1})	8.51 ± 1.40	11.1 ± 4.78	14.3 ± 2.82*
30 min insulin (µU.ml^{-1})	33.9 (26.4)	73.2 (19.2)	91.3 (38.1)*
2 hour insulin (µU.ml^{-1})	31.3 (31.7)	21.9 (24.9)	84.1 (56.1)
HOMA index	1.97 (0.48)	2.32 (0.97)	3.26 (1.61)*
Insulinogenic index	24.7 ± 19.8	20.8 ± 22.6	28.9 ± 21.9
VO_2 Peak (ml.min^{-1}.kg^{-1})	33.8 ± 5.14	29.3 ± 7.07	23.5 ± 2.59*
Velocity at AT (km.h^{-1})	5.37 ± 0.70	5.27 ± 1.53	5.06 ± 0.65

Data reported as median (IQR) or mean ± SD
*p<0.05, **p<0.005 vs Non-MetSV; †p<0.05 vs MetSV. Data from ANOVA with Tukeys post hoc test.
HOMA index = glucose×insulin/22.5.
Insulinogenic index = $(Insulin_{30} – Insulin_0)/(Glucose_{30} – Glucose_0)$.

3.5.2 Intra-group comparisons

Within the Non-MetSV group (Table 8 and 9), body mass did not change significantly at any week, with the p- values near significance at weeks 8, 16 and 20 (p= 0.06 - 0.07). Waist circumference changed significantly at weeks 16 and 20, yet week 4 had a p-value

close to significance (p=0.09). As opposed to VO_2 peak that did not change significantly at any week, AT changed significantly at all weeks. The only metabolic parameter in this group that got close to a significant change was OGTT glucose level at 2 hours, at week 12 (p=0.06).

Table 8 Changes in physical and physiological parameters at weeks 4, 8, 12, 16 and 20 for Non-MetSV group

Non-MetSV	**Comparison of baseline data with weeks 4, 8 and 12 (n=9)**				**Comparison of baseline data with weeks 16 and 20 (n=8)**		
	Wk0^{+}	**Wk4**	**Wk8**	**Wk12**	**Wk0^{++}**	**Wk16**	**Wk20**
Body mass (kg)	101 (15.2)	100 (15.3)	97.6 (15.8)	97.0 (15.3)	102 (20.3)	97.6 (16)	98.0 (15.6)
BMI (kg.m^{-2})	31.0 (6.10)	-	-	29.3 (4.70)*	31.1 (5.80)	-	29.9 (4.30)*
Waist circumference (cm)	104 (13.2)	104 (10.0)	103 (10.5)	103 (8.60)	105 (13.3)	101 (12.0)*	102 (12.7)*
VO_2 peak (ml.min^{-1}.kg^{-1})	33.8 ± 5.10	34.1 ± 4.61	35.6 ± 3.82	36.3 ± 4.21	33.8 ± 5.50	35.9 ± 3.36	37.0 ± 5.32
Velocity at AT (km.h^{-1})	5.37 ± 0.74	5.91 ± 0.69*	5.95 ± 0.61*	6.22 ± 0.73*	5.30 ± 0.72	6.22 ± 0.78*	6.31 ± 0.73*
Systolic Blood Pressure (mmHg)	120 ± 11.1	-	-	123 ± 10.8	120 ± 11.8	-	120 ± 8.86
Diastolic Blood Pressure (mmHg)	80.0 ± 6.61	-	-	79.4 ± 9.50	81.3 ± 5.82	-	78.8 ± 6.41

* Significant difference at p< 0.05 level

$^{+}$ These values used in Dunnett's tests against week 4, 8 and 12; $^{++}$these values used in Dunnett's tests against weeks 16 and 20

Data reported as mean ± SD or median (IQR)

Table 9 Changes in metabolic parameters at weeks 12 and 20 for the Non-MetSV group

Non-MetSV	**Comparison of baseline and week 12 data (n=9)**		**Comparison of baseline and week 20 data (n=8)**	
	Wk0^{+}	**Wk12**	**Wk0^{++}**	**Wk20**
Triglycerides (mmol.L^{-1})	1.21 (0.45)	1.02 (0.37)	1.24 (0.45)	0.94 (0.42)
Total cholesterol (mmol.L^{-1})	5.27 ± 1.18	5.25 ± 1.23	5.03 ± 0.09	5.09 ± 1.26
LDL (mmol.L^{-1})	3.65 ± 1.19	3.72 ± 1.16	3.42 ± 1.03	3.53 ± 1.36
HDL (mmol.L^{-1})	1.06 (0.20)	1.10 (0.20)	1.05 (0.17)	1.20 (0.25)
Fasting glucose (mmol.L^{-1})	5.10 (0.40)	5.00 (0.30)	5.15 (0.50)	5.15 (0.15)
30 min glucose (mmol.L^{-1})	7.40 ± 1.64	8.07 ± 1.86	7.42 ± 1.76	7.62 ± 1.82
2 hour glucose (mmol.L^{-1})	6.20 (2.20)	4.80 (2.20)	5.95 (2.20)	5.20 (1.95)
Fasting insulin (µU.ml^{-1})	8.51 ± 1.40	8.01 ± 4.34	8.70 ± 1.37	9.26 ± 5.98
30 min insulin (µU.ml^{-1})	33.9 (26.4)	43.0 (39.1)	42.4 (31.8)	59.0 (48.0)
2 hour insulin (µU.ml^{-1})	31.3 (31.7)	15.4 (47.0)	31.9 (47.0)	34.3 (47.8)
HOMA index	1.97 (0.48)	1.65 (0.72)	1.99 (0.57)	1.96 (0.84)
Insulinogenic index	24.7 ± 19.8	16.7 ± 8.30	26.3 ± 20.5	21.4 ± 110

$^{+}$These values used in paired t-tests against week 12
$^{++}$These values used in paired t-test against week 20
Data reported as mean ± SD or median (IQR). No differences were significant
HOMA index = glucose×insulin/22.5.
Insulinogenic index = (Insulin30 –Insulin0)/(Glucose30 – Glucose0).

Results of the MetSV intra-group analysis (Table 10 and Table 11) showed significant decreases in body mass at week 4, 16 and 20, with p-values near significance (≤ 0.07) at week 8 and 12. Waist circumference also decreased significantly only at week 4, with p-values at 0.06 at weeks 8 and 12. VO_2 peak and AT changed significantly at all measurement points, except for AT at week 4 and 16 (with p-values near significance at 0.06 for both weeks) and for VO_2 peak at week 4 (with p-value near significance at 0.06). As opposed to systolic blood pressure, diastolic blood pressure changed significantly at weeks 12 and 20. The only metabolic parameters that showed a significant change in this

training group were fasting insulin and HOMA index at week 20. Changes in triglycerides (at week 20), HDL (at week 12), LDL (at week 20) and OGTT insulin level at 30 minutes (at week 20) were marginally not significant ($p \leq 0.09$).

Table 10 Changes in physical and physiological parameters at weeks 4, 8, 12, 16 and 20 for MetSV group.

MetSV	**Comparison of baseline data with weeks 4, 8 and 12 (n=9)**				**Comparison of baseline data with weeks 16 and 20 (n=5)**		
	Wk0^{+}	**Wk4**	**Wk8**	**Wk12**	**Wk0^{++}**	**Wk16**	**Wk20**
Body mass (kg)	99.8 (29.6)	97.5 (27.8)*	96.6 (31.4)	97.0 (32.2)	93.2 (15.6)	90.5 (16.2)*	90.0 (18.2)*
BMI (kg.m^{-2})	31.8 (4.80)	-	-	29.8 (5.60)*	29.4 (1.10)	-	28.5 (0.10)*
Waist circumference (cm)	111 (11.9)	110 (14.0)*	107 (10.7)	107 (11.5)	110 (18.6)	107 (14.7)	107 (14.1)
VO_2peak (ml.min^{-1}.kg^{-1})	29.3 ± 7.10	31.9 ± 6.50	33.9 ± 6.20*	36.6 ± 7.70*	33.8 ± 5.62	41.3 ± 6.90*	44.0 ± 7.60*
Velocity at AT (km.h^{-1})	5.27 ± 1.53	5.60 ± 1.19	6.03 ± 1.33*	6.09 ± 1.34*	5.94 ± 1.43	6.92 ± 2.02	6.90 ± 1.64*
Systolic Blood Pressure (mmHg)	134 ± 14.2	-	-	128 ± 9.28	132 ± 16.4	-	120 ± 23.5
Diastolic Blood Pressure (mmHg)	88.3 ± 6.61	-	-	84.1 ± 4.70*	88.1 ± 7.58	-	78.0 ± 8.37*

* Significant difference at $p < 0.05$ level

$^{+}$ These values used in Dunnett's tests against week 4, 8 and 12; $^{++}$these values used in Dunnett's test against weeks 16 and 20

Data reported as mean ± SD or median (IQR)

The MetSL training group (Table 12 and 13) showed significant changes in body mass at weeks 12, 16 and 20 (week 8 had a p-value near significance at 0.06). Waist circumference changed significantly at all weeks. VO_2 peak changed significantly at only weeks16 and 20, with week 12 at a p-value near significance (0.06). AT changed significantly at all weeks except at week 4 and 8 with the AT value at week 4 being close to significance (p=0.06). Systolic and diastolic blood pressure changed significantly at week 12 and week 20. No metabolic parameters changed in this group. Fasting glucose (week 12 and 20), fasting insulin and OGTT insulin level at 30 min (at week 12) and

HOMA (at week 12) showed p-values that were marginally not significant (p value between 0.06 and 0.08).

Table 11 Changes in metabolic parameters at weeks 12 and 20 for the MetSV group

MetSV	**Comparison of baseline and week 12 data (n=9)**		**Comparison of baseline and week 20 data (n=5)**	
	Wk0[+]	**Wk12**	**Wk0[++]**	**Wk20**
Triglycerides (mmol.L^{-1})	1.72 (1.02)	1.48 (0.73)	1.32 (1.03)	0.81 (0.35)
Total cholesterol (mmol.L^{-1})	5.48 ± 1.23	5.11 ± 1.19	5.79 ± 1.12	4.63 ± 1.04
LDL (mmol.L^{-1})	3.76 ± 0.95	3.36 ± 1.05	4.07 ± 0.77	3.19 ± 0.89
HDL (mmol.L^{-1})	0.90 (0.01)	1.00 (0.25)	0.90 (0.01)	0.95 (0.01)
Fasting glucose (mmol.L^{-1})	4.80 (0.60)	4.70 (0.50)	4.80 (0.60)	4.80 (0.50)
30 min glucose (mmol.L^{-1})	6.76 ± 2.38	7.42 ± 1.64	6.83 ± 1.28	9.16 ± 1.92
2 hour glucose (mmol.L^{-1})	3.80 (2.00)	4.60 (0.70)	3.70 (0.50)	4.50 (2.60)
Fasting insulin (μU.ml^{-1})	11.1 ± 4.78	9.23 ± 3.56	10.27 ± 1.48	7.04 ± 2.56[*]
30 min insulin (μU.ml^{-1})	73.2 (19.2)	40.8 (71.0)	74.0 (34.9)	46.9 (21.6)
2 hour insulin (μU.ml^{-1})	21.9 (24.9)	40.4 (50.4)	17.7 (7.40)	15.2 (11.1)
HOMA index	2.32 (0.97)	1.53 (1.36)	2.09 (0.48)	1.53 (0.26)[*]
Insulinogenic index	20.8 ± 22.6	13.5 ± 36.2	33.8 ± 13.9	8.54 ± 47.7

[*] Significant difference at $p < 0.05$ level
[+] These values used in paired t-tests against week 12
[++]These values used in paired t-test against week 20
Data reported as mean ± SD or median (IQR)
HOMA index = glucose×insulin/22.5.
Insulinogenic index = $(Insulin_{30} - Insulin_0)/(Glucose_{30} - Glucose_0)$.

Table 12 Changes in physical and physiological parameters at weeks 4, 8, 12, 16 and 20 for MetSL group

MetSL	Comparison of baseline data with weeks 4, 8 and 12 (n=7)				Comparison of baseline data with weeks 16 and 20 (n=6)		
	Wk0[+]	Wk4	Wk8	Wk12	Wk0[++]	Wk16	Wk20
Body mass (kg)	114 (35.1)	111 (30.7)	112 (32.5)	110 (34.2)*	112 (35.1)	105 (35.8)*	104 (34.8)*
BMI (kg.m^{-2})	33.9 (11.1)	-	-	32.0 (11.1)*	35.9 (11.1)	-	33.5 (11.4)*
Waist circumference (cm)	116 (27.2)	115 (26.1)*	114 (25.3)*	113 (27.5)*	121 (27.2)	115 (28.1)*	114 (27.0)*
VO_2peak (ml.min^{-1}.kg^{-1})	23.5 ± 2.61	26.8 ± 5.75	27.7 ± 4.62	29.2 ± 5.34	22.8 ± 2.17	29.6 ± 4.25*	30.8 ± 4.90*
Velocity at AT (km.h^{-1})	5.06 ± 0.65	5.36 ± 0.79	5.67 ± 0.64	5.93 ± 0.91*	4.91 ± 0.56	5.87 ± 0.53*	5.89 ± 0.75*
Systolic Blood Pressure (mmHg)	143 ± 8.52	-	-	130 ± 10.6*	144 ± 9.17	-	127 ± 13.3*
Diastolic Blood Pressure (mmHg)	89.3 ± 9.32	-	-	80.7 ± 9.76*	89.2 ± 10.2	-	77.5 ± 7.58*

* Significant difference at $p < 0.05$ level

[+] These values used in Dunnett's tests against week 4, 8 and 12; [++]these values used in Dunnett's tests against weeks 16 and 20

Data reported as mean ± SD or median (IQR)

Table 13 Changes in metabolic parameters at weeks 12 and 20 for the MetSL group

MetSL	Comparison of baseline and week 12 data (n=7)		Comparison of baseline and week 20 data (n=6)	
	Wk0[+]	Wk12	Wk0[++]	Wk20
Triglycerides (mmol.L^{-1})	1.28 (0.69)	1.20 (0.58)	1.25 (0.32)	1.14 (0.6)
Total cholesterol (mmol.L^{-1})	5.41 ± 1.61	5.09 ± 1.14	5.18 ± 1.64	4.84 ± 1.16
LDL (mmol.L^{-1})	3.65 ± 1.48	3.38 ± 1.04	3.45 ± 1.52	3.08 ± 0.94
HDL (mmol.L^{-1})	1.00 (0.49)	1.01 (0.55)	1.10 (0.49)	1.13 (0.60)
Fasting glucose (mmol.L^{-1})	5.90 (0.60)	5.00 (1.00)	5.90 (0.50)	5.00 (1.40)
30 min glucose (mmol.L^{-1})	9.16 ± 1.92	8.39 ± 1.99	9.47 ± 1.97	8.89 ± 1.53
2 hour glucose (mmol.L^{-1})	7.40 (3.90)	5.25 (3.70)	7.40 (3.60)	6.30 (1.20)
Fasting insulin (μU.ml^{-1})	14.3 ± 2.82	10.3 ± 4.12	14.7 ± 2.93	11.4 ± 5.29
30 min insulin (μU.ml^{-1})	91.3 (38.1)	60.7 (15.2)	95.4 (8.40)	99.0 (16.4)
2 hour insulin (μU.ml^{-1})	84.1 (56.1)	35.6 (46.8)	81.9 (49.8)	69.5 (55.4)
HOMA index	3.26 (1.61)	2.29 (0.82)	3.82 (1.61)	2.04 (0.89)
Insulinogenic index	28.9 ± 21.9	33.6 ± 42.4	30.8 ± 24.1	28.7 ± 17.7

[+]These values used in paired t-tests against week 12

[++]These values used in paired t-test against week 20

Data reported as mean ± SD or median (IQR). No differences were significant.

HOMA index = glucose×insulin/22.5. Insulinogenic index = $(Insulin_{30} - Insulin_0)/(Glucose_{30} - Glucose_0)$.

3.5.3 Absolute changes in body mass

Table 14 Absolute changes in body mass (kg) (Mean ± SD) compared to week 0

Group	**Week 12**	**Week 20**
Non-MetSV	-3.10 ± 3.60	-3.26 ±3.82
MetSV	-2.18 ±3.06	-4.12 ±1.83
MetSL	-8.79 ±6.57	-1.05 ±6.81

The MetSL group showed the greatest absolute change in body mass (Table 14). ANOVA analysis did not find any significant differences between the 3 groups in absolute changes in body mass at week 12 or at week 20 (F=3.22, p=0.06 at week 12; F=2.18, p=0.15 at week 20).

3.5.4 Inter-group comparison of the % change in variables from week 0 to week 12.

Analysis of the comparison of the % change in variables from week 0 to week 12 across the 3 study groups is depicted in Table 15. This data compares ANOVA results with the respective ANCOVA, after adjustment for % change in body mass. The % change in body mass across the groups just missed significance (p=0.07, Table 15) however it was still included in the ANCOVA as a precautionary measure. It was found to not substantially affect any of the ANOVA results (see Table 15). Table 16 shows the results of the *post hoc* analysis of the ANCOVA data.

The MetSL group showed the greatest decrease in systolic blood pressure (8.8%) (Table 16). Although systolic blood pressure also decreased in the MetSV group, the % change

was only significantly different between the Non-MetSV and MetSL groups (Table 16). The only other significant change during this period was the % change in OGTT glucose level at 2 hours (Table 16). This value increased in the MetSV group and was significantly different to the decrease that occurred in the Non-MetSV and the MetSL groups. Body mass decreased in all groups during this period (2% in the MetSV group, 3.1% in the Non-MetSV group and 6.8% in the MetSL group), however the *post hoc* analysis showed no significant differences between the groups (Table16).

Table 15 ANOVA and ANCOVA results for comparison of percent change in data from week 0 to week 12 across the three subject groups.

Variables	**Results of ANOVA**	**Results of ANCOVA (adjusted for body mass)**
Body mass (kg)	2.80 (0.07)	
BMI (kg.m^{-2})	2.43 (0.11)	
Waist circumference (cm)	2.02 (0.16)	
Triglycerides (mmol.L^{-1})	0.06 (0.94)	0.04 (0.96)
Total Cholesterol (mmol.L^{-1})	0.20 (0.82)	0.28 (0.76)
LDL (mmol.L^{-1})	0.84 (0.44)	0.82 (0.46)
HDL (mmol.L^{-1})	1.38 (0.28)	1.20 (0.32)
Systolic Blood Pressure (mmHg)	**5.66 (0.01)**	**4.28 (0.01)**
Diastolic Blood Pressure (mmHg)	1.78 (0.19)	1.85 (0.18)
Fasting glucose (mmol.L^{-1})	2.30 (0.13)	2.16 (0.14)
30 min glucose (mmol.L^{-1})	0.72 (0.50)	0.69 (0.51)
2 hour glucose (mmol.L^{-1})	**7.07 (0.01)**	**6.93 (0.02)**
Fasting insulin (µU.ml^{-1})	0.78 (0.47)	0.72 (0.5)
30 min insulin (µU.ml^{-1})	0.6 (0.56)	0.8 (0.46)
2 hour insulin (µU.ml^{-1})	2.58 (0.10)	2.56 (0.10)
HOMA index	0.5 (0.61)	0.41 (0.67)
Insulinogenic index	0.39 (0.68)	0.37 (0.70)
VO_2 Peak (ml.min^{-1}.kg^{-1})	1.97 (0.17)	2.18 (0.14)
Velocity at AT (km.h^{-1})	0.24 (0.79)	0.20 (0.82)

Data is given as F-value (p-value); figures in bold are those showing significant trends. See Table 16 for results of *post hoc* analysis of ANCOVAs
HOMA index = glucose×insulin/22.5.
Insulinogenic index = $(Insulin_{30} – Insulin_0)/(Glucose_{30} – Glucose_0)$.

Table 16 Comparison of Week 0 vs Week 12 percent change data across the three subject groups

Variables	Non-MetS V (n=9)	MetS V (n=9)	MetS L (n=7)
Body mass	-3.05 (-5.14)	-2.0 (-2.52)	-6.79 (-10.4)
BMI	-2.60 (-6.09)	-2.05 (-2.38)	-6.93 (-10.6)
Waist circumference	-2.15 ± 2.64	-2.11 ± 2.87	-4.57 ± 2.64
Triglycerides	-13.1 ± 30.9	-8.37 ± 39.9	-7.49 ± 32.6
Total Cholesterol	0.08 ± 13.7	-4.92 ± 18.7	-2.96 ± 17.7
LDL	3.87 ± 18.3	-8.98 ± 20.7	1.76 ± 24.6
HDL	-3.85 (-7.69)	14.6 (6.74)	0 (-4.17)
Systolic Blood Pressure	2.97 ± 6.75	-3.69 ± 6.37	-8.76 ± 8.06*
Diastolic Blood Pressure	-0.31 ± 12.8	-4.56 ± 5.0	-9.32 ± 8.84
Fasting glucose	-3.85 (-5.56)	-2.08 (-6.52)	-7.41 (-18.6)
30 min glucose	6.17 (2.70)	-5.80 (-24.6)	-12.4 (-23.2)
2 hour glucose	-12.9 ± 16.7	16.9 ± 23.6*	-22.7 ± 25.8**
Fasting insulin	-7.04 (-29.1)	-25.2 (-37.6)	-30.1 (-43.6)
30 min insulin	-3.83 (-49.8)	-44 (-55.1)	-28.7 (-36.4)
2 hour insulin	-23.5 (-41.7)	98.6 (16.7)	-53.6 (-76.4)
HOMA index	-13.2 (-30.7)	-20.7 (-34.9)	-30.1 (-51.7)
Insulinogenic index	-21.2 (-62.7)	-38.6 (-148)	-17.6 (-38.3)
VO_2 Peak	11.1 (6.67)	18.8 (10.3)	15.5 (11.9)
Velocity at AT	22.2 (15.8)	10.4 (8.33)	17.4 (11.2)

Data reported as % change and as mean ± SD or median (IQR):*p<0.05 vs Non-MetS V; **p<0.005 vs MetS V; data from ANCOVA with adjustment for % change in body mass.
HOMA index = glucose×insulin/22.5.
Insulinogenic index = $(Insulin_{30} - Insulin_0)/(Glucose_{30} - Glucose_0)$.

3.5.5 Inter-group comparison of the % change in variables from week 0 to week 20.

ANOVA and ANCOVA results for the comparison of the % change in variables between week 0 and week 20 is depicted in Table 18. Both body mass and BMI showed significant trends across the groups and therefore body mass was adjusted for in the ANCOVAs (Table 17). Adjustment for BMI showed very similar effects (data not shown). Adjusting for % body mass changes had minimal effects on any of the ANOVA data (Table 17).

Table 18 shows the results of the *post hoc* analysis of the ANCOVA for the week 0 to week 20 % change data. Body mass decreased in all groups with the highest decrease occurring in the MetSL group (8.7%) and this group was the only group that changed significantly when compared to the Non-MetSV group (Table 18). Similar results were observed for the % change in BMI and the same trend was also shown for systolic and diastolic blood pressures, with a significant difference in % change across the Non-MetSV and MetSL groups. The greatest change in systolic and diastolic blood pressure occurred in the MetSL group (11.9% and 12.6% respectively) (Table18). VO_2 peak increased by 35.3% in the MetSL group; 30.5% in the MetSV group and by 10.7% in the Non-MetSV group. The change was only significant across the Non-MetSV and MetSL groups (Table 18). Percentage change in OGTT insulin level at 30 minutes decreased only in the MetSV group and the % change was near significance across the Non-MetSV and MetSL groups ($p=0.07$) (Table 18).

Table 17 ANOVA and ANCOVA results for comparison of the percent change in data from week 0 to week 20 across the three subject groups

Variables	Results of ANOVA	Results of ANCOVA (adjusted for body mass)
Body mass (kg)	**3.88 (0.04)**	
BMI (kg.m^{-2})	**3.88 (0.04)**	
Waist circumference (cm)	1.87 (0.19)	
Triglycerides (mmol.L^{-1})	1.27 (0.31)	1.14 (0.35)
Total Cholesterol (mmol.L^{-1})	2.01 (0.17)	1.95 (0.18)
LDL (mmol.L^{-1})	1.63 (0.23)	1.63 (0.23)
HDL (mmol.L^{-1})	1.15 (0.34)	0.92 (0.42)
Systolic Blood Pressure (mmHg)	**3.59 (0.05)**	**5.20 (0.04)**
Diastolic Blood Pressure (mmHg)	**3.96 (0.04)**	**6.45 (0.03)**
Fasting glucose (mmol.L^{-1})	1.38 (0.29)	0.86 (0.45)
30 min glucose (mmol.L^{-1})	0.42 (0.67)	0.47 (0.64)
2 hour glucose (mmol.L^{-1})	0.83 (0.46)	0.64 (0.54)
Fasting insulin (µU.ml^{-1})	0.18 (0.84)	0.22 (0.81)
30 min insulin (µU.ml^{-1})	3.14 (0.07)	3.12 (0.08)
2 hour insulin (µU.ml^{-1})	0.12 (0.89)	0.11 (0.90)
HOMA index	0.01 (0.99)	0.02 (0.98)
Insulinogenic index	0.13 (0.88)	0.18 (0.84)
VO_2 Peak (ml.min^{-1}.kg^{-1})	**4.85 (0.03)**	**3.95 (0.02)**
Velocity at AT (km.h^{-1})	0.31 (0.74)	0.61 (0.56)

Data is given as F-value (p-value); figures in bold are those showing significant trends. See Table 18 for results of *post hoc* analysis of ANCOVAs

HOMA index = glucose×insulin/22.5.

Insulinogenic index = $(Insulin_{30} – Insulin_0)/(Glucose_{30} – Glucose_0)$.

Table 18 Comparison of Week 0 vs Week 20 percent change data across the three subject groups

Variables	Non-MetS V (n=8)	MetS V (n=5)	MetS L (n=6)
Body mass	-3.40 ± 3.61	-4.26 ± 1.36	-8.66 ± 4.99*
BMI	-3.39 ± 3.42	-4.23 ± 1.36	-8.67 ± 4.97*
Waist circumference	-3.42 ± 2.45	-3.86 ± 3.05	-6.21 ± 2.94
Triglycerides	-11.5 ± 33.7	-35.7 ± 35.1	-8.68 ± 21.1
Total Cholesterol	1.51 ± 16.3	-18.3 ± 19.7	-4.02 ± 16.9
LDL	3.82 ± 27.3	-20.7 ± 20.4	-5.12 ± 20.9
HDL	6.16 ± 14.9	16.4 ± 17.7	3.87 ± 10.5
Systolic Blood Pressure	-0.12 ± 6.85	-9.36 ± 10.1	-11.9 ± 9.79*
Diastolic Blood Pressure	-3.03 ± 4.66	-11.2 ± 8.92	-12.6 ± 7.58*
Fasting glucose	1.92 (-0.46)	4.35 (1.92)	-11.4 (-17.2)
30 min glucose	5.48 ± 27.6	-5.17 ± 25.6	-4.97 ± 15.1
2 hour glucose	-7.79 (-22.1)	21.6 (0)	-14.9 (-45.9)
Fasting insulin	-18.5 (-30.7)	-35.3 (-43.8)	-33.3 (-39.8)
30 min insulin	20.4 (-40.8)	-31.4 (-42.5)	2.94 (-2.76)
2 hour insulin	-1.79 ± 47.6	16.6 ± 77.9	8.09 ± 84.9
HOMA index	-18.7 (-31.6)	-32.6 (-35.7)	-37.7 (-47.5)
Insulinogenic index	-25.8 (-50.8)	-39.9 (-125)	44.7 (16.3)
VO_2 Peak	10.7 ± 13.5	30.5 ± 12.8	35.3 ± 18.7*
Velocity at AT	19.6 ± 7.79	16.1 ± 8.05	20.3 ± 11.8

Data reported as a % and as mean ± SD or median (IQR): *$p<0.05$ vs Non-MetS V

HOMA index = glucose×insulin/22.5.

Insulinogenic index = $(Insulin_{30} – Insulin_0)/(Glucose_{30} – Glucose_0)$.

3.5.6 Determinants of the percent change in VO_2 peak and Velocity at AT

Table 19 Determinants of the % change in VO_2 peak and Velocity at AT

Regression model number	**Dependent variable**	**Independent variables with standardised beta coefficient and (p-value)**	**R^2 for full model with (p-value)**
1	% change in VO_2 peak (log)	Age: -0.03 (0.0004) Baseline VO_2 peak: -0.03 (0.004) % change in WC: -0.04 (0.05) % change in insulin (log): -0.15 (0.01)	0.80 (<0.002)
2	% change in Velocity at AT (log)	Baseline velocity at AT: -0.14 (0.004)	0.56 (<0.004)

WC= Waist Circumference
(Data of week 0 and week 12 were used for the regression model)

Pearson correlation analysis demonstrated that the % change in VO_2 peak correlated with the following variables: age, baseline VO_2 peak, % change in waist circumference, % change in systolic and diastolic blood pressure and % change in fasting insulin and OGTT 2 - hour glucose level. Percentage change in velocity at AT correlated only with baseline VO_2 , baseline velocity at AT and % change in fasting glucose. These variables, as well as coding variables for the training groups with metabolic syndrome, were then included as independent variables in two separate backward, stepwise regression models in which % change in VO_2 peak and % change in velocity at AT were the dependent variables. In the first regression model age, baseline VO_2 peak, % change in waist

circumference and % change in fasting insulin levels were found to correlate with the % change in VO_2 peak (see Table 19). In the second regression model, baseline velocity at AT was found to correlate with the % change in velocity at AT (see Table 19).

3.5.7 Exercise energy expenditure

Table 20 Weekly exercise energy expenditure over 12 weeks (Mean ± SD)

	Non-MetS V	**MetS V**	**MetS L**
Average weekly expenditure (kcal/wk)	1110 ± 280*	1238 ± 173*	3994 ± 1089

*p <0.005 vs MetS L
(To convert to joules, multiply by 4.184)

Table 21 Energy expenditure per kilogram body mass-loss over 12 weeks (Median (IQR))

	Non-MetS V	**MetS V**	**MetS L**
Energy expenditure (kcal/kg.body mass-loss)	286 (166)	399 (251)	358 (292)

(To convert to joules, multiply by 4.184)

Table 20 reports the weekly exercise energy expenditure of each group. The MetSL group expended a greater amount of energy via their exercise program when compared to the MetSL and Non-MetSL groups (who were on the same training program). The MetSL expended 36.6 kcal/kg.wk^{-1} and 399 kcal/kg body mass - loss. The MetSV and Non-MetSV groups expended 19 kcal/kg.wk^{-1}; 399 kcal/kg body mass - loss and 21 kcal/kg.wk^{-1}; 286 kcal/kg body mass - loss respectively (Table 21). ANOVA analysis did not show any significant differences in energy expenditure per kilogram body mass - loss between the groups ($F=0.49$; $p=0.62$).

3.5.8 Nutritional intake

Table 22 Nutritional intake (kcal) for all groups during the training period

Week number	MetSV (n=5)	Non-MetSV (n=6)	MetS L (n=6)
Week 0	1826 ± 574	2046 ± 845	1515 ± 362
Week 8	1642 ± 622	1633 ± 835	1393 ± 341
Week 20	1688 ± 969	1858 ± 845	1665 ± 456

Data given as mean ± SEM
(To convert to joules, multiply by 4.184)

An ANOVA showed no significant differences in nutritional intake or the components of nutritional intake within each group, across all the weeks. Also, nutritional intake (kcal) did not differ across the 3 groups at each week (ANOVA; Table 22).

3.5.9 Incidence of metabolic syndrome

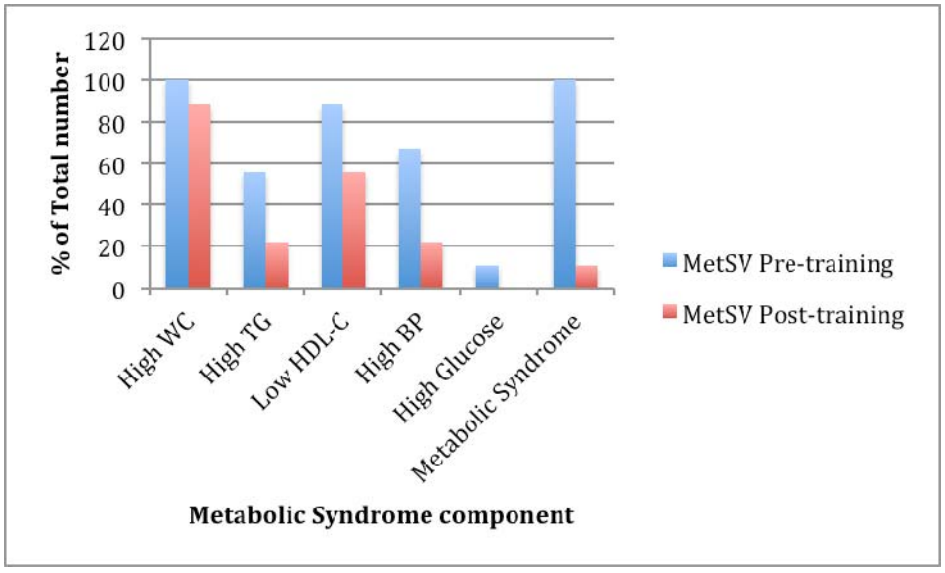


Fig 3 Change in components of metabolic syndrome and incidence of metabolic syndrome in the MetSV group.
WC= Waist circumference; TG= plasma triglycerides; HDL-C= plasma high-density lipoproteins; BP= Blood pressure. High and low values are based on the diagnosis criteria of MetS.

Both metabolic syndrome training groups showed a significant reduction in the incidence of the syndrome after the training period (p value for chi-squared < 0.05) (Fig 3 and 4). A smaller percent of individuals were still diagnosed with MetS after the training period in the MetSV group (1 out of 9; 11.1%), as opposed to the MetSL group (3 out of 7; 42.9%).

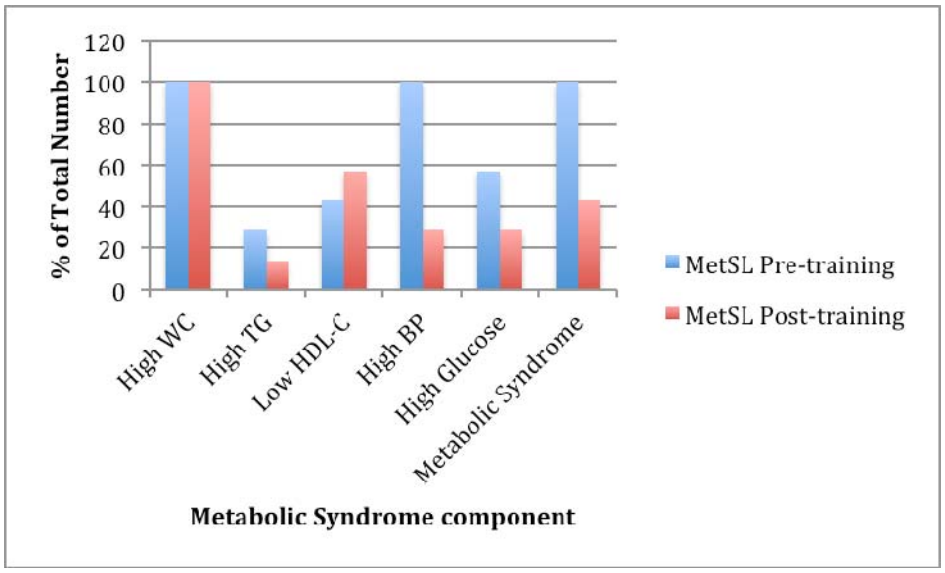


Fig 4 Change in components of metabolic syndrome and incidence of metabolic syndrome in the MetS L group.
WC= Waist circumference; TG= plasma triglycerides; HDL-C= plasma high-density lipoproteins; BP= Blood pressure. High and low values are based on the diagnosis criteria of MetS.

3.6 Discussion

Body mass decreased significantly in the MetS training groups. BMI and waist circumference decreased significantly in all training groups with the training program using AT and the one using the method of Leon et al. (1979) showing similar outcomes in these variables among persons with MetS. Velocity at AT also improved in all training groups yet VO_2 peak did not change significantly in the group without MetS. Similarly, the blood pressure training response was favourable in the groups with MetS yet absent in the group without MetS. The training group with MetS that used AT was the only group to show significant, positive changes in metabolic parameters i.e. fasting insulin and HOMA, as shown in Table 11. In addition, the training programs had a significant influence on the incidence of MetS

This study aimed to compare outcomes of our training program based on AT determination (MetSV) to the outcomes of a training program proven in the literature. The Leon et al. (1979) training program was chosen for the following reasons:

- The training program changed in a progressive manner during the training period. Our training program was also based on a periodised model.
- It achieved impressive outcomes with respect to the metabolic syndrome components that our study was measuring.
- The study measured the same variables that our study was investigating. This allowed for effective comparison of the two types of training programs.
- The mode of exercise was the same as our training program.

- The training program was very reproducible and easy to implement in our subject groups i.e only treadmill velocity and gradient determined intensity (not % of maximal calculations). Our training intensity also used treadmill velocity and gradient.

This study set our control group as the Non-MetSV group, because our study wanted to investigate the exercise responses of individuals with MetS (MetSV group) to those of individuals without MetS (Non-MetSV) and of two different exercise programs (MetSV vs MetSL). Our focus was not to compare the outcomes of non-exercisers with MetS to exercisers with MetS.

Two of the statistically significant differences observed between the MetSL groups and the control group in this study are reflective of the definition used to classify MetS (waist circumference and systolic blood pressure) (Table 7). The other differences (VO_2 peak, fasting insulin, OGTT insulin level at 30 minutes and HOMA index) support the findings that VO_2 peak is lower in persons with MetS (Lakka et al. 2003) and that insulin resistance is a major component of MetS (De Fronzo et al. 1991; Eckel et al. 2005), respectively. The baseline characteristics of the MetSV group were not significantly different to the Non-MetSV group. This could be due to the low sample number, since all the diagnostic parameters for MetS were higher in the MetSV group compared to the Non-MetSV group, yet did not reach statistical significance.

Both training programs used in this study showed favourable training responses. BMI and waist circumference decreased significantly in all training groups. Body mass decreased significantly only in the groups with MetS (Tables 8, 10 and 12). The decreases in all these parameters however, were not significantly different across the three groups at week 12 (Tables 15 and 16), but at week 20 the MetSL group decreased their body mass and BMI significantly more than that of the Non-MetSV group (Tables 17 and 18). There was no significant difference in the change of body mass, BMI and waist circumference across the two different training groups (MetSV and MetSL) at weeks 12 and week 20 (Table 16 and 18). This indicates that the training program utilizing AT had a similar effect on these variables with persons with MetS as the training program of Leon et al. (1979). When compared though, to a Non-MetS group the Leon et al. (1979) walking program seems superior in the outcomes of body mass and BMI.

The importance of decreasing body mass, BMI and waist circumference in persons with metabolic disease has been highlighted (Carroll et al. 2004; Haffner et al. 2003; Lemieux et al. 2000). There is contradictory evidence whether exercise alone causes changes in body mass in persons with MetS. Some studies have found no changes (Katzel et al. 1997; Lavrencic et al. 2000; Smutok et al. 1993) while others have shown decreases in body mass (Dengel et al. 1998; Kraus et al. 2002, Wing et al. 1998). Differences in the exercise program frequency and intensity used by these studies may contribute to these contradictory results. The STTRIDE studies aimed to address this issue and investigated the effect of different exercise amounts and intensities in sedentary, obese, dyslipidaemic participants (Slentz et al. 2005; Slentz et al. 2007). These studies showed that body mass

and visceral fat responded in a dose-dependent manner. The greater the amount of exercise the greater the decrease in these parameters. The present study also found a dose-response with respect to body mass - loss. At 19 $kcal.kg^{-1}.wk^{-1}$ and 36 $kcal.kg^{-1}.wk^{-1}$ energy expenditure for the MetSV and MetSL groups respectively, the body mass - loss was 4.3% and 8.7% respectively at week 20 (Table 18). The absolute body mass - loss that occurred in the groups with metabolic syndrome after the training programs used in this study (2.1 – 10 kg) (Table 14) was greater than that reported in the review of Carroll et al. (2004) (1.5 – 1.9 kg).

The measures of VO_2 peak and AT were used as measures of cardio-respiratory fitness. AT improved significantly in all training groups (Table 8, 10 and 12). VO_2 peak though, improved significantly only in the MetS groups and did not change significantly in the group without MetS (Table 9). Studies by Weltman et al. (1992) and Weltman (1995) have demonstrated that it is possible for AT to improve without VO_2 peak changing. Furthermore, many studies have also reported that the workload and VO_2 associated with AT improve to a greater degree with training than does VO_2 max (Denis et al. 1982; Hurley et al. 1984; Sjodin et al. 1982; Yoshida et al. 1982). In addition, the VO_2 peak response in this study indicates a difference in cardio-vascular responses to this training program between persons with MetS and those without MetS. The central training adaptations were more evident in the MetS groups than in the Non-MetS groups.

The only significant difference in the change of VO_2 peak and AT across the three groups was in VO_2 peak at week 20 and specifically between the Non-MetSV and MetSL groups

(Table 16 and 18). Similar to the response of body mass, BMI and waist circumference there was no significant difference in the changes that occurred in VO_2 peak and AT between the MetSV and MetSL groups (Table 16 and 18). This indicates that the training program utilizing AT was as effective in improving the cardio-respiratory fitness of persons with MetS as the training program of Leon et al. (1979). The training program using AT though achieved this improvement at a third of the exercise energy expenditure of the training program not using AT (Table 20).

The improvement in VO_2 peak with MetS persons after an exercise program has also been shown by other studies that ranged from a 9-19% increase in this variable (Dengel et al. 1998; Juneau et al. 1987; Katzel et al. 1997; Katzmarzyk et al. 2003; Smutok et al. 1993). The present study showed an increase in VO_2 peak of 19% (week 12) and 31% (week 20) in the group using the training program by AT and 16% (week 12) and 35% (week 20) in the group using the Leon et al. (1997) program (Tables 16 and 18). These changes in VO_2 peak were consistent and greater in week 20 than the range (1-25%) reported by the review of Carroll et al. (2004).

To our knowledge there are no studies that have shown the response of AT to a training program in persons with MetS. These data show a favourable response indicative of an increase in cardio-respiratory fitness. The training program using AT and the Leon et al. program elicited similar improvements in this parameter. There was no significant difference in the improvement in velocity at AT across the three groups (Table 16 and

18). This suggests that persons with MetS and persons without MetS have a similar blood lactate response to endurance exercise.

Endurance training has been shown to reduce blood lactate concentrations at any given VO_2 (MacRae et al. 1992; Stanley et al. 1985). These researchers suggested that training results in a diminished blood lactate response during exercise by decreasing the rate of lactate production or increasing the rate of lactate clearance or both. The decrease in blood lactate production may be related to the reduced carbohydrate utilization during exercise after endurance training (Saltin et al. 1976). It has also been suggested that a training intensity that approximates AT is optimal in eliciting the local training adaptation changes in muscle metabolism (Kindermann, 1979; Sjodin et al. 1982; Tanaka et al. 1986).

The research of Weltman et al. (1992) showed that the increase in physical activity associated with the onset of endurance training is sufficient to elicit a training effect provided the initial training intensity is at or above LT (55% to 81% of VO_2 max). The current study did not find that training at AT improved the velocity at AT to a greater degree than training without using AT to set intensity in persons with MetS (Table 16 and 18). Furthermore, there was no difference in the response to exercise between MetS and Non-MetS individuals with respect to AT.

The regression analyses (Table 19) suggest that the improvement in VO_2 peak was associated with age, baseline VO_2 peak, the decrease in waist circumference and the decrease in fasting insulin levels that occurred as adaptations to the training programs.

The improvement in velocity at AT with training is associated with baseline BLTT levels only. These analyses support data from the previous chapter that demonstrated the influence of waist circumference on VO_2 peak. Furthermore, waist circumference is a proxy indicator of visceral fat mass (Pouliot et al. 1994) and this body fat depot is a negative regulator of whole body insulin sensitivity (Ross, 2002). This may also explain the association of the change in fasting insulin with the change in VO_2 peak. It may be argued that expressing and analysing VO_2 peak as $ml.min^{-1}kg^{-1}$ may have polluted the regeression analysis because if mass and waist girth are highly correlated, then waist girth and $V0_2$ peak (in $ml.min^{-1}kg^{-1}$) will be highly correlated. However if that was true, mass would have come through in the final regeression analysis. This did not occur.

Systolic and diastolic blood pressure decreased significantly in the MetSL group (Table 13). This change was significantly different between the MetSL and Non-MetSV groups at week 20 (Tables 17 and 18). At week 12, only the change in systolic blood pressure was significantly different across these groups (Tables 15 and 16). In addition, only diastolic blood pressure decreased significantly in the MetSV group (Table 10). The changes that occurred with blood pressure variables were not significantly different across the two groups with MetS (Tables 16 and 18). There was no change in blood pressures within the Non-MetSV group (Table 8). This may once more allude to differences in adaptations to endurance training in persons with MetS as opposed to those without MetS. This may be due to the fact that the latter group had normal baseline blood pressures. The training groups with MetS had elevated blood pressure values (Table 7). Studies by Dengel et al. (1998), Katzmarzyk et al. (2003) and the review by Carroll et al.

(2004) have also reported the beneficial effect of exercise on blood pressure. In contrast, some studies have shown no changes in blood pressure after exercise intervention (Katzel et al. 1997; Smutok et al. 1993; Watkins et al. 2003). All these studies involved participants that had components of the MetS.

The MetSV group showed significant intra-group changes in metabolic parameters. Fasting insulin and the HOMA index fell at week 20 (Table 11). Thus, insulin sensitivity may have been positively influenced by the training program using AT to set intensity. No such improvements were noted in the Non-MetSV group, but fasting insulin and HOMA levels did fall in the MetSL group to a magnitude similar to that seen in the MetSV group, however these falls were not statistically significant. The insulinogenic index was not affected by the training program using AT. More specific tests and a greater number of participants would be needed to confirm this result. It is speculated that exercise training at the AT may improve insulin sensitivity due to increases in Glut-4 transports related to an increase in the demand for glucose when training at the AT. This speculation is based on the finding that exercise has been shown to increase the Glut-4 isoform of the glucose transporter which in turn results in a more rapid glucose uptake (Holloszy, 2008). This speculation will need to be addressed with further research.

Research in this area has been contradictory with some studies showing improved glucose tolerance and reduced insulin responses to oral glucose as training adaptations (Dengel et al. 1998; Kraus et al. 2002; McAuley et al. 2002; Ross et al. 2000; Smutok et al. 1993; Watkins et al. 2003), and other studies finding no change in this parameter

(Katzel et al. 1997; Potteiger et al. 2002; Stefanick et al. 1998). The current study showed that at week 12, the 2 hour glucose levels decreased relative to baseline in the MetSL group but increased in the MetSV group, and both these changes were significantly different to those observed in the Non-MetSV group, where glucose levels fell (Table 16). These differences were not significant at week 20 (Table 18). These results may have also been influenced by the very low fasting glucose levels at baseline of the MetSV group (Table 7).

This study's training programs did not affect any lipoprotein levels (Table 9, 11 and 13). The studies of Smutok et al. (1993); Katzel et al. (1997) and Watkins et al. (2003) are in agreement with this finding. Yet, some researchers have shown improvements in lipoprotein levels after exercise intervention (Dengel et al. 1998; Katzmarzyk et al. 2003; Kraus et al. 2002). A longer training period with attention to body mass - loss via dietary interventions in this study may have elicited improved lipoprotein profiles. This was highlighted by the research of Katzel et al. (1997) and Anderssen et al. (1998). The lack of change in lipoprotein levels may also be due to the relatively normal values in all three groups at baseline. However, it should be noted that at week 20, (Table 18) the percentage change in each of the 4 different lipid types was higher in the MetSV group than either of the other 2 groups, although these differences were not statistically significant.

This study used the Leon et al. (1979) exercise program and applied it to a group with MetS (MetSL group). The Leon et al. (1979) study used a 16-week walking program to

train obese men aged 19 – 31 years (without MetS). These researchers showed that the walking program reduced body mass (4.9 – 6kg); increased the HDL/ LDL ratio; reduced fasting blood glucose; reduced the ratio of plasma insulin / glucose concentrations. Thus exercising 5 times per week, 7.5h/wk, at an intensity eliciting 1100 kcal/session (4602J/session), suggested a reversal of metabolic disease. A limitation of the Leon et al. study is that no control group was investigated. The effect of this exercise program on a group with MetS elicited similar results in body mass - loss (Table 12) yet not in any metabolic parameters (Table 13). Thus, the metabolic response to the training program was different to that elicited in a younger group of obese men without MetS. The difference may be in the lower caloric expenditure per exercise session (1100 vs 799 kcal; 4602 vs 3343 J) of this study's metabolic group.

Carroll et al. (2004), in their review of metabolic abnormalities and exercise, concluded that there is now more evidence that long-term exercise, without body mass reduction, modestly decreases abdominal adipose tissue and improves insulin action among overweight/obese adults. In addition, exercise alone is effective in improving impaired glucose control and reducing the incidence of type 2 diabetes in both sexes. Furthermore, exercise alone was associated with modest but clinically relevant lipoprotein profile improvements in raising HDL-C and lowering triglycerides. More often than not, though, exercise did not alter total cholesterol or LDL-C concentrations. The review also found that exercise alone modestly reduces blood pressure with greatest changes evident in overweight individuals with hypertension. The majority of the randomised controlled studies that Carroll et al. (2004) analysed have suggested aerobic endurance activity, 3-5

days/wk, 30-60 minutes per session at moderate to moderately vigorous intensity (40-80% VO_2 max with median weekly energy expenditure of 1600 kcal/wk). The authors did however state that more trials are needed to establish the lower threshold for exercise amount and intensity for metabolic outcomes. The present study found that median weekly energy expenditure as low as 1238 kcal/wk (Table 20) produced substantial physical changes in persons with MetS, and some metabolic changes.

Yamaoka et al. (2012) also performed a systematic review and meta-analysis of lifestyle modification interventions (LMI) effects on individuals with MetS. Their analysis however included "diet only" and "diet and exercise" randomised, controlled trials as opposed to the Carroll et al. (2004) review that analysed "exercise only" interventions. Like the Carroll et al. (2004) review, the Yamaoka et al. (2012) review also showed that LMI decreases the prevalence of MetS and associated abnormalities of MetS. Yamaoka et al. (2012) though suggested that their review indicates that dietary modifications may be more effective than exercise interventions.

The training programs used in this study had a significant influence on the incidence of MetS. There was a marked reduction in the number of individuals that were still diagnosed with MetS after the training program (Fig 3 and 4). The research of Katzmarzyk et al. (2003) supports this finding. It should be noted that the MetSV group at baseline had no significant differences in the absolute levels of anthropometric and metabolic factors when compared to the Non-MetSV group. However, they did differ in

terms of the prevalence of the individual components of the MetS, and it was these prevalence levels that fell in response to the exercise programme.

The nutritional intake of the participants in this study did not change significantly throughout the training period (Table 22) and there was no difference in caloric intake across the groups throughout the training period. Thus, exercise was the main effector of the reported outcomes of this study.

It should also be noted that a *post hoc* sample size calculation showed that in order to observe significant differences across groups for a percentage change in waist circumference, an n of 18 participants per group would be required. Thus, our study was under -powered to observe changes in waist across the groups. A sample size calculation based on percentage change in BMI gave an n of 8 per group, which is close to the actual number used in this study. It is therefore possible that the small sample size used in the current investigation was not large enough to observe significant changes in all the variables analysed.

3.7 Conclusion

When comparing the endurance exercise program using AT to set intensity with the walking program of Leon et al. (1997), the latter led to greater falls in blood pressure and anthropometric variables whilst the former led to greater falls in cholesterol and triglycerides and higher increases in HDL, although none of these changes were significantly different between the 2 groups. The program using AT significantly reduced

insulin resistance whilst the fall in this parameter in the MetSL group was not significant. The AT-based exercise program led to greater increases in VO_2 peak and greater falls in insulin resistance in subjects with MetS than in those without.

An important finding of this research was that a smaller percent of individuals were still diagnosed with MetS after a 12 week training period in the MetS group using AT to set intensity, as opposed to the MetS group not using AT to set intensity, although this difference was not statistically significant. The main advantage of the training program using AT is that its effects occurred at a reduced exercise frequency and lower exercise energy expenditure than that of the walking program. The data also indicated that 12 weeks can elicit such a result and that an effective training program would not have to last for 20 weeks.

Length of training program, dietary intervention and subject profile may be factors influencing this output.

3.8 References

1) Alberti KG. Eckel RH. Grundy SM et al. Harmonizing the Metabolic Syndrome. Circulation 2009, 120:1640-1645.
2) Anderssen SA. Holme I. Urdal P et al. Associations between central obesity and indexes of hemostatic, carbohydrate and lipid metabolism: Results of a 1 year intervention from the Oslo Diet and Exercise Study. Scand J Med Sci Sports 1998, 8:109-115.

3) Carroll S. Dudfield M. What is the relationship between exercise and Metabolic Abnormalities? A review of Metabolic Syndrome. Sports Med 2004, 34(6):371-418.

4) Coen B. Schwarz L. Urhausen A et al. Control of training in middle and long-distance running by means of the individual anaerobic threshold. Int J Sports Med 1991, 12:519–524.

5) De Fronzo RA. Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for non-insulin dependent diabetes, obesity, hypertension, dyslipidemia, and artherosclerotic cardiovascular disease. Diabetes Care 1991, 14: 173-194.

6) Dengel DR. Hagberg JM. Pratley RE et al. Improvements in blood pressure, glucose metabolism, and lipoprotein lipids after aerobic exercise plus weight loss in obese, hypertensive middle-aged men. Metabolism 1998, 47(9):1075-1082.

7) Denis C. Fouquet R. Poty P et al. Effect of 40 weeks of endurance training on the anaerobic threshold. Int J Sports Med 1982, 3:208-214.

8) Despres JP. Visceral obesity, insulin resistance, and dyslipidemia: contribution of endurance exercise training to the treatment of the plurimetabolic syndrome. Exerc Sport Sci Rev 1997, 25:271-300.

9) Eckel RH. The metabolic syndrome. Lancet 2005, 365:1415-1428.

10) Erdfelder E. Faul F. Buchner A. (1996) GPower : A general power analysis program. Behav Res Meth Instr Comp 1996, 28:1-11.

11) Friedewald WT. Levy RI. Fredrickson DS. Estimation of the concentration of Low-Density Lipoprotein cholesterol in Plasma, without use of the Preparative Ultracentrifuge. Clin Chem 1972, 18:499-502.

12) Gibala MJ. Little JP. Macdonald MJ et al. Physiological adaptations to low-volume, high-intensity interval training in health and disease. J Physiol 2012, 590(5):1077-1084.

13) Haffner S. Taegtmeyer H. Epidemic obesity and the Metabolic Syndrome. Circulation 2003, 108:1541–1545.

14) Holloszy JO. Regulation by exercise of skeletal muscle content of mitochondria and GLUT-4. J Physiol & Pharm 2008, 59(Suppl 7):5-18.

15) Hurley BF. Hagberg JM. Allen WK et al. Effect of training on blood lactate levels during submaximal exercise. J Appl Physiol 1984, 56(5):1260-1264.

16) Ivy JL. Role of exercise training in the prevention and treatment of insulin resistance and non-insulin dependent diabetes mellitus. Sports Med 1997, 24:321-336.

17) Juneau M. Rogers F. De Santos V et al. Effectiveness of self-monitored, home-based, moderate-intensity exercise training in middle-aged men and women. Am J Cardiol 1987, 60:66-70.

18) Katzel LI. Bleecker ER. Rogus EM. Sequential effects of aerobic exercise training and weight loss on risk factors for coronary disease in healthy, obese middle-aged and older men. Metabolism 1997, 46:1441-1447.

19) Katzmarzyk PT. Leon AS. Wilmore JH et al. Targeting the metabolic syndrome with exercise: Evidence from the HERITAGE Family Study. Med Sci Sports Ex 2003, 35(10):1703-1709.

20) Kindermann W. Simon G. and Keul J. The significance of the aerobic-anaerobic transition for the determination of workload intensities during endurance training. Eur J Appl Physiol 1979, 42:25–34.

21) Kraus W. Houmard J. Duscha B et al. Exercise training amount and intensity effects on plasma lipoproteins: a randomised, controlled trial. N Engl J Med 2002, 347(19):1483-1492.

22) Lakka TA. Laaksonen DE. Lakka H-M et al. Sedentary life-style, poor cardiorespiratory fitness and the metabolic syndrome. Med Sci Sports Ex 2003, 35:1279-1286.

23) Lavrencic A. Salobir BG. Keber I. Physical training improves flow-mediated dilation in patients with the polymetabolic syndrome. Arterioscler Thromb Vasc Biol 2000, 20:551-560.

24) Lemieux I. Pascot A. Coillard C et al. Hypertriglyceridemic waist- a marker of the artherogenic metabolic triad in men? Circulation 2000, 102:179-184.

25) Leon AS. Conrad J. Hunninghake DB et al. Effects of a vigorous walking program on body composition, and carbohydrate and lipid metabolism of obese young men. Am J Clin Nutr 1979, 33:1776-1787.

26) Lee RD. Nieman DC. Nutritional assessment (2nd ed) McGraw-Hill Companies Inc, USA, 1996:92-109.

27) MacRae HS. Dennis S. Bosch AN et al. Effects of training on lactate production and removal during progressive exercise in humans. J Appl Physiol 1992, 72:1649-1656.

28) Matthews DR. Hosker JP. Rudenski AS et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985, 28:412-419.

29) McAuley KA. Williams SM. Mann JL et al. Intensive lifestyle changes are necessary to improve insulin sensitivity: a randomised controlled trial. Diabetes Care 2002, 25:445-452.

30) National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001, 285:2486-2497.

31) Potteiger JA. Jacobsen DJ. Donnelly JE. A comparison of methods for analysing glucose and insulin areas under the curve following nine months of exercise in overweight adults. Int J Obes Relat Metab Disorder 2002, 26:87-99.

32) Pouliot MC. Despres JP. Lemieux S et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994, 73:460–468.

33) Ross R. Aru J. Freeman J et al. Abdominal adiposity and insulin resistance in obese men. Am J Physiol Endocrinol Metab 2002, 282:E657–663.

34) Ross R. Dugnone D. Jones PJH et al. Reduction in Obesity and related comorbid conditions after diet-induced weightloss or exercise-induced weightloss in men. Ann Intern Med 2000, 133:92-103.

35) Rynders CA. Weltman A. High-intensity exercise training for the prevention of type 2 diabetes mellitus. Phys Sportsmed 2014, 42(1):7-14.

36) Saltin B. Nazar K. Costill DL et al. The nature of the training response : peripheral and central adaptations to one-legged exercise. Acta Physiol Scand 1976, 96:289-305.

37) Sjodin B. Jacobs I. Svedenhag J. Changes in onset of blood lactate accumulation and muscle enzymes after training at OBLA. Eur J Appl Physiol 1982, 49:45–57.

38) Slentz CA. Aiken LB. Houmard JA et al. Inactivity, exercise, and visceral fat. STRRIDE: a randomized, controlled study of exercise intensity and amount. J Appl Physiol 2005, 99:1613–1618.

39) Slentz CA. Houmard JA. Kraus WE. Modest exercise prevents the progressive disease associated with physical inactivity. Ex Sport Sci Rev 2007, 35:18-23.

40) Smutock MA. Reece PF. Kokkinos PF. Aerobic versus strength training for risk factor intervention in middle-aged men at high risk for coronary heart disease. Metabolism 1993, 42:177-184.

41) Stanley WC. Gertz EW. Wisneski JA et al. Systematic lactate kinetics during graded exercise in man. Am J Physiol Endocrinol Metab 1985, 249:E595-E602.

42) Stefanick ML. Mackey S. Sheehan M et al. Effects of diet and exercise in men and post menopausal women with low levels of HDL Cholesterol and high levels of LDL cholesterol. N Engl J Med 1998, 339:12-20.

43) Tanaka K. Watanabe H. Konishi Yet al. Longitudinal associations between anaerobic threshold and distance running performance. Eur J Appl Physiol 1986, 55:248-252.

44) Toth MJ. Sites CK. Cefalu WT et al. Determinants of insulin-stimulated glucose disposal in middle-aged premenopausal women. Am J Physiol Endocrinol Metab 2001, E113-E121.

45) Utzschneider KM. Prigeon RL. Faulenbach MV et al. An oral disposition index predicts the development of future diabetes above and beyond fasting and 2-hour glucose levels. Diabetes Care 2009, 32:335–341.

46) Watkins LL. Sherwood A. Feinglos M. et al. Effects of exercise and weight loss on cardiac risk factors associated with syndrome X. Arch Intern Med 2003, 163:1889-1895.

47) Weltman A. Seip RL. Snead D. Exercise training at and above the lactate threshold in previously untrained women. Int J Sports Med 1992, 13:257–263.

48) Wing RR. Venditti EV. Jakicic JM et al. Lifestyle intervention in overweight individuals with a family history of diabetes. Diabetes Care 1998, 21:350-359.

49) Yamaoka K. Tango T. Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. BMC Medicine 2012, 10:138.

50) Yoshida T. Suda Y. Takeuchi N. Endurance training regimen based upon arterial blood lactate: Effects on anaerobic threshold. Eur J Appl Physiol 1982, 49:223–230.

CHAPTER 4

FACTORS THAT INFLUENCE VO_2 PEAK , BLOOD LACTATE TRANSITION THRESHOLDS AND THE COMPONENTS OF METABOLIC SYNDROME

4.1 Abstract

Background

The role of cardio-respiratory fitness in the attenuation of the metabolic syndrome (MetS) has been noted in the literature. However, the determinants of cardio-respiratory fitness measurements such as VO_2 peak and anaerobic threshold (AT) have not been investigated in persons with MetS. This study developed multiple regression models to find the variables that correlated with these measurements of cardio-respiratory fitness in persons with MetS. Regression models were also developed to investigate whether cardio-respiratory fitness measurements were associated with the individual metabolic and cardiovascular components of the metabolic syndrome.

Methods

Thirty one males diagnosed with MetS and twenty-four healthy male participants each performed a VO_2 peak and a blood lactate transition thresholds (BLTT) test. Height, body mass, waist circumference, blood pressure, fasting plasma triglyceride, total cholesterol, HDL-cholesterol and insulin levels were also measured. In addition, oral glucose tolerance tests (OGTT) were administered to all participants and HOMA indices were calculated. Separate multiple regression models were developed in which VO_2 peak, AT and components of MetS were the dependent variables.

Results

MetS, waist circumference (indirect relationship) and AT (direct relationship) were found to correlate with VO_2 peak and VO_2 peak had a strong correlation with AT (direct relationship). Age (direct relationship) and body mass (direct relationship) were found to correlate with fasting glucose, whilst only age (direct relationship) correlated with HDL-cholesterol. Age (direct relationship) and VO_2 peak (indirect relationship) both correlated with systolic blood pressure but only VO_2 peak (indirect relationship) correlated with diastolic blood pressure.

Conclusion

The lower VO_2 peak of participants with MetS is associated with their higher waist circumference. The VO_2 peak, in turn, was shown to correlate strongly with anaerobic threshold. Therefore, reducing waist circumference in persons with MetS needs to be a focus of intervention programs for such a group. This study also found that both diastolic and systolic blood pressures were associated with cardio-respiratory fitness (VO_2 peak). This further supports the benefit of increasing cardio-respiratory fitness in persons with MetS.

4.2 Introduction

Researchers have shown an inverse relationship between cardio-respiratory fitness and the incidence of MetS (Carroll et al. 2000; Irwin et al. 2002; Kullo et al. 2002; Lakka et al. 2003; LaMonte et al. 2005; Whaley et al. 1999). Katzmarzyk et al. (2004) showed that cardio-respiratory fitness has a strong protective effect against all-cause and cardio-

vascular disease mortality in healthy men and in men with MetS. However, the determinants of cardio-respiratory fitness measurements such as VO_2 peak and AT in persons with MetS have not been identified. Therefore, this study sought to develop multiple regression models to find variables that had strong relationships with cardio-respiratory fitness measures. The importance of identifying these variables lies in intervention programs targeting the determinants to increase cardio-respiratory fitness in such a group. In addition, regression models were developed to investigate whether the measurements of cardio-respiratory fitness were associated with the individual metabolic and cardiovascular components of the metabolic syndrome. The hypothesis of this study was that cardio-respiratory fitness measurements correlate with the individual components of MetS.

4.3 Methods

The Human Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa, approved the study protocol (MO61104).

4.3.1 Participants and definition of metabolic syndrome

Thirty one (31) males diagnosed with metabolic syndrome (MetS) and twenty-four (24) healthy male subjects each performed a VO_2 peak and a BLTT test. All healthy participants were age-matched with the patient group and had one or no components of the MetS. Patients were diagnosed with MetS by clinicians using the harmonised guidelines (Alberti, 2009). The presence of any 3 of the 5 criteria denoted below constituted a diagnosis of MetS: waist circumference ($\geq$94 cm); triglycerides ($\geq$1.7

mmol.L^{-1}) or drug treatment for high triglycerides; HDL-cholesterol (<1.0 mmol.L^{-1}) or drug treatment for reduced HDL-cholesterol; elevated blood pressure (≥130/85) or on anti-hypertensive drug treatment; elevated fasting glucose (≥5.6mmol.L^{-1}) or drug treatment for glucose intolerance. Any individuals taking lipid lowering agents, anti-hypertensive drugs or treatments for dysglycaemia were not included in this study.

4.3.2 Measurements

All participants underwent an OGTT for the detection of undiagnosed diabetes. Fasting and two hour glucose levels were measured using a glucose oxidase method (Roche Diagnostics, Mannheim, Germany, measured on the Architect i2000 Abbott autoanalyser). Plasma triglyceride, total cholesterol and HDL-cholesterol levels were assayed using enzymatic assay methods (Roche Diagnostics, Mannheim, Germany, measured on the Architect i2000 Abbott autoanalyser). Fasting insulin levels were also measured on the Architect i2000 Abbott instrument using the Chemiluminescent Microparticle Immunoassay. The HOMA-IR (Matthews et al. 1985) was calculated to assess insulin sensitivity. Fasting blood samples were analysed by a pathology laboratory (Lancet Laboratories, Richmond, Johannesburg) as part of the diagnosis.

Height was measured to the nearest millimetre using a Seca Stadiometer [Hamburg, Germany]. Body mass was measured to the nearest gram by a Charder electronic scale [Taiwan, China]. Waist circumference was taken as the greatest reading around the girth, midway between lateral lower ribs and the iliac crests. Blood pressure was measured by a

Honsun sphygmomanometer [Shanghai, China], sitting and using the average of two readings.

4.3.3 The blood lactate transition thresholds test

The BLTT test used an initial treadmill speed of 2.5 kph at a 5% gradient with speed increments every 4 minutes. The treadmill speed was modified depending on the response of a participant to ensure the collection of at least six blood samples for lactate analysis. After signalling impending exhaustion, participants were encouraged to continue to complete the 30 seconds period already begun. Electrocardiographic responses and oxygen consumption (VO_2) were measured at the same time (Cortex Biophysik Metalyzer 3b CPX system, Leipzig, Germany). The ECG was used to monitor electrocardiographic responses during testing of the participants. Testing was stopped if any ECG abnormalities were observed. VO_2 at exhaustion was recorded as the VO_2 peak. No abnormalities in ECG readings were observed. This protocol was designed taking into consideration the low level of physical conditioning of persons with MetS. All participants were requested not to exercise for at least 12 hours before the testing session.

Lactate concentration was measured from whole-blood samples taken from the fingertip using the Lactate Scout automated analyser (Lactate Scout, SensLab, Leipzig). Blood samples (collected from finger capillary vessels using a lancet) were taken at the end of each exercise period within 30 – 40 seconds of the participants standing still on the treadmill. The fingertip was first wiped with water to remove the sweat and then it was

dried before the blood sample was collected. The participant continued exercising within one minute of standing.

4.3.4 Determination of anaerobic threshold

The blood lactate transition threshold (BLTT) that was determined for each participant will be defined in this study, for purposes of terminology, as anaerobic threshold (AT). AT, in this study, will be defined as the workload (treadmill velocity given as $km.h^{-1}$) marked by a rapid rise in blood lactate denoting the upper limit of equilibrium between lactate production and clearance (Bourdon, 2000). The treadmill velocity at AT for the BLTT tests was determined using the ADAPT method (Cheng et al. 1992).

The ADAPT method determines AT from the individual shape of the velocity – blood lactate curve (not from a fixed blood lactate concentration) and is based on the $Dmax_{mod}$ method (Cheng et al. 1992). A modification of the ADAPT method was used for determining AT in this study and has been discussed in our previous investigation (Torres et al. 2013).

4.4 Statistical analysis

Data distribution was analysed using Shapiro-Wilk's W test, and any variables that were found to be significantly skewed were log transformed to normality. ANOVA was used to compare variables between the MetS and non-MetS groups. Waist circumference and body mass were found to differ between these groups and therefore an ANCOVA was set

up in which waist was included as an independent variable and a second ANCOVA was performed in which body mass was included with waist as independent variable. Pearson correlation analyses were used to determine the principal correlates of the VO_2 peak, AT and the metabolic and cardiovascular components of the metabolic syndrome (MetS). The variables included in the correlation matrices were chosen based on evidence from the literature and that relationships were physiologically feasible. Variables that gave significant correlations in the univariate analyses with ($p<0.1$) were then used as independent variables in separate multiple regression models in which VO_2 peak, AT and components of MetS were the dependent variables. Backward, stepwise regression analysis was then performed until only variables with $p<0.05$ remained in the model.

4.5 Results

4.5.1 Participants

Table 23 Physical and biochemical characteristics of study participants

Variables	MetS (n= 31)	Non-MetS (n=24)
Age (years)	43.8 ± 7.91	42.7 ± 6.93
Body mass (kg)	99.8 (25.1)	101 (21.3)*
BMI (kg.m^{-2})	32.2 (5.20)	30.3 (7.00)
Waist circumference (cm)	115 (9.00)	105 (16.8)***
Triglycerides (mmol.L^{-1})	1.75 ± 0.54	1.32 ±0.49**
Total cholesterol (mmol.L^{-1})	5.58 ± 1.37	5.50 ± 1.11
HDL (mmol.L^{-1})	0.94 ± 0.22	1.11 ± 0.17*
Systolic blood pressure (mmHg)	137 ± 12.2	121 ± 10.4***
Diastolic blood pressure (mmHg)	87.7 ± 6.60	81.7 ± 6.88**
Fasting glucose (mmol.L^{-1})	5.30 (1.00)	5.10 (0.45)
2 hour glucose (mmol.L^{-1})	5.60 (3.40)	5.35 (1.80)
Fasting insulin (µU.ml^{-1})	12.2 (7.40)	8.50 (2.20)
HOMA index	2.81 (1.67)	2.09 (0.65)
VO_2 Peak (ml.min^{-1}.kg^{-1})	27.9 (8.00)	35.0 (13.0)***
Velocity at AT (km.h^{-1})	5.21 (1.31)	5.94 (2.75)*

Data is given as mean ± SD or median (IQR); *p< 0.05; **p< 0.005; ***p<0.0005 vs MetS
HOMA index = glucose×insulin/22.5.
HDL= High-density lipoproteins

Table 24 ANOVA and ANCOVA results for comparison of data between the MetS and Non-MetS groups

Variables	Results of ANOVA	Results of ANCOVA (adjusted for waist)	Results of ANCOVA (adjusted for body mass and waist)
Triglycerides (mmol.L^{-1})	9.02 (0.004)	11.3 (0.002)	14.7 (0.0004)
Total cholesterol (mmol.L^{-1})	0.06 (0.81)	0.32 (0.57)	0.31 (0.58)
HDL (mmol.L^{-1})	9.38 (0.03)	12.9 (0.0007)	12.3 (0.0009)
Systolic blood pressure (mmHg)	25.5 (0.00001)	15.5 (0.0002)	15.6 (0.0002)
Diastolic blood pressure (mmHg)	11.0 (0.002)	5.69 (0.02)	4.83 (0.03)
Fasting glucose (mmol.L^{-1})	0.84 (0.36)	0.28 (0.60)	0.14 (0.71)
2 hour glucose (mmol.L^{-1})	0.01 (0.90)	0.76 (0.39)	0.40 (0.53)
Fasting insulin (µU.ml^{-1})	1.88 (0.18)	1.14 (0.30)	1.33 (0.26)
HOMA index	1.84 (0.18)	0.60 (0.44)	0.79 (0.38)
VO_2 peak (ml.min^{-1}.kg^{-1})	21.7 (0.0002)	5.91 (0.02)	5.79 (0.02)
Velocity at AT (km.h^{-1})	7.96 (0.007)	1.76 (0.19)	0.28 (0.60)

Data is given as F-value (p-value)
HOMA index = glucose×insulin/22.5.
HDL= High-density lipoproteins

Table 23 describes the study participants' baseline characteristics. Significant differences between the non-MetS and MetS groups were found for body mass, waist circumference, triglycerides, HDL, systolic and diastolic blood pressure AT and VO_2 peak. Waist circumference is known to be a major determinant of these variables and therefore ANCOVAs were performed comparing the metabolic, cardiovascular and fitness variables between the two groups with waist circumference included as an independent

variable. The results are shown in Table 24. Adjusting for waist circumference, strengthened the significant p-values for triglycerides and HDL-cholesterol and weakened the significant p-values for systolic, diastolic blood pressure and VO_2 peak. Velocity at AT was no longer significantly different between the groups, once adjusted for waist circumference. Adding body mass to the ANCOVA with waist circumference, had no effect on HDL, systolic and diastolic blood pressure and VO2 peak, however, it increased the F- and decreased the p-values for triglycerides. In addition, adding body mass to the ANCOVA with waist circumference further attenuated the F and p-values for velocity at AT. This may be due to the strong correlation between velocity at AT and VO2 max (see Table 27) and the strong correlations of waist and BMI with VO2 max (see Table 25). Therefore an ANCOVA was set up for velocity at AT, with VO2 max as an independent variable. The F- and p-values were 2.69 and 0.11 respectively. Adding body mass and waist to the model had a minimal effect on the F- (2.60) and the p-value (0.11).

4.5.2 Univariate correlation and multiple regression analyses for VO_2 peak and AT

Table 25 Univariate correlations between VO_2 peak and selected variables

Variables	**VO_2 peak**
Metabolic syndrome[†]	-0.56 (<0.0001)
Age	-0.21 (0.15)
Body Mass	-0.63 (<0.0001)
BMI	-0.69 (<0.0001)
Waist circumference	-0.76 (<0.0001)
Diastolic blood pressure	-0.36 (0.10)
Systolic blood pressure	-0.46 (0.001)
Fasting glucose level	-0.26 (0.07)
OGTT glucose level at 2 hours	-0.24 (0.12)
Velocity at AT	0.78 (<0.0001)
Fasting insulin level	-0.12 (0.46)
HOMA index	-0.21 (0.21)

[†]Presence of the metabolic syndrome was coded as 1 and absence was coded as 0; data given as r-value (p-value). r-values were obtained from Pearson correlation analysis.
OGTT = Oral glucose tolerance test
HOMA index = glucose×insulin/22.5.

Table 26 Univariate correlations between velocity at AT (anaerobic threshold) and selected variables

Variables	**Velocity at AT**
Metabolic syndrome [†]	-0.34 (0.01)
Age	-0.12 (0.39)
Body mass	-0.65 (<0.0001)
BMI	-0.58 (<0.0001)
Waist circumference	-0.66 (<0.0001)
Diastolic blood pressure	-0.25 (0.07)
Systolic blood pressure	-0.28 (0.04)
Fasting glucose level	-0.16 (0.23)
OGTT glucose level at 2 hours	-0.17 (0.24)
VO_2 peak	0.78 (<0.0001)
Fasting insulin level	-0.07 (0.67)
HOMA index	-0.12 (0.44)

[†]Presence of the metabolic syndrome was coded as 1 and absence was coded as 0; data given as r-value (p-value). r-values were obtained from Pearson correlation analysis
OGTT = Oral glucose tolerance test
HOMA index = glucose×insulin/22.5.

Table 27 Results of backward, stepwise multiple regression analyses for isolating principle determinants of VO_2 peak and anaerobic threshold (AT)

Regression model number	**Dependent variable**	**Independent variables with standardised beta coefficient and (p-value)**	**R^2 for full model with p-value**
1	VO_2 peak (log)	Metabolic syndrome†: -0.24 (0.005) Waist: -0.33 (0.003) Anaerobic threshold (log): 0.48 (<0.0001)	0.77 (<0.0001)
2	Anaerobic threshold (log)	VO_2 peak (log): 0.78 (<0.0001)	0.61 (<0.0001)

†Presence of the metabolic syndrome was coded as 1 and absence was coded as 0
R^2 values were obtained from backward stepwise multiple linear regression analyses

Pearson correlation analysis demonstrated that the VO_2 peak correlated with the following variables: body mass, BMI, waist circumference, diastolic and systolic blood pressure, fasting glucose levels and AT (Table 25). Velocity at AT correlated with the following variables: body mass, BMI, waist circumference, diastolic and systolic blood pressure and VO_2 peak (Table 26). These variables, as well as coding variables for the presence/absence of metabolic syndrome, were then included as independent variables in two separate backward, stepwise regression models in which VO_2 peak and AT were the dependent variables. In the first regression model, metabolic syndrome (negative relationship), waist circumference (negative relationship) and AT (positive relationship) were found to correlate with VO_2 peak (Table 27). In the second regression model, VO_2 peak (positive relationship) was the only correlate of AT (Table 27). The variable VO_2 peak is expressed per kg body mass. Body mass and waist are strongly correlated with

each other (r=0.88, p<0.0001 from Pearson univariate analysis) and therefore the relation between VO2 peak and waist observed in Table 27 may be due to confounding from body mass. Body mass was therefore placed into model 1 as an independent variable. Body mass did not displace waist from the model, as would be expected if the former variable was a confounder. Body mass was in fact not correlated with VO_2 peak (beta=0.33, p=0.054) whereas the correlation of waist with VO_2 peak was strengthened by the addition of body mass (beta=-0.62, p=0.0007).

4.5.3 Univariate correlation and multiple regression analyses for components of MetS and HOMA

Pearson correlation analysis was also performed for components of MetS that are used in diagnosis of this syndrome (Tables 28 – 31). Fasting glucose levels correlated with age, body mass, BMI, and waist circumference, with a close-to-significant correlation with VO_2 peak and fasting insulin (Table 28).

Table 28 Univariate correlations between fasting blood glucose levels and selected variables

Variables	**Fasting blood glucose**
Age	0.50 (0.0001)
Body mass	0.37 (0.005)
BMI	0.27 (0.05)
Waist circumference	0.38 (0.004)
VO_2 peak	-0.26 (0.07)
Velocity at AT	-0.16 (0.23)
Fasting insulin level	0.29 (0.06)

Data is given as r-value (p-value). r-values were obtained from Pearson correlation analysis
AT= Anaerobic Threshold

HDL-cholesterol correlated only with age (Table 29). Our analysis did not find any variables correlating with plasma triglycerides (Table 30).

Table 29 Univariate correlations between HDL-cholesterol and selected variables

Variables	**HDL-cholesterol**
Age	0.29 (0.03)
Body mass	0.05 (0.74)
BMI	0.04 (0.75)
Waist circumference	0.01 (0.94)
Triglycerides	-0.18 (0.19)
VO_2 peak	-0.08 (0.57)
Velocity at AT	0.07 (0.64)
Fasting insulin level	-0.08 (0.59)
HOMA index	0.03 (0.84)

Data given as r-value (p-value). r-values were obtained from Pearson correlation analysis
HOMA index = glucose×insulin/22.5.
AT= Anaerobic Threshold

Table 30 Univariate correlations between plasma triglycerides and selected variables

Variables	**Plasma triglycerides**
Age	-0.17 (0.22)
Body mass	0.08 (0.58)
BMI	-0.002 (0.99)
Waist circumference	0.002 (0.99)
HDL-cholesterol	-0.18 (0.19)
VO_2 peak	0.01 (0.93)
Velocity at AT	0.06 (0.66)
Fasting insulin level	0.01 (0.94)
HOMA index	0.02 (0.92)

Data given as r-value (p-value). r-values were obtained from Pearson correlation analysis
HOMA index = glucose×insulin/22.5. AT= Anaerobic Threshold

Correlation coefficients for the blood pressures are shown in Table 31. Systolic blood pressure correlated with age, body mass, BMI, waist circumference, VO_2 peak and AT and a close-to-significant correlation with HOMA (Table 31). Diastolic blood pressure correlated with body mass, BMI, waist circumference, VO_2 peak and AT (Table 31).

Table 31 Univariate correlations between systolic and diastolic blood pressure and selected variables

Variables	**Systolic blood pressure**	**Diastolic blood pressure**
Age	0.35 (0.008)	0.16 (0.25)
Body mass	0.33 (0.01)	0.29 (0.03)
BMI	0.36 (0.007)	0.33 (0.01)
Waist circumference	0.38 (0.004)	0.33 (0.02)
HDL-cholesterol	0.03 (0.81)	-0.09 (0.52)
Triglycerides	-0.03 (0.86)	0.05 (0.70)
VO_2 peak	-0.46 (0. 001)	-0.37 (0.01)
Velocity at AT	-0.28 (0.04)	-0.25 (0.07)
Fasting insulin	0.24 (0.13)	0.19 (0.23)
HOMA index	0.28 (0.07)	0.18 (0.25)

Data given as r-value (p-value). r-values were obtained from Pearson correlation analysis
HOMA index = glucose×insulin/22.5.
AT= Anaerobic Threshold

Insulin resistance has been identified as one of the possible causes of MetS (Eckel 2005). Therefore, this study also set up a regression model for HOMA to determine the variables that correlated with this measure of insulin resistance. Correlation coefficients for HOMA are shown in Table 32. HOMA correlated with body mass and waist circumference with p=0.1 (Table 32).

Table 32 Univariate correlations between HOMA index and selected variables

Variables	**Homa**
Age	0.17 (0.28)
Body mass	0.25 (0.10)
BMI	-0.07 (0.66)
Waist circumference	0.25 (0.10)
VO_2 peak	-0.21 (0.20)
Velocity at AT	-0.12 (0.44)

Data is given as r-value (p-value). r-values were obtained from Pearson correlation analysis
AT= Anaerobic Threshold

Correlating variables were included as independent variables in separate backward, stepwise regression models in which components of the MetS and HOMA were the dependent variables (Table 33). In the first regression model, age and body mass were found to correlate with fasting glucose (positive relationships). The second regression model showed age to correlate with HDL-cholesterol (positive relationship). In the third and fourth model, age (direct relationship) and VO_2 peak (negative relationship) both correlated with systolic blood pressure whilst in the fourth model, only VO_2 peak was related to diastolic blood pressure (negtive relationship). In the last regression model, no variables were retained (Table 33).

Table 33 Results of backward, stepwise multiple regression analyses for isolating principle determinants of components of the metabolic syndrome and HOMA

Regression model number	**Dependent variable**	**Independent variables with standardised beta coefficient (p-value)**	**R^2 for full model (p-value)**
1	Glucose (log)	Body mass (log): 0.16 (0.06) Age: 0.003 (0.001)	0.54 (<0.0001)
2	HDL-cholesterol	Age: 0.01 (0.03)	0.30 (<0.05)
3	Systolic blood pressure	Age: 0.47 (0.05) VO_2 peak (log): -46.3 (0.003)	0.53 (<0.0005)
4	Diastolic blood pressure	VO_2 peak (log): -21.9 (0.01)	0.36 (<0.01)

HDL = High-density lipoproteins.

R^2 values were obtained from backward stepwise multiple linear regression analyses

4.6 Discussion

The majority of differences in metabolic, cardiovascular and physical characteristics between the 2 subject groups of this study agree with the diagnosis criteria for MetS. The reason for including the non-MetS group in this study was so that we could identify variables that differed between the two groups and which may therefore be possible factors involved in the aetiology of the disease.

The VO_2 peak was lower in participants with MetS. Multiple regression analysis found that the lower VO_2 peak of participants with MetS is associated with their higher waist circumference. The VO_2 peak, in turn, was shown to correlate strongly with anaerobic

threshold. This study also found that both diastolic and systolic blood pressures were the only MetS components associated with cardio-respiratory fitness (VO_2 peak).

The MetS group in this study had higher body mass and waist circumference, higher triglyceride and blood pressure levels and lower HDL-cholesterol levels when compared to the healthy group. When adjusted for waist circumference in an ANCOVA (Table 25), the differences in systolic and diastolic blood pressure between the 2 subject groups became less significant suggesting that waist circumference explains some of the difference in blood pressures between MetS participants and healthy participants. The same was evident with VO2 peak and AT (Table 25). However, in the multiple regression analysis waist circumference did not correlate with AT, and only correlated with VO2 peak. This suggests that the reason adjusting for waist circumference in the ANCOVA for AT makes the p-value less significant is because of the correlation of waist circumference with VO2 peak. In addition, adjusting for waist circumference made the p-value for HDL-cholesterol much more significant and also slightly strengthened the p-level for triglycerides. This suggests that correcting for waist circumference uncovers unknown factors that cause HDL-cholesterol to be much lower in MetS than control participants.

Adding body mass to the ANCOVA with waist circumference had little effect on the F- and p-values for HDL-cholesterol, showing that waist is the main variable responsible for the difference in HDL-cholesterol between the two subject groups. This was also the case for systolic and diastolic blood pressure measures and VO2 peak. The finding further highlights the importance of reducing waist circumference in a person with MetS. For

triglycerides, adding body mass to the waist-adjusted ANCOVA increased the F- and reduced the p-value. This suggests that waist and body mass adjustment uncovers other variables that affect triglycerides levels and that are associated with waist and body mass. For velocity at AT, both waist and body mass attenuated the F- and increased the p-values in the ANCOVA comparing healthy and MetS participants. This shows that these variables may be responsible for the difference in AT between the two groups. However, neither waist or body mass correlated with AT in the multiple regression model for AT. However, waist and body mass did correlate with VO2 peak, which in turn correlated strongly with AT in a multiple regression model. This suggests that the effect of waist and body mass on the ANCOVA for AT was principally due to their correlation with VO2 peak. This was confirmed by performing an ANCOVA for AT with VO_2 peak as the independent variable. Adding body mass and waist circumference to this ANCOVA had minimal effect on the F- and p-values.

Even when corrected for waist circumference (and body mass) the MetS group had a significantly lower VO_2 peak than the non-MetS group (Table 24). This demonstares that waist is not the sole reason for the lower VO_2 peak in subjects with MetS. This finding agrees with the Kuoppio study (Lakka et al. 2003) that found directly determined VO_2 max to be lower in persons with MetS. Also, Laaksonen et al. (2002) showed that men with a VO_2 max of < 29.1 $ml.min^{-1}.kg^{-1}$ were 3 – 4 times more likely to have MetS than those with VO_2 max of $\geq 35.5 ml.min^{-1}.kg^{-1}$. These 2 values are in agreement with the VO_2 peak values of the subject groups in this study (Table 25). Furthermore, researchers have also found an inverse relationship between cardio-respiratory fitness and the

incidence of MetS (Carroll et al. 2000; Irwin et al. 2002; LaMonte et al. 2005). The difference in VO_2 peak between the two groups cannot be due to the healthy group training more than the MetS group, because all participants in the study had not exercised regularly for a minimum of 4 weeks prior to the testing. Adjusting for body mass had no effect on the ANCOVA for VO_2 peak, which suggests that the difference in VO2 peak between the 2 groups is due to waist circumference and not to total body mass .

The regression analysis using VO_2 peak as the dependent variable (Table 27) suggests that the lower VO_2 peak of participants with metabolic syndrome is associated with their higher waist circumference. This was confirmed in an ANCOVA comparing VO_2 peak between the two participant groups, where waist circumference was added as a covariate. This attenuated the F-value from 21.7 to 5.91 and the p-value from 0.0002 to 0.02 (Table 24). This finding confirms the data from chapter 2 that demonstrated that waist circumference correlates with VO_2 peak, and highlights the importance of reducing waist circumference in individuals with MetS, in order to improve energy production and health. It is interesting to note that both longitudinal (Eisenmann et al. 2005) and cross sectional studies (Jago et al. 2010) have shown that, of all anthropometric variables measured, only waist circumference was negatively correlated with level of fitness. It is not known why waist circumference specifically influences VO_2 peak. However, waist circumference is a proxy indicator of visceral fat mass (Pouliot et al. 1994) and this body fat depot is a negative regulator of whole body insulin sensitivity (Ross, 2002) and may therefore limit glucose metabolism in skeletal muscle.

The current study did not show a relationship between insulin resistance, as measured using HOMA, and VO_2 peak, however it did show that MetS was associated with VO_2 peak independently of waist circumference. A number of studies (Bogardus et al. 1985; Brochu et al. 2000; Goodpaster et al. 1997; Nyholm et al. 1996; Rosenthal et al. 1983) did identify a negative relationship between insulin resistance and VO_2 peak. Our divergent results may be due to differing profiles of the study participants. The limited range of VO_2 max achieved in sedentary participants (like those recruited into our study) may reduce the correlation between VO_2 max and insulin sensitivity (Smith, 1981). In addition, the relationship between VO_2 max and insulin sensitivity may be less apparent in obese individuals as the effect of adiposity becomes dominant (Toth et al. 2001). It is also possible that our study is insufficiently powered to pick up a relationship between HOMA and MetS and a larger cohort of participants is necessary to further investigate the correlation of MetS with VO_2 peak, particularly looking at MetS-related variables such as HOMA or visceral fat mass.

The regression model using HOMA as the dependent variable did not show any significant relationships with the included variables. This may be a result of the small sample number. The only variables included in the initial regression model were body mass and waist circumference, each having $p=0.1$ in the univariate analysis. These variables have been shown to have strong relationships with insulin resistance in many studies.

The regression analysis data using AT as the dependent variable demonstrated that the lower AT values in participants with the metabolic syndrome is largely associated with their lower VO_2 peak levels. This finding supports the notion of a lower level of aerobic fitness in patients with MetS, as has been demonstrated in other studies (Church, 2009; Eisenmann, 2007). Also, the higher velocity attained at AT by the healthy participants when compared to the participants with MetS, confirms the observation that persons with MetS exhibit a lower level of physical conditioning than their healthier counterparts (Lakka et al. 2003). This finding also agrees with the data of the study in a previous chapter (Chapter 2).

Aunola et al. (1988) constructed a factor model for aerobic work capacity. The model showed that maximal aerobic power (VO_2 max) correlated strongly with AT and vice-versa (r=0.92). This is also a reason why AT was included in the regression model for VO_2 peak and VO_2 peak was included in the regression model for AT. The model agrees with our findings and showed that AT correlated strongly with VO_2 max.
Another reason for the reciprocal inclusion of these parameters in the regression models, is that if AT changes, VO_2 peak or max does not necessarily change and if VO_2 peak or max changes, AT does not necessarily change.

Comparing the regression models for VO_2 peak and AT shown in Table 27 to those for the same dependent variables in Table 4 of Chapter 2, it can be seen that R^2 values are slightly higher for both models in Table 27. Furthermore, AT appears as a significant correlate of VO_2 peak in this study but not in the previous study, and body mass occurs as

a correlate of AT in the earlier study, but not in this study. These differences are most likely due to the higher N (55) in the current study (Table 27), as compared to 30 in the study from Chapter 2. The higher N will lead to a wider range for all variables.

Body mass and age were the only variables associated with fasting glucose in this study (Table 29). The cardio-respiratory parameters were not associated with this component of MetS. VO_2 max has been shown to be a significant predictor of total and non-oxidative glucose disposal (Toth et al. 2001). Furthermore, this measure of cardio-respiratory fitness has been found to be a stronger determinant of variation in glucose disposal than adiposity or caloric expenditure from physical activity in healthy individuals (Bogardus et al. 1985; Toth et al. 2001). However, the cited studies did not measure blood glucose levels but used the hyperinsulinemic euglycemic clamp and glucose dilution technique to assess glucose disposal (mg.kg fat-free mass (FFM)$^{-1}$.min^{-1}).

Age correlated with three of the five metabolic syndrome components (glucose, HDL-cholesterol and systolic blood pressure). This agrees with the finding that MetS is diagnosed in the latter years of life (Carroll et al. 2004).

Cardio-respiratory fitness (VO_2 peak) was shown to be associated with the MetS components of systolic and diastolic blood pressure. VO_2 peak is equal to cardiac output x arterio-venous oxygen difference and cardiac output is equal to mean arterial blood pressure / total peripheral resistance. These equations indicate that there is a degree of association between mean blood pressure and VO_2 peak. Mean arterial blood pressure

(MAP) obviously consists of elements of both systolic (SBP) and diastolic blood pressure(DBP) [MAP = (SBP/3-DBP/3)+DBP]. This highlights the involvement of systolic and diastolic blood pressure in the central cardio-vascular component of maximal aerobic capacity.

4.7 Conclusions

Multiple regression analysis found that the lower VO_2 peak of participants with MetS is associated with their higher waist circumference. The VO_2 peak, in turn, was shown to correlate with anaerobic threshold. This highlights the importance of reducing waist circumference in the treatment of MetS. Furthermore, increasing cardio-respiratory fitness in persons with MetS may positively influence their systolic and diastolic blood pressures. Also, the relationship observed here between waist and VO_2 peak is confirmed by the observation in Chapter 3 that an improvement of VO_2 peak is related to a fall in waist circumference.

4.8 References

1) Alberti KG. Eckel RH. Grundy SM et al. Harmonizing the Metabolic Syndrome. Circulation 2009, 120:1640-1645.
2) Aunola J. Merniemi E. Alanen M et al. Muscle metabolic profile and oxygen transport capacity as determinants of aerobic and anaerobic thresholds. Eur J Appl Physiol 1988, 57:726-734.

3) Bogardus C. Lillioja S. Mott DM et al. Relationship between degree of obesity and in vivo insulin action in man. Am J Physiol Endocrinol Metab 1985, 248:E286-E291.

4) Bourdon P. Blood Lactate Transition Thresholds: Concepts and Controversies. In: Gore CJ, Physiological Tests for Elite Athletes. Human Kinetics, Illinois, 2000:50-65.

5) Brochu M. Starling RD. Tchernof A et al. Visceral adipose tissue is an independent correlate of glucose disposal in older, obese, post-menopausal women. J Clin Endocrinol Metab 2000, 85:2378-2384.

6) Carroll S. Dudfield M. What is the relationship between exercise and Metabolic Abnormalities? A review of Metabolic Syndrome. Sports Med 2004, 34(6):371-418.

7) Carroll S. Cooke CB. Butterly RJ. Metabolic risk factor clustering , associations of both physical activity and cardiorespiratory fitness in middle-aged men. Med Sci Sports Exerc 2000, 32:2079-2086.

8) Cheng B. Kuipers H. Snyder A. A new approach for the determination of ventilatory and lactate thresholds. Int J Sports Med 1992, 13:518–522.

9) Church T. The low-fitness phenotype as a risk factor: more than just being sedentary? Obesity 2009, 17(3):S39–42.

10) Eckel RH. The metabolic syndrome. Lancet 2005, 365:1415-1428.

11) Eisenmann JC Wickel EE Welk GJ et al. Relationship between adolescent fitness and fatness and cardiovascular disease risk factors in adulthood: the Aerobics Center Longitudinal Study (ACLS). Am Heart J 2005, 149:46–53.

12) Eisenmann JC. Aerobic fitness, fatness and the metabolic syndrome in children and adolescents. Acta Paediatr 2007, 96:1723–1729.

13) Goodpaster BH. Thaete FL. Simoneau JA et al. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. Diabetes 1997, 46:1579-1585.

14) Irwin ML. Ainsworth BE. Mayer-Davis EJ. Physical activity and the multiple metabolic Syndrome in a tri-ethnic sample of women. Obes Res 2002, 10:1030-1037.

15) Jago R. Drews KL. McMurray RG et al. Fatness, fitness, and cardiometabolic risk factors among sixth-grade youth. Med Sci Sports Exerc 2010, 42:1502–1510.

16) Katzmarzyk PT. Church T. Blair S. Cardiorespiratory fitness attenuates the effects of metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004, 164(10):1092-1097.

17) Kullo IJ. Hensrud DD. Allison TG. Relation of low cardiorespiratory fitness to the metabolic syndrome in middle-aged men. Am J Cardiol 2002, 90:795-797.

18) Laaksonen DE. Lakka H-M. Salonen JT. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. Diabetes Care 2002, 25:1612-1618.

19) Lakka TA. Laaksonen DE. Lakka H-M et al. Sedentary life-style, poor cardiorespiratory fitness and the metabolic syndrome. Med Sci Sports Ex 2003, 35:1279-1286.

20) LaMonte MJ. Barlow CE. Jurca R et al. Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome. A prospective study of men and women. Circulation 2005, 112:505-512.

21) Matthews DR. Hosker JP. Rudenski AS et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985, 28:412-419.

22) Nyholm B. Mengel A. Nielsen S et al. Insulin resistance in relatives of NIDDM patients: the role of physical fitness and muscle metabolism. Diabetologia 1996, 39:822-831.

23) Pouliot MC. Despres JP. Lemieux S et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994, 73:460–468.

24) Rosenthal M. Haskell WL. Solomon R et al. Demonstration of a relationship between level of physical training and insulin-stimulated glucose utilization in normal humans. Diabetes 1983, 32:408-411.

25) Ross R. Aru J. Freeman J et al. Abdominal adiposity and insulin resistance in obese men. Am J Physiol Endocrinol Metab 2002, 282:E657–663.

26) Smith RJ. Interpretation of correlations in intraspecific and interspecific allometry. Growth 1981, 45:291-297.

27) Toth MJ. Sites CK. Cefalu WT et al. Determinants of insulin-stimulated glucose disposal in middle-aged premenopausal women. Am J Physiol Endocrinol Metab 2001, E113-E121.

28) Torres G. Crowther N. Rogers G. Reproducibility and levels of blood lactate transition thresholds in persons with metabolic syndrome. Metab Synd Rel Disord 2013, 11(2):121-127.

29) Whaley MH. Kampert JB. Kohl HW. Physical fitness and clustering of risk factors associated with the metabolic syndrome. Med Sci Sports Ex 1999, 31:287-293.

CHAPTER 5

5.1 Conclusions

The main aim of this thesis was to design an exercise program to optimize the effects on the metabolic profile of persons with MetS by using AT to set the exercise intensity. The study thus, firstly showed that AT is reproducible in persons with metabolic syndrome; AT tests can be used to set the exercise load for persons with MetS and that the Mader and ADAPT methods of determining the AT were similarly reproducible. The study then showed that an exercise program using AT to set exercise intensity was effective in improving the metabolic profile of persons with MetS. The exercise program using AT had similar outcomes on persons with MetS as the training program not using AT. The training program using AT however positively influenced insulin sensitivity. This was not evident in the other training groups. Furthermore, a smaller percent of individuals were still diagnosed with MetS after the training period in the training group using AT, as opposed to the training group not using AT. The training program using AT produced these outcomes at a training volume that was less than the training program not using AT. Thus, the training program designed in this study positively influenced the physical, physiological and metabolic profile of persons with MetS at a training volume that is practically possible in such a cohort. Our data also indicated that a 12 week training period is as effective in eliciting such improvements as a 20 week training duration.

A unique finding of this thesis was that the lower VO_2 peak and velocity at AT in individuals with MetS was associated with a greater waist circumference and a lower

VO_2 peak respectively. A decrease in waist circumference was also found to be associated with the improvement in VO_2 peak. This was confirmed by the regression model in the third study (Chapter 4) of this thesis which showed that waist circumference correlated with VO_2 peak. Therefore, reducing waist circumference in persons with MetS should be an important aim of an intervention program for the syndrome.

Another unique finding was that with training, VO_2 peak improved significantly only in the MetS groups and did not change significantly in the group without MetS. This indicates central training adaptation differences between these groups. In addition, the thesis found that increasing cardio-respiratory fitness in persons with MetS may positively influence their systolic and diastolic blood pressures and that a median weekly energy expenditure as low as 1238 kcal/wk produced substantial physical changes in persons with MetS, and some metabolic changes.

The BLTT test and modified ADAPT method of determining AT are simple, low-cost, reproducible ways of setting exercise intensity for persons with MetS that can be incorporated in the routine cardio-respiratory fitness assessment of an individual (e.g. can be done during the routine stress electro-cardiogram test). The test is a more specific cardio-respiratory fitness test for the person with MetS that can also be used by the health and fitness professional to design an exercise program and monitor progress.

Current blood lactate analysers (like the Nova biomedical lactate plus machine) (www.novabiomedical.com/products/lactate-plus) make testing additionally easier by

using very small capillary blood samples (0.7 μL as opposed to the 25 μL required by the lactate analyser used in this thesis), taking 13 seconds (as opposed to 60 seconds) for analysis and not requiring calibration codes for the testing strips which eliminates a source of measurement error. The pricing of these analysers has also reduced due to many types now becoming available in the market place.

The training program using AT can also be applied where there is no access to a gym facility. This can be done by using the heart rate (instead of the treadmill velocity) at which AT occurred in the BLTT test. Thus, pace of walking/jogging or inclined terrain can be used to increase heart rate into the required training zone. The training program using AT has a simple periodization that can be implemented in any setting using exercise intervention programs for MetS.

5.2 Limitations of the thesis

All participants in the three studies of this thesis were white males, and thus it cannot be assumed that the results will be the same for other ethnic groups and/ or females.

The second and third study had low numbers in each group, due to the subject drop-out rate. However, despite this limitation we were able to pick up significant trends in the data. The second study (Chapter 3) also did not have a non-exercising control group or a group without MetS that undertook the Leon et al. exercise programme (these groups were originally included in the study, but had to be removed due to financial constraints). The low N and the lack of sufficient control groups in the second study mean that the

conclusions drawn from this study must be treated with some reservation. Despite this, the training program using AT did produce comparable results to the walking program but at a lower training volume.

The nutritional intervention was not performed intensively. Furthermore, the study did not measure other MetS related factors e.g. inflammatory markers, markers of fibrinolysis and coagulation, endothelial markers etc. Visceral and subcutaneous fat mass were also not measured in this thesis. In addition the MetSV group in Chapter 3 did not differ in a statistically significant degree to the Non-MetS group in terms of metabolic or anthropometric parameters despite each subject in the former group being diagnosed with MetS. This may be a result of the small n numbers.

Also, the second study (Chapter 3) compared against only one other exercise regime (Leon et al. 1979) and insulin sensitivity was measured using HOMA and not the gold standard method (euglycaemic, hyperinsulinaemic clamp).
Furthermore, all blood lactate measures were taken on a portable machine rather than a laboratory autoanalyser. Also, the average of two blood pressure readings was used in the second study. The white-coat effect may have influenced the readings.

This was a cross sectional study and therefore causative agents could not be identified. Furthermore, regression models were used to find variables that correlated with a selection of different outcome variables, however such models can only identify correlations and cannot pinpoint causative factors. Furthermore, the current study did not

investigate the mechanisms involved by direct experimentation but used correlation analyses. Correlations can only show associations and do not demonstrate causality. Future experiments are required to determine whether the findings from correlation analysis are true causative.

5.3 Future research

A larger cohort of participants needs to be investigated with the inclusion of a non-exercising control group and a group without MetS that undertake an exercise program not using AT. Also, the MetSV training program needs to be compared to other training programs that are of different methodology to the Leon et al. 1979 program.

The response of women and other ethnic groups to such training programs needs to also be determined. In addition, the applicability of this method of exercise design to a large population group using primary health care facilities needs to be investigated.

The influence of psychological intervention programs in lifestyle modification therapies for MetS on exercise adherence levels needs further investigation.

A larger cohort of participants and more specific tests (i.e euglycemic clamp, muscle biopsies and MRI scans) are also necessary to further investigate the correlation of MetS with VO_2 peak, particularly looking at MetS-related variables such as HOMA, and visceral fat mass. The relationship between exercise training at the AT, insulin sensitivity

and skeletal muscle Glut-4 transporter levels also needs to be addressed with further research.

Analysis of waist circumference, visceral fat mass, insulin sensitivity measures and markers of skeletal muscle glucose metabolism and their relationship to different levels of VO2 peak may help investigate why the relationship between waist circumference and VO2 peak exists.

APPENDIX

A. Standardized nutrition program used in study of chapter 3

Nutrition programme

Follow the programme 6 days per week – one day free!

- Alcohol intake: preferably not more than 4 drinks a week

- No cakes/chocolates/sweets/fruit juice (unless very diluted)/sugar

Examples

Breakfast:

1 large Boiled/poached/scrambled egg

1 piece of Low GI or rye toast – lightly buttered

Tomato/mushroom/onion

OR

Poached haddock/smoked kippers/sardines

1 piece of Low GI or rye toast – lightly buttered

Tomato

OR

½ papino or few berries

Pure Whey Protein powder- 1 scoop

1 tablespoon plain yoghurt (optional)

½ glass water, ½ glass milk low fat

Blend together into a smoothie

OR

Small bowl of Oats + Whey Protein powder

+/- milk

Can add 1 tablespoon ground seeds

OR

Lean mince meat

1 piece Low GI or rye toast – lightly buttered

Tomato

OR

½ tub cottage cheese

1 piece low GI or rye toast-lighly buttered

Tomato/few slices of avo

LUNCH:

- Protein: ie. Chicken breast or tuna (1/2 – 1 tin)
- Salad ingredients – eg.Greens/tomato/cucumber/peppers/

/mushrooms/nuts/olives/sprouts/grated carrot/

- Add ½ an avocado
- Add Low fat cheese – mozzarella/cottage/feta/halloumi/
- Always have olive oil and may have other dressing
- May have a piece of Low Gi or rye bread or 2 provitas

OR

Cold lean meat – preferably not processed

Salad

Avocado

Olive Oil dressing

2 provita or 1 ryvita or Low Gi bread

SUPPER

Lean meat/chicken/fish (any sort) Red meat twice a week

Variety of salads and vegetables

NO starch at night or a little brown rice/sweet potato/new potato/quinoa

****

Snacks between meals: ie 11am and 3-4pm

- Nuts (any except peanuts). Almonds best. Small handful.
- Cottage cheese with tomato/cucumber/or berries
- Hummous with carrots
- Cold chicken, cold meat or Pickled fish
- Biltong. Only 30g. lean, low salt.
- NOT more than 2 fruit per day!!!! Try to combine protein eg. Nuts (5-7 almonds).Best fruit: strawberries, cherries, plums. Pears, apple, citrus

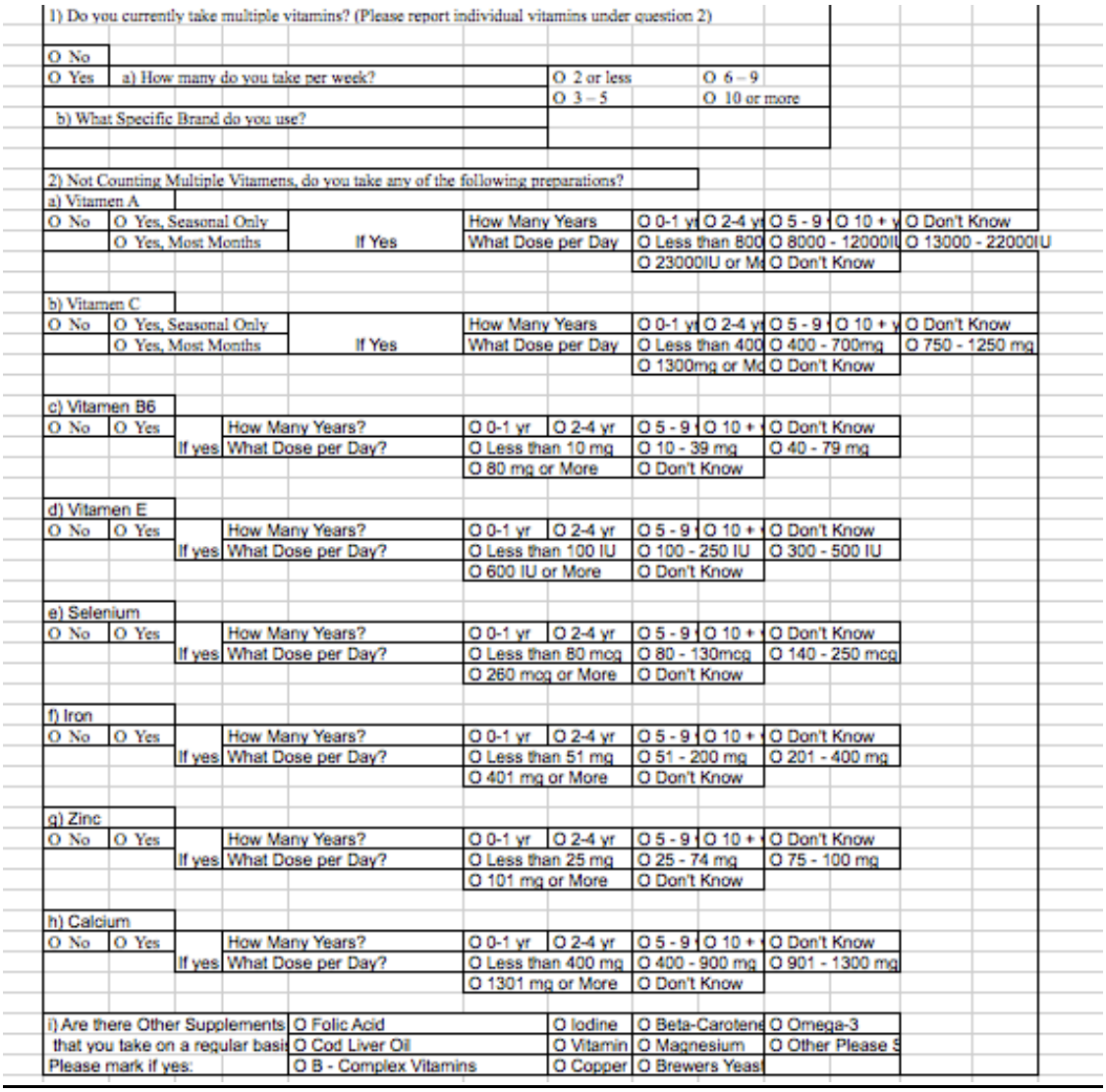
Ideas for Vegetables:

- Spinach – particularly baby spinach leaves
- Broccoli/cauliflower
- peas
- Baby marrow
- Green beans

- Gem squash
- Patty pans – green or yellow
- Asparagus
- Tomato/ peppers
- Butternut/pumpkin/carrot/corn – watch quantities!

May grill veg with olive oil and herbs or have with hummous/pesto/avo/pine nuts.

B: The Willett food frequency questionnaire



1) Do you currently take multiple vitamins? (Please report individual vitamins under question 2)									
O No									
O Yes	a) How many do you take per week?			O 2 or less		O 6 – 9			
				O 3 – 5		O 10 or more			
	b) What Specific Brand do you use?								
2) Not Counting Multiple Vitamens, do you take any of the following preparations?									
a) Vitamen A									
O No	O Yes, Seasonal Only		How Many Years	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 + y	O Don't Know	
	O Yes, Most Months	If Yes	What Dose per Day	O Less than 800		O 8000 - 12000IU		O 13000 - 22000IU	
				O 23000IU or Mo		O Don't Know			
b) Vitamen C									
O No	O Yes, Seasonal Only		How Many Years	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 + y	O Don't Know	
	O Yes, Most Months	If Yes	What Dose per Day	O Less than 400		O 400 - 700mg		O 750 - 1250 mg	
				O 1300mg or Mo		O Don't Know			
c) Vitamen B6									
O No	O Yes		How Many Years?	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 +	O Don't Know	
		If yes	What Dose per Day?	O Less than 10 mg		O 10 - 39 mg		O 40 - 79 mg	
				O 80 mg or More		O Don't Know			
d) Vitamen E									
O No	O Yes		How Many Years?	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 +	O Don't Know	
		If yes	What Dose per Day?	O Less than 100 IU		O 100 - 250 IU		O 300 - 500 IU	
				O 600 IU or More		O Don't Know			
e) Selenium									
O No	O Yes		How Many Years?	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 +	O Don't Know	
		If yes	What Dose per Day?	O Less than 80 mcg		O 80 - 130mcg		O 140 - 250 mcg	
				O 260 mcg or More		O Don't Know			
f) Iron									
O No	O Yes		How Many Years?	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 +	O Don't Know	
		If yes	What Dose per Day?	O Less than 51 mg		O 51 - 200 mg		O 201 - 400 mg	
				O 401 mg or More		O Don't Know			
g) Zinc									
O No	O Yes		How Many Years?	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 +	O Don't Know	
		If yes	What Dose per Day?	O Less than 25 mg		O 25 - 74 mg		O 75 - 100 mg	
				O 101 mg or More		O Don't Know			
h) Calcium									
O No	O Yes		How Many Years?	O 0-1 yr	O 2-4 yr	O 5 - 9	O 10 +	O Don't Know	
		If yes	What Dose per Day?	O Less than 400 mg		O 400 - 900 mg		O 901 - 1300 mg	
				O 1301 mg or More		O Don't Know			
i) Are there Other Supplements		O Folic Acid		O Iodine		O Beta-Carotene		O Omega-3	
that you take on a regular basi		O Cod Liver Oil		O Vitamin		O Magnesium		O Other Please S	
Please mark if yes:		O B - Complex Vitamins		O Copper		O Brewers Yeast			

3) For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year:	Average Use Last Year								
Dairy Foods	Never or less than once per month	1-3 per Month	1 per Week	2 - 4 per Week	5 - 6 per Week	1 per day	2 - 3 per Day	4 - 5 per day	6 + per day
Skim or Low Fat Milk (8 oz. glass)	O	O	O	O	O	O	O	O	O
Whole Milk (8 Oz. glass)	O	O	O	O	O	O	O	O	O
Cream, e.g. Coffee Whipped (Tbs)	O	O	O	O	O	O	O	O	O
Sour Cream (Tbs)	O	O	O	O	O	O	O	O	O
Non-Dairy Coffee Whitener (Tsp)	O	O	O	O	O	O	O	O	O
Sherbet or Ice Milk (¼ Cup)	O	O	O	O	O	O	O	O	O
Ice Cream	O	O	O	O	O	O	O	O	O
Yoghurt (1 Cup)	O	O	O	O	O	O	O	O	O
Cottage or Ricotta Cheese (½ Cup)	O	O	O	O	O	O	O	O	O
Cream Cheese (1 oz.)	O	O	O	O	O	O	O	O	O
Other Cheese (1 Slice or 1 oz.)	O	O	O	O	O	O	O	O	O
Margerine (Added to food or bread Exclude Use in Cooking	O	O	O	O	O	O	O	O	O
Butter (Added to food or bread Exclude Use in Cooking	O	O	O	O	O	O	O	O	O

	Average Use Last Year								
Fruits	Never or less than once per month	1-3 per Month	1 per Week	2 - 4 per Week	5 - 6 per Week	1 per day	2 - 3 per Day	4 - 5 per day	6 + per day
Raisins (1 oz. or small packet of grapes)	O	O	O	O	O	O	O	O	O
Prunes (½ Cup)	O	O	O	O	O	O	O	O	O
Bananas (1)	O	O	O	O	O	O	O	O	O
Cantaloupe (½ Melon)	O	O	O	O	O	O	O	O	O
Watermelon (1 Slice)	O	O	O	O	O	O	O	O	O
Fresh Apples or Pears (1)	O	O	O	O	O	O	O	O	O
Apple Juice or Cider (Small Glass)	O	O	O	O	O	O	O	O	O
Oranges (1)	O	O	O	O	O	O	O	O	O
Orange Juice (Small Glass)	O	O	O	O	O	O	O	O	O
Grapefruit (½)	O	O	O	O	O	O	O	O	O
Grapefruit Juice (Small Glass)	O	O	O	O	O	O	O	O	O
Other Fruit Juices (Small Glass)	O	O	O	O	O	O	O	O	O
Strawberries (Fresh, Frozen or Canned)(½ Cu	O	O	O	O	O	O	O	O	O
Blueberries (Fresh, Frozen or Canned)(½ Cup	O	O	O	O	O	O	O	O	O
Peaches, Apricots or Plums (1 Fresh or ½ Cup Canned	O	O	O	O	O	O	O	O	O

Vegetables	Average Use Last Year: Never or less than once per month	1-3 per Month	1 per Week	2 - 4 per Week	5 - 6 per Week	1 per day	2 - 3 per Day	4 - 5 per day	6 + per day
Tomatoes (1)	O	O	O	O	O	O	O	O	O
Tomato Juice (Small Glass)	O	O	O	O	O	O	O	O	O
Tomato Sauce (½ Cup) e.g. Spaghetti Sauce	O	O	O	O	O	O	O	O	O
Red Chili Sauce (1 Tbs)	O	O	O	O	O	O	O	O	O
Tofu or Soybeans (3 - 4oz.)	O	O	O	O	O	O	O	O	O
String Beans (½ Cup)	O	O	O	O	O	O	O	O	O
Broccoli (½ Cup)	O	O	O	O	O	O	O	O	O
Cabbage or Coleslaw (½ Cup)	O	O	O	O	O	O	O	O	O
Cauliflower (½ Cup)	O	O	O	O	O	O	O	O	O
Brussel Sprouts (½ Cup)	O	O	O	O	O	O	O	O	O
Carrots, Raw (½ Carrot or 2 - 4 sticks)	O	O	O	O	O	O	O	O	O
Carrots, Cooked (½ Cup)	O	O	O	O	O	O	O	O	O
Corn (1 Ear or ½ Cup Frozen or Canned)	O	O	O	O	O	O	O	O	O
Peas, or Lima Beans (½ Cup Fresh, Frozen or Canne	O	O	O	O	O	O	O	O	O
Mixed Vegetables (½ Cup)	O	O	O	O	O	O	O	O	O
Beans or Lentils, Baked or Dried (½ Cup)	O	O	O	O	O	O	O	O	O
Yellow (winter) Squash (½ Cup)	O	O	O	O	O	O	O	O	O
Eggplant, Zucchini or other Summer Squash (½ Cup)	O	O	O	O	O	O	O	O	O
Yams or Sweet Potatoes (½ Cup)	O	O	O	O	O	O	O	O	O
Spinach, Cooked (½ Cup)	O	O	O	O	O	O	O	O	O
Spinach, Raw as in Salad	O	O	O	O	O	O	O	O	O
Kale, Mustard or Chard Greens (½ Cup)	O	O	O	O	O	O	O	O	O
Iceberg or Head Lettuce (Serving)	O	O	O	O	O	O	O	O	O
Romaine or Leaf Lettuce (Serving)	O	O	O	O	O	O	O	O	O
Celery (4 Sticks)	O	O	O	O	O	O	O	O	O
Beets (½ Cup)	O	O	O	O	O	O	O	O	O
Alfalfa Sprouts (½ Cup)	O	O	O	O	O	O	O	O	O
Garlic Fresh or Powdered (1 Clove or Shake)	O	O	O	O	O	O	O	O	O

Eggs, Meat, etc.	Average Use Last Year: Never or less than once per month	1-3 per Month	1 per Week	2 - 4 per Week	5 - 6 per Week	1 per day	2 - 3 per Day	4 - 5 per day	6 + per day
Eggs (1)	O	O	O	O	O	O	O	O	O
Chicken and Turkey with Skin (4-6oz.)	O	O	O	O	O	O	O	O	O
Chicken and Turkey without Skin (4-6 oz.)	O	O	O	O	O	O	O	O	O
Bacon (2 Slices)	O	O	O	O	O	O	O	O	O
Hot Dogs (1)	O	O	O	O	O	O	O	O	O
Processed Meats e.g. sausage, salami etc. (piece/sli	O	O	O	O	O	O	O	O	O
Liver (3 - 4 oz.)	O	O	O	O	O	O	O	O	O
Hamburger (1 Patty)	O	O	O	O	O	O	O	O	O
Beef, Pork or Lamb as a Sandwich or Mixed Dish e.g. Stew, Cassarole, Lasagne etc.	O	O	O	O	O	O	O	O	O
Beef, Pork or Lamb as a Main Dish e.g. Steak, Roast, Ham etc. (4 - 6oz.)	O	O	O	O	O	O	O	O	O
Canned Tuna Fish (3 - 4oz.)	O	O	O	O	O	O	O	O	O
Dark Meat Fish e.g. Salmon, Sardines (3 - 5oz.)	O	O	O	O	O	O	O	O	O
Other Fish (3 - 5oz.)	O	O	O	O	O	O	O	O	O
Shrimp, Lobster, Scallops as a Main Dish	O	O	O	O	O	O	O	O	O

			Average Use Last Year								
			Never or less than once per month	1-3 per Month	1 per Week	2 - 4 per Week	5 - 6 per Week	1 per day	2 - 3 per Day	4 - 5 per day	6 + per day
		Breads, Cereals, Starches									
		Cold Breakfast Cereal (1 Cup)	O	O	O	O	O	O	O	O	O
		Cooked Oatmeal (1 Cup)	O	O	O	O	O	O	O	O	O
		Other Cooked Breakfast Cereal (1 Cup)	O	O	O	O	O	O	O	O	O
		White Bread (slice), including Pita Bread	O	O	O	O	O	O	O	O	O
		Dark Bread (slice)	O	O	O	O	O	O	O	O	O
		English Muffins, Bagels or Rolls (1)	O	O	O	O	O	O	O	O	O
		Muffins or Biscuits (1)	O	O	O	O	O	O	O	O	O
		Brown Rice (1 Cup)	O	O	O	O	O	O	O	O	O
		White Rice (1 Cup)	O	O	O	O	O	O	O	O	O
		Pasta e.g. Spaghetti, Noodles etc (1 Cup)	O	O	O	O	O	O	O	O	O
		Other Grains e.g. Bulgar, Couscouc etc. (1 Cu	O	O	O	O	O	O	O	O	O
		Pancakes or Waffles (serving)	O	O	O	O	O	O	O	O	O
		French Fried Potatoes (4 oz.)	O	O	O	O	O	O	O	O	O
		Potatoes Baked, Boiled (1) or Mashed (1 Cup	O	O	O	O	O	O	O	O	O
		Potato Chips or Corn Chips (Small Bag or 1 o	O	O	O	O	O	O	O	O	O
		Crackers, Triskets, Wheat Thins (1)	O	O	O	O	O	O	O	O	O
		Pizza (2 slices)	O	O	O	O	O	O	O	O	O

			Average Use Last Year								
			Never or less than once per month	1-3 per Month	1 per Week	2 - 4 per Week	5 - 6 per Week	1 per day	2 - 3 per Day	4 - 5 per day	6 + per day
		Beverages									
Carbonated	Low Calorie	Low Calorie Cola e.g. Tab with Caffeine	O	O	O	O	O	O	O	O	O
Beverages	(Sugar Free)	Low Calorie Caffiene Free Cola e.g. Pepsi Fre	O	O	O	O	O	O	O	O	O
Serving Siz	Types	Other Low Calorie Carbonated Beverages e.g									
1 Glass,		Fresca, Diet Ginger Ale	O	O	O	O	O	O	O	O	O
Bottle or	Regular Types	Coke, Pepsi or other Cola with Sugar	O	O	O	O	O	O	O	O	O
Can for	(Not Sugar	Caffiene Free Coke, Pepsi or other Cola with	O	O	O	O	O	O	O	O	O
these	Free)	Other Carbonated Beverage with Sugar e.g. 7	O	O	O	O	O	O	O	O	O
	Other Beverages	Hawaiian Punch, Lemonade or other Non-Carl									
		Fruit Drinks (1 Glass, Bottle, Can)	O	O	O	O	O	O	O	O	O
		Decaffeinated Coffee (1 Cup)	O	O	O	O	O	O	O	O	O
		Coffee (1 Cup)	O	O	O	O	O	O	O	O	O
		Tea (1 Cup) Not Herbal Teas	O	O	O	O	O	O	O	O	O
		Beer (1 Glass, Bottle, Can)	O	O	O	O	O	O	O	O	O
		Red Wine (4 oz. Glass)	O	O	O	O	O	O	O	O	O
		White Wine (4 oz. Glass)	O	O	O	O	O	O	O	O	O
		Liquor e.g. Whiskey, Gin etc (1 Drink or Shot)	O	O	O	O	O	O	O	O	O

	Average Use Last Year								
Sweets, Baked Goods, Miscellaneous	Never or less than once per month	1-3 per Month	1 per Week	2 - 4 per Week	5 - 6 per Week	1 per day	2 - 3 per Day	4 - 5 per day	6 + per day
Chocolates (Bars or Pieces)	O	O	O	O	O	O	O	O	O
Candy Bars	O	O	O	O	O	O	O	O	O
Candy without Chocolate	O	O	O	O	O	O	O	O	O
Cookies, Home Baked (1)	O	O	O	O	O	O	O	O	O
Cookies, Ready Made (1)	O	O	O	O	O	O	O	O	O
Brownies (1)	O	O	O	O	O	O	O	O	O
Doughnuts (1)	O	O	O	O	O	O	O	O	O
Cake, Home Baked (slice)	O	O	O	O	O	O	O	O	O
Cake, Ready Made (slice)	O	O	O	O	O	O	O	O	O
Sweet Roll, Coffee Cake or other Pastry Hom	O	O	O	O	O	O	O	O	O
Sweet Roll, Coffee Cake or other Pastry Read	O	O	O	O	O	O	O	O	O
Pie, Home Made (slice)	O	O	O	O	O	O	O	O	O
Pie, Ready Made (slice)	O	O	O	O	O	O	O	O	O
Jams, Jellies, Preserves, Syrup or Honey (1 T	O	O	O	O	O	O	O	O	O
Peanut Butter (Tbs)	O	O	O	O	O	O	O	O	O
Popcorn (1 Cup)	O	O	O	O	O	O	O	O	O
Nuts (Small Packet or 1 oz.)	O	O	O	O	O	O	O	O	O
Bran (Added to Food 1 Tbs)	O	O	O	O	O	O	O	O	O
Wheatgerm (1 Tbs)	O	O	O	O	O	O	O	O	O
Chowder or Cream Soup (1 Cup)	O	O	O	O	O	O	O	O	O
Oil and Vinegar Dressing e.g. Italian (1 Tbs)	O	O	O	O	O	O	O	O	O
Mayonnaise or other Creamy Salad Dressing	O	O	O	O	O	O	O	O	O
Mustard, Dry or Prepared (1 tsp)	O	O	O	O	O	O	O	O	O
Pepper (1 Shake)	O	O	O	O	O	O	O	O	O
Salt (1 Shake)	O	O	O	O	O	O	O	O	O

4) How much of the visible fats on your meats do you remove before eating?

O Remove all visible fa | O Remove Small Part of Fat
O Remove Majority | O Remove None
O Don't Eat Meat

5) What kind of fat do you usually use for frying and sauteing?

O Real Butter | O Vegetable Oil
O Margerine | O Vegetable Shortening
O Lard

6) What kind of fat do you usually use for Baking?

O Real Butter | O Vegetable Oil
O Margerine | O Vegetable Shortening
O Lard

7) What form of Margerine do you usually use?

O None | O Tub
O Stick | O Low Calorie Tub
O Low Calorie Stick | O Spread

8) How often do you eat food that is fried at home?

O Daily | O 4-6 times per week
O 1-3 times per week | O Less than once per week

9) How often do you eat fried food away from home?

O Daily | O 4-6 times per week
O 1-3 times per week | O Less than once per week

10) How many teaspoons of sugar d add to your beverages or food e

Specify type and brand

11) What type of Cooking Oil do you usually use?

Specify type and brand

12) What type of cold Breakfast Cer do you usually use?

Specify type and brand

13) Are there any other important foods that you usually eat at least once per week?

Include for example: paté, tortillas, yeast, cream sauce, custard, horseradish, parsnips, rhubarb, radishes, fava beans, carrot juice, coconut, avocado, mango, papaya, dried apricots, dates, figs

(Do not include dry spices and do not include something that has been listed in the previous sections)

Other foods that you usually use at least once per week	Usual Serving Size	Servings per week
a)		
b)		
c)		
d)		

C: 24 hour eating record used for study of chapter 3

Date:			Name:			
	Beverage		Food			
Time	Type	Quantity	Type	Quantity	Preperation	Comments

D: Copy of published paper:

METABOLIC SYNDROME AND RELATED DISORDERS
Volume 11, Number 2, 2013
© Mary Ann Liebert, Inc.
Pp. 121–127
DOI: 10.1089/met.2012.0092

Reproducibility and Levels of Blood Lactate Transition Thresholds in Persons with Metabolic Syndrome

Georgia Torres, MSc Med,[1] Nigel John Crowther, PhD,[2] and Geoff Rogers, PhD[2]

Abstract

Background: The optimal exercise load/intensity for exercise programs for individuals with metabolic syndrome has not been investigated. One method of determining optimal exercise load is to measure the blood lactate transition threshold (BLTT), referred to as the anaerobic threshold (AT). This study investigated the reproducibility of BLTT testing and the consequent determination of AT via the Mader method and a modified form of the Automatic Data Analysis for Progressive Tests (ADAPT) method in patients with metabolic syndrome.
Methods: Fifteen, male patients diagnosed with metabolic syndrome and 15 healthy, male subjects each performed BLTT measurements on a treadmill at the same daily times on three different days. Peak oxygen consumption was also determined during testing.
Results: There was no significant difference in treadmill velocity at AT determined by the Mader method or the modified ADAPT method within both groups ($P > 0.05$). Both methods yielded good coefficients of variation. When combining both groups, the typical error also demonstrated good reproducibility. The mean treadmill velocity at AT was higher in the healthy compared to the metabolic syndrome group using both the Mader and the ADAPT method. Regression analysis and analysis of covariance (ANCOVA) demonstrated that this difference was largely due to a higher oxygen consumption (VO_2) peak in the healthy group. The study also found an association between VO_2 peak and waist circumference among the metabolic syndrome group.
Conclusions: This study demonstrated that BLTT tests are reproducible in persons with metabolic syndrome. The modified ADAPT method may be the preferred method of determining treadmill velocity at AT because fewer factors are known to influence its determination.

Introduction

The metabolic syndrome has been identified as a major health challenge[1–3] and has been shown to be a significant predictor of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).[3–5] In addition, the syndrome confers additional risk to those accounted for by traditional CVD scoring paradigms.[6]

Lifestyle changes, most especially following a controlled exercise program, have been shown to play a major role in the therapeutic management of metabolic syndrome.[6] To maximize the exercise response for any person involved with a training program (including persons with metabolic syndrome), one needs to identify an individual's optimal exercise load (exercise intensity), duration of exercise, and exercise frequency. Standards have been set for the last two,[7] but it is more difficult to determine the first. Blood lactate transition thresholds (BLTT) have been shown to be the best indices for setting exercise intensity.[8–13] It has been shown that an increase in physical activity is sufficient to elicit a training effect provided that the initial training intensity is at or above the anaerobic threshold (AT).[8] It is speculated that at intensities close to 100% of AT, sympathetic activity increases to a level that results in adaptive changes of regulatory hormones and muscle metabolism.[13,14] This method of exercise intensity determination has not been applied to training programs for individuals with metabolic syndrome. Optimizing exercise results for metabolic syndrome patients may also be important in improving exercise adherence levels, which are low in individuals with this syndrome.[15]

Therefore, the main aim of this study was to investigate the most appropriate method of determining BLTT in persons with metabolic syndrome. Most BLTT methods can be broadly classified into two categories: Those using fixed blood lactate concentrations (*e.g.*, the Mader method), and

[1]Department of Physiology and [2]Department of Chemical Pathology, National Health Laboratory Service, University of the Witwatersrand Faculty of Health Sciences, Johannesburg, South Africa.

those using individualized lactate and ATs [*e.g.*, the Automatic Data Analysis for Progressive Tests (ADAPT) method].

To use BLTT for determining the appropriate exercise intensity to be used in subjects with metabolic syndrome, it is necessary to determine the best method for measuring BLTT in such subjects, because this has not previously been attempted. In addition, because the BLTT of patients with metabolic syndrome has not been measured in other studies, this investigation aimed to determine the BLTT of such patients.

Methods

The Human Ethics Committee of the University of the Witwatersrand, Gauteng, accepted the study protocol.

Fifteen male patients diagnosed with metabolic syndrome and 15 healthy subjects each performed three BLTT tests. All healthy participants were age-matched with the patient group and had one or no components of metabolic syndrome. Patients were diagnosed with metabolic syndrome by clinicians using the harmonized guidelines.[2] The presence of any three of the five criteria denoted below constituted a diagnosis of metabolic syndrome: Waist circumference ($\geq$94 cm), triglycerides ($\geq$1.7 mmol/L) or drug treatment for high triglycerides, high-density lipoprotein cholesterol (HDL-C) ($<$1.0 mmol/L) or drug treatment for reduced HDL-C, elevated blood pressure ($\geq$130/85) or on antihypertensive drug treatment, and elevated fasting glucose ($\geq$5.6mmol/L) or drug treatment for glucose intolerance.

All participants underwent an oral glucose tolerance test (OGTT) for the detection of undiagnosed diabetes. Fasting and 2-hr glucose levels were measured using a glucose oxidase method (Roche Diagnostics, Mannheim, Germany) whereas fasting triglyceride, total cholesterol, and HDL-C levels were assayed using enzymatic assay methods (Roche Diagnostics, Mannheim, Germany).

The following were determined on the first day of laboratory testing: Height (measured to the nearest millimeter by a Seca Stadiometer, Hamburg, Germany); weight (measured to the nearest gram by a Charder electronic scale, Taiwan, China); waist circumference (taken as the greatest reading around the girth, midway between lateral lower ribs and the iliac crests); blood pressure (measured by a Honsun sphygmomanometer, Shanghai, China; sitting, average of two readings), and a BLTT test was performed and the time of day was noted.

The BLTT test was repeated at the same time of day a total of three times, with 1 day rest in between tests. As in the study of Heitcamp et al.,[16] participants did not vary their usual dietary habits, exercise, or leisure-time activities between the three tests. All participants did not exercise for 12 hr before the testing sessions.

The BLTT test used an initial treadmill speed of 2.5 kph at a 5% gradient with speed increments every 4 min. The treadmill speed was modified depending on the response of a participant to ensure the collection of at least six blood samples for lactate analysis. After signaling impending exhaustion, participants were encouraged to continue to complete the 30-sec period already begun.

Electrocardiographic responses and oxygen consumption (VO_2) were measured at the same time (Cortex Biophysik Metalyzer 3b CPX system, Leipzig, Germany). The electrocardiograph (ECG) was used to monitor electrocardiographic responses during testing of the participants. Testing was stopped if any ECG abnormalities were observed. VO_2 at exhaustion was recorded as the VO_2 peak. No abnormalities in ECG readings were observed. This protocol was designed taking into consideration the low level of physical conditioning of patients with metabolic syndrome.

Lactate concentration was measured from whole-blood samples taken from the fingertip using the Lactate Scout automated analyzer (Lactate Scout, SensLab, Leipzig). Blood samples (collected from finger capillary vessels using a lancet) were taken at the end of each exercise period within 30–40 sec of the participants standing still on the treadmill. The fingertip was first wiped with water to remove the sweat and then it was dried before the blood sample was collected. The participant continued exercising within one minute of standing.

The BLTT that was determined for each participant will be defined in this study, for purposes of terminology, as AT. AT, in this study, will be defined as the workload (treadmill velocity given as $km \cdot h^{-1}$) marked by a rapid rise in blood lactate denoting the upper limit of equilibrium between lactate production and clearance.[17] The treadmill velocity at AT for each BLTT test was determined using two methods: The Mader method and the ADAPT method, as these are the two most frequently used and recognized methods for assessing AT.

The Mader method determines AT as the workload that corresponds to the fixed blood lactate level of 4 $mmol \cdot L^{-1}$.[18] This was calculated using Lactate Scout software. The software fits the data with a third-degree polynomial regression curve and then determines the velocity at 4 $mmol \cdot L^{-1}$ blood lactate

The ADAPT method determines AT from the individual shape of the velocity–blood lactate curve (not from a fixed blood lactate concentration). The ADAPT method is based on the $Dmax_{mod}$ method.[19] It determines AT by calculating the workload corresponding to the greatest perpendicular distance from a regression curve relating workload to blood lactate and a straight line formed by the first and last points of the curve. When using the ADAPT method, the Australian Sports Commission modified the $Dmax_{mod}$ analysis by defining the first point as the workload preceding a 0.4 mmol/L rise in blood lactate above the baseline.[17] However, the use of a particular datapoint on the curve to determine the first point is artificial and arbitrary, and this study redefined this point as the lowest point on the curve. This point was then connected to the last point of the curve that was defined as the lactate concentration measured at VO_2 peak (Fig. 1). The modified ADAPT method used in this study allows for a consistent and reproducible first and last point of the curve. A two-phase exponential regression was fitted to the datapoints in our modification of the ADAPT method (GraphPad Prism Version 3.02) (Fig. 1). The regression curves fitted to our data yielded high correlations (R^2=0.9691–0.9995).

The % VO_2 peak at AT was calculated by first determining the VO_2 at AT. This was determined in the same way described above (ADAPT method), but with VO_2 on the x axis as opposed to velocity. The VO_2 at AT was then expressed as a percentage of VO_2 peak.

Statistical analysis

Data distribution was analyzed using Shapiro–Wilk W test, and any variables that were found to be significantly

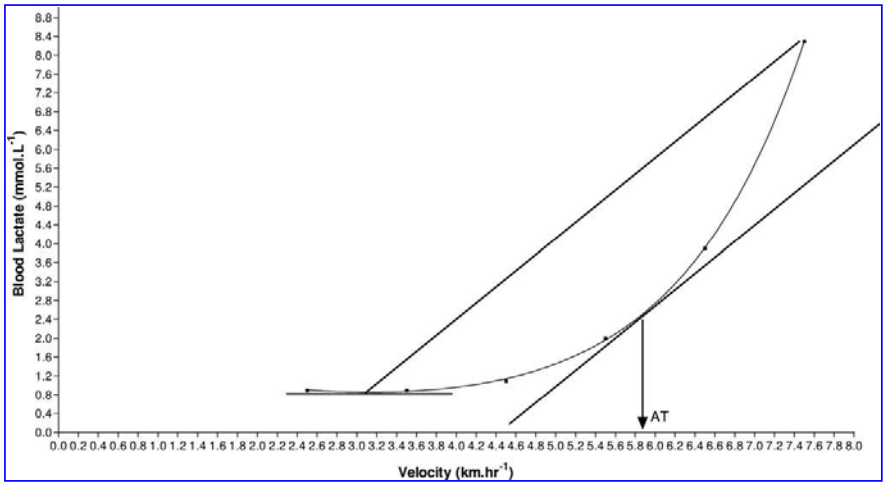


FIG. 1. The modified Automatic Data Analysis for Progressive Tests (ADAPT) method, using the lactate value at oxygen consumption (VO_2) peak as the end point and the lowest point on the curve as the first point, to measure anaerobic threshold (AT).

skewed were log transformed to normality, *i.e.*, $P > 0.05$ by the Shapiro–Wilk W test. Coefficients of variation [CV = (Standard deviation/Mean) × 100] were calculated between testing sessions for the two groups. We confirmed our findings by also using the typical error technique as reported by Hopkins.[20] The Bland–Altman method was used to assess agreement between the Mader and modified ADAPT methods. The average values of the two groups were compared using the independent *t* statistic. Pearson correlation analyses were used to determine the principal correlates of the VO_2 peak and the AT. Variables that gave significant correlations in the univariate analyses ($P < 0.1$) were then used as independent variables in two separate multiple regression models in which VO_2 peak and AT were the dependent variables. Collinearity was assessed by calculating the variance inflation factors (VIFs) and variables with a VIF >10 were excluded from the initial regression models. Backward, stepwise regression analysis was then performed until only variables with $P < 0.05$ remained in the model. One-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were then used to confirm the data from the regression models. The results of the multiple regression models were the same for AT measured using the ADAPT or Mader methods.

Results

Table 1 depicts the physical characteristics of the participants. There were significant differences between the groups in waist circumference, HDL, triglycerides, systolic blood pressure, and VO_2 peak. Fasting and 2-hr glucose levels, total cholesterol, diastolic blood pressure, body mass, and age were not significantly different between the groups. No undiagnosed diabetic subjects were detected.

The percentage of VO_2 peak associated with AT was 73.4 ± 7.8% in the group with metabolic syndrome, and 75.8 ± 8.8% in the group without metabolic syndrome. This difference was not significant ($P > 0.05$). There was no significant difference ($P > 0.05$) in velocity at AT determined by the Mader method or the modified ADAPT method in both participant groups. Both methods of determining velocity at AT yielded good (<4%) CV values. There was no statistical difference between the CV values of the two groups (Table 2). The healthy males attained a significantly higher velocity at AT than that attained by the males with metabolic syndrome for both the Mader method ($P < 0.05$) and the modified ADAPT method ($P < 0.05$) (Table 2).

Our findings of good reproducibility were confirmed when we used an alternate method of calculating reproducibility, *i.e.*, the typical error technique reported by Hopkins,[20] which gave values of 3.1%, 0.29 $km \cdot h^{-1}$ and 4%, 0.27 $km \cdot h^{-1}$ for the Mader and modified ADAPT methods, respectively. The Bland–Altman plot was used for determining the level of agreement between the two methods (Fig. 2) and demonstrated that the Mader method gave a higher value than ADAPT, with a mean difference of 0.82 ± 0.37 $km \cdot h^{-1}$ ($P = 0.03$). In addition, this study found a close exponential relationship between treadmill speed and plasma lactate concentration using a two-phase exponential regression fit to the blood lactate values ($R^2 = 0.96$–0.99).

Pearson correlation analysis demonstrated that the VO_2 peak and the AT both correlated with each other and with the following variables: Body mass index (BMI), weight, waist circumference, diastolic and systolic blood pressure, and 2-hr plasma glucose levels. These variables, as well as coding variables for the presence/absence of metabolic syndrome, were then included as independent variables in

Table 1. Mean ± Standard Deviation Levels of the Physical Characteristics of Study Participants

Parameter	*Metabolic syndrome* (n = 15)	*Healthy, males* (n = 15)
Age (years)	43.5 ± 7.52	44.1 ± 6.08
Body mass (kg)	103.3 ± 13.93	94.2 ± 15.22
Body mass index ($kg \cdot m^{-2}$)	32.1 ± 3.2	29.2 ± 4.5
Waist circumference (cm)	112.4 ± 8.43	102.3 ± 12.37*
High-density lipoprotein ($mmol \cdot L^{-1}$)	0.9 ± 0.19	1.1 ± 0.18*
Triglycerides ($mmol \cdot L^{-1}$)	1.87 ± 0.45	1.38 ± 0.55*
Total cholesterol ($mmol \cdot L^{-1}$)	5.72 ± 1.41	5.63 ± 1.07
Systolic blood pressure (mmHg)	135.8 ± 12.02	122 ± 10.34*
Diastolic blood pressure (mmHg)	86.7 ± 5.34	82.7 ± 7.06
Fasting glucose ($mmol \cdot ^{-1}L$)	5.2 ± 0.6	5.0 ± 0.3
2 hour glucose ($mmol \cdot L^{-1}$)	5.3 ± 1.5	5.2 ± 1.1
VO_2 peak ($mL \cdot min \cdot kg^{-1}$)	30.3 ± 6.6	42.7 ± 11.3*

*$P < 0.05$.

two separate backward, stepwise regression models in which VO_2 peak and AT were the dependent variables. In both models, BMI and waist had a VIF >10 and therefore BMI was excluded from each of the initial regression models. In the first regression model, waist circumference and metabolic syndrome were found to be the principal determinants of the VO_2 peak (see Table 3). These data suggest that the lower VO_2 peak of participants with metabolic syndrome is associated with their higher waist circumference. This was confirmed in an ANCOVA comparing VO_2 peak between the two participant groups, where waist circumference was added as a covariate. This attenuated the F value from 11.4 to 4.34 and the *P* value from 0.002 to 0.05. In the second regression model, weight and VO_2 peak were found to be the principal determinants of AT (see Table 3). This suggests that the lower AT of participants with the metabolic syndrome may be due to differences in weight and/or VO_2 peak. This hypothesis was tested by comparing AT in control and metabolic syndrome patients using ANCOVA adjusted for either weight or VO_2 peak. Adjusting for weight attenuated the F value from 7.49 to 4.46 and the *P* value from 0.01 to 0.04, whereas adjusting for VO_2 peak attenuated the F value to 0.0006 and the *P* value to 0.98. This demonstrates that the lower AT values in subjects with the metabolic syndrome is largely associated with their lower VO_2 peak levels.

Discussion

The metabolic syndrome group in this study had higher waist circumference, higher triglyceride levels, and lower HDL-C levels when compared to the healthy group. These results agree with the definition used in this study to classify metabolic syndrome.

Considering that body mass and age were not different between the two groups, the lower VO_2 peak found in the metabolic syndrome group agrees with the Kuoppio study,[21] which found directly determined VO_2 max to be lower in persons with metabolic syndrome. Also, Laaksonen et al[22] showed that men with a VO_2 max of $< 29.1\,mL \cdot min^{-1} \cdot kg^{-1}$ were three to four times more likely to have metabolic syndrome than those with VO_2 max of $\geq 35.5\,mL \cdot min^{-1} \cdot kg^{-1}$. The difference in VO_2 peak between the two groups cannot be due to the healthy group training more than the metabolic syndrome group, because all subjects in the study had not exercised regularly for a minimum of 4 weeks prior to the testing.

Multiple regression analysis suggested that the lower VO_2 peak of metabolic syndrome participants is associated with their higher waist circumference. This is an original finding, and it highlights the importance of reducing waist circumference in individuals with metabolic syndrome to improve energy production and health. It is interesting to note that both longitudinal[23] and cross-sectional studies[24] have shown that, of all anthropometric variables measured, only waist circumference was negatively correlated with level of fitness. It is not known why waist circumference specifically influences VO_2 peak. However, waist circumference is a proxy indicator of visceral fat mass,[25] and this body fat depot is a negative regulator of whole-body insulin sensitivity[26] and may therefore limit glucose metabolism in skeletal muscle.

To our knowledge, no other study has shown that the velocity at AT is lower in patients with metabolic syndrome and that this is largely associated with their lower VO_2 peak. This finding supports the notion of a lower level of aerobic fitness in patients with metabolic syndrome, as has been demonstrated in other studies.[27,28] Also, the higher velocity

Table 2. Mean ± Standard Deviation and Coefficient of Variation for Velocity at Anaerobic Threshold

	Metabolic syndrome (n = 15)		*Healthy, males* (n = 15)	
	Mader method	*Modified adapt method*	*Mader method*	*Modified adapt method*
Coefficient of variation (%)	2.61	3.52	2.97	3.44
Mean of velocity at AT ($km \cdot h^{-1}$)	6.78 ± 0.19*	5.87 ± 0.21*	8.62 ± 0.26	7.89 ± 0.26

*$P < 0.05$ versus healthy males.
AT, anaerobic threshold.

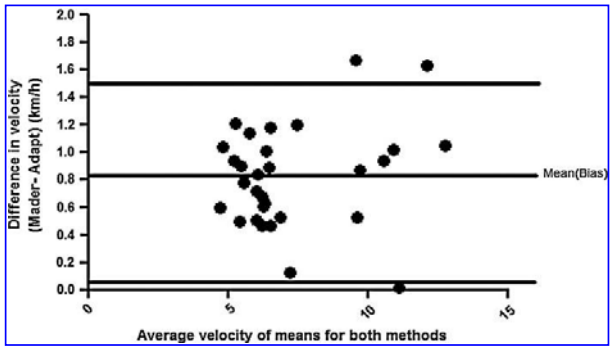


FIG. 2. Bland–Altman comparison between the Mader method and the modified Automatic Data Analysis for Progressive Tests (ADAPT) technique (data for the two groups of subjects have been combined). The two horizontal lines depict the 95% limits of agreement (from 0.09 to 1.55), with a mean difference of $0.82 \pm 0.37\,km \cdot h^{-1}$ ($P = 0.03$).

attained at AT by the healthy participants when compared to the participants with metabolic syndrome, confirms the observation that persons with metabolic syndrome exhibit a lower level of physical conditioning than their healthier counterparts.[21]

The percentage of VO_2 peak associated with AT (% VO_2 peak @ AT) is not significantly different in the group with metabolic syndrome when compared to the group without metabolic syndrome. It is believed that the % VO_2 peak @ AT and VO_2 peak are determined by different factors, with VO_2 peak being dependent on cardiovascular factors, such as cardiac output, stroke volume, and the % VO_2 peak @ AT being dependent on peripheral factors such as number of mitochondria and muscle fiber type.[8,9] This suggests that the metabolic syndrome group had a lower performance in an index of central, cardiovascular function yet similar characteristics in peripheral muscle morphology when compared to individuals without metabolic syndrome.

The Mader method of determining AT yielded good reproducibility in this study (see Table 2). Heitkamp et al.[16] used correlation coefficients for treadmill speed and also found good reproducibility of AT at $4\,mmol \cdot L^{-1}$ for the Mader method. CV values for velocity at AT determined by the modified ADAPT method in our study were not different from those yielded by the Mader method (Table 2).

The advantage of the ADAPT method is that it calculates AT from the shape of the lactate–work intensity curve. Frohlich et al.[29] found that nutritional factors (glycogen depletion as a result of dietary or training manipulations) did not alter the shape nor the slope of the lactate–work intensity curve. In contrast, nutritional and training/recovery factors will influence the calculation of AT when fixed blood lactate levels are used, as is the case with the Mader method.[17] Urhausen and Kinderman[30] also showed that AT determined via fixed blood lactate levels in a glycogen-depleted state will overestimate endurance capacity, while this threshold determined from the shape of the lactate–workload curve is hardly changed. Furthermore, some individuals with very low levels of conditioning do not reach $4\,mmol \cdot L^{-1}$ lactate, but one can still use the shape of their curve to determine AT. In addition, the Bland–Altman analysis showed that, when data from the two subject groups were combined, the Mader method gave a higher value for the AT compared to the ADAPT method, with a mean difference of $0.82 \pm 0.37\,km \cdot h^{-1}$. The Mader method uses a fixed blood lactate level of $4\,mmol \cdot L^{-1}$, yet mean maximal steady-state exercise blood lactate values range from 3.0 to $5.5\,mmol \cdot L^{-1}$.[9] In view of our results, it is possible that a fixed lactate level of $4\,mmol \cdot L^{-1}$ is too high and more studies need to be performed to determine if this fixed level of lactate is appropriate for determining AT.

The technical error of measurement (TEM, also called the standard error of measurement: $\sqrt{\Sigma d^2/2n}$) for AT determination using the ADAPT method has been shown to have good precision for athletes tested at the South Australian Sports Institute (TEM% = 1.5%).[17] No study has investigated

TABLE 3. RESULTS OF BACKWARD, STEPWISE MULTIPLE REGRESSION ANALYSES FOR ISOLATING PRINCIPLE DETERMINANTS OF OXYGEN CONSUMPTION PEAK AND ANAEROBIC THRESHOLD

Regression model number	*Dependent variable*	*Independent variables with beta coefficient* (P *value)*	r^2 *for full model* (P *value)*
1	VO_2 peak (log)	Waist: −0.82 (<0.0001) Metabolic syndrome[a]: −0.22 (0.02)	0.85 (<0.0001)
2	Anaerobic threshold (log)	Weight: −0.61 (<0.0001) VO_2 peak (log): 0.38 (0.007)	0.84 (<0.0001)

[a]Presence of the metabolic syndrome was coded as 1 and absence was coded as 0.
VO_2, oxygen consumption.

the applicability of this method in the clinical environment. This study found that the modified ADAPT method can be used in the clinical environment with good reproducibility. This finding was also confirmed by the method that Hopkins[20] has set up to test reliability of data. The typical error obtained via this method also shows good reproducibility of velocity at AT using both the Mader and the modified ADAPT methods.

Swart et al.[31] reviewed the reliability and accuracy of the Accusport and Lactate Pro portable blood lactate analyzers. These researchers stated that the changes in blood lactate concentration at threshold that occur with training (approximately 0.7 $mmol \cdot l^{-1}$) might be of a smaller magnitude than the level of error inherent in the portable blood lactate analyzers (up to 0.35 $mmol \cdot L^{-1}$ at 5 $mmol \cdot L^{-1}$, or 0.7 $mmol \cdot L^{-1}$ at 10 $mmol \cdot L^{-1}$). This study used the ADAPT method and velocity at AT in determining BLTT, and found the level of error inherent in the Lactate Scout (0.27–0.29 $km \cdot h^{-1}$) is smaller than the changes that can occur with training (0.5–1.6 $km \cdot h^{-1}$).[17] Thus, the use of treadmill speed (work load) rather than blood lactate concentration to denote the threshold has improved the reliability of the BLTT.

The AT has been used in prescribing exercise intensity among healthy, nonathletes[8] and among adults with cardiac disease.[12] As far as the authors are aware, this is the first study to investigate AT among adults with metabolic syndrome. Measuring AT on a regular basis in such individuals is straightforward. The test takes only 20–30 min to complete, and automated blood lactate analyzers have made lactate measurement simple and accessible. Most patients find the VO_2 peak tests uncomfortable and difficult to perform. Lactate measurements are easier to administer because they can be performed during subpeak exercise and do not require highly specialized staff. In addition, regular monitoring of changes in AT motivates individuals by showing their improvement in endurance capacity as their BLTT curve shifts to the right.

Typical changes in blood lactate levels during exercise range from 1.2 mmol/L to 11 mmol/L for athletes,[17] 5 mmol/L in heart disease patients,[12] and 8 mmol/L in healthy subjects.[8,9,12] The changes are similar across different modes of activity (running, cycling, arm ergometer).[9]

The current study shows that AT measurements can be used to establish an exercise prescription for persons with metabolic syndrome. This can be accomplished by first asking the subject to exercise for 20 min at 85% of the treadmill velocity at which AT occurred. This would slowly be increased over 12 weeks to 45 min at 100% of the treadmill velocity at which AT occurred (if a cycle is used, watts will be used instead of velocity). The intention of using AT to prescribe exercise is to prevent an exercise load that is too small or too strenuous.

Conclusions

This study showed that the BLTT is reproducible in persons with metabolic syndrome, and that BLTT tests can be used to set the exercise load for persons with metabolic syndrome. The Mader and ADAPT methods of determining the AT were similarly reproducible. The ADAPT method may be preferable because fewer factors influence its determination. In addition, our modifications to the ADAPT method yielded acceptable reproducibility. In addition, this study found that the lower VO_2 peak and velocity at AT in individuals with metabolic syndrome was associated with a greater waist circumference and a lower VO_2 peak respectively.

Acknowledgments

The authors would like to thank Lancet Laboratories for their support with the blood analyses.

Author Disclosure Statement

There is no conflict of interest in connection with the submission of this manuscript

References

1. Chan NN, Kong APS, Chan JCN. Metabolic syndrome and type 2 diabetes: The Hong Kong perspective. *Clin Biochem Rev* 2005;26:51–57.
2. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. *Circulation* 2009;120:1640–1645.
3. Wilson PWF, Grundy SM. The metabolic Syndrome: Practical guide to origins and treatment: Part 1. *Circulation* 2003;108:1422–1424.
4. Meigs J. Metabolic syndrome: In search of a clinical role. *Diabetes Care* 2004;227:2761–2763.
5. Wannamethee SG, Sharper G, Lennon L, et al. Metabolic syndrome vs Framingham risk score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med* 2005;165:2644–2650.
6. Carroll S, Dudfield M. What is the relationship between exercise and metabolic abnormalities? A review of Metabolic Syndrome. *Sports Med* 2004;34:371–418.
7. Wallace J. Principles of cardiorespiratory endurance programming, American College of Sports Medicine (ACSM). In: *Resource Manual for Guidelines for Exercise Testing and Prescription*, 5th ed. Philadelphia: Lippincott Williams and Wilkins, 2006.
8. Weltman A, Seip RL, Snead D. Exercise training at and above the lactate threshold in previously untrained women. *Int J Sports Med* 1992;13:257–263.
9. Weltman A. Use of blood lactate for exercise training. In: *The Blood Lactate Response to Exercise*. Champaign: Human Kinetics, 1995.
10. Yoshida T, Suda Y, Takeuchi N. Endurance training regimen based upon arterial blood lactate: Effects on anaerobic threshold. *European J Appl Physiol* 1982;49:223–230.
11. Stegmann H, Kindermann W. Comparison of prolonged exercise tests at the individual anaerobic threshold and the fixed anaerobic threshold of 4 mmol/L lactate. *Int J Sports Med* 1982;3:105–110.
12. Coyle EF, Martin WH, Ehsani AA. Blood lactate threshold in some well-trained ischemic heart disease patients. *J Appl Physiol* 1983;54:18–23.
13. Coen B, Schwarz L, Urhausen A, et al. Control of training in middle and long-distance running by means of the individual anaerobic threshold. *Int J Sports Med* 1991;12:519–524.
14. Kindermann W, Simon G, Keul J. The significance of the aerobic-anaerobic transition for the determination of workload intensities during endurance training. *Eur J Appl Physiol* 1979;42:25–34.
15. Magkos F, Yannakoulia M, Chan JL, et al. Management of metabolic syndrome and type 2 diabetes through lifestyle modification. *Annu Rev Nutr* 2009;29:223–256.

16. Heitkamp HC, Holdt M, Scheib K. The reproducibility of the 4 mmol/L lactate threshold in trained and untrained women. *Int J Sports Med* 1991;12:363–369.
17. Bourdon P. Blood lactate transition thresholds: Concepts and controversies. In: Gore CJ (ed). *Physiological Tests for Elite Athletes*. Illinois: Human Kinetics, 2000.
18. Mader A, Heck H. A theory of the metabolic origin of anaerobic threshold. *Int J Sports Med* 1986;7:45–65.
19. Cheng B, Kuipers H, Snyder A. A new approach for the determination of ventilatory and lactate thresholds. *Int J Sports Med* 1992;13:518–522.
20. Hopkins WG. Measures of reliability in sports medicine and science. *Sports Med* 2000;30:1–15.
21. Lakka TA, Laaksonen DE. Sedentary life-style, poor cardiorespiratory ftness and metabolic syndrome. *Med Sci Sports Exerc* 2003;35:1279–1286.
22. Laaksonen DE, Lakka HM. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of metabolic syndrome. *Diabetes Care* 2002;25: 1612–1618.
23. Eisenmann JC, Wickel EE, Welk GJ, et al. Relationship between adolescent fitness and fatness and cardiovascular disease risk factors in adulthood: The Aerobics Center Longitudinal Study (ACLS). *Am Heart J* 2005;149:46–53.
24. Jago R, Drews KL, McMurray RG, et al. Fatness, fitness, and cardiometabolic risk factors among sixth-grade youth. *Med Sci Sports Exerc* 2010;42:1502–1510.
25. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: Best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;73:460–468.
26. Ross R, Aru J, Freeman J, et al. Abdominal adiposity and insulin resistance in obese men. *Am J Physiol Endocrinol Metab* 2002;282:E657–E663.
27. Eisenmann JC. Aerobic fitness, fatness and the metabolic syndrome in children and adolescents. *Acta Paediatr* 2007;96:1723–1729.
28. Church T. The low-fitness phenotype as a risk factor: More than just being sedentary? *Obesity* 2009;17(Suppl 3):S39–S42.
29. Frohlich L, Urhausen A, Seul U. The influence of low-carbohydrate and high carbohydrate diets on the individual anaerobic threshold. *Leistungs Spor* 1989;19: 18–20.
30. Urhausen A, Kindermann W. Exercise physiology: Performance diagnostics and training control. In: Haag H, Grupe O, Kirsch A (ed). *Sports Science in Germany*. Berlin: Springer, 1992.
31. Swart J, Jennings C. Use of blood lactate concentration as a marker of training status. *SA J Sports Med* 2004;16:3–7.

Address correspondence to:
Georgia Torres, MSc Med
School of Physiology
University of the Witwatersrand
Private Bag 3, WITS 2050
Johannesburg, South Africa

E-mail: gtorres.fiziq@gmail.com