OBESITY AS A METABOLIC SYNDROME DETERMINANT AND THE INFLUENCE OF PHYSICAL ACTIVITY IN TREATMENT AND PREVENTION

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Dissertation submitted in fulfillment of the requirements for the M.A. degree in the School for Biokinetics, Recreation and Sport Science in the Faculty of Health Sciences at the North-West University, Potchefstroom Campus

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LAAT MY ELKE MÔRE U LIEFDE ONDERVIND, WANT IN U STEL EK MY VERTROUE. WYS MY DIE PAD WAT EK MOET LOOP, WANT MY HOOP IS OP U GEVESTIG

[PSALM 143:8]

FOREWORD

"I am enough of an artist to draw freely upon my imagination. Imagination is more important than knowledge. Knowledge is limited. Imagination encircles the world." [Albert Einstein]

It is a privilege to thank the following people for their help and support in completing this study:

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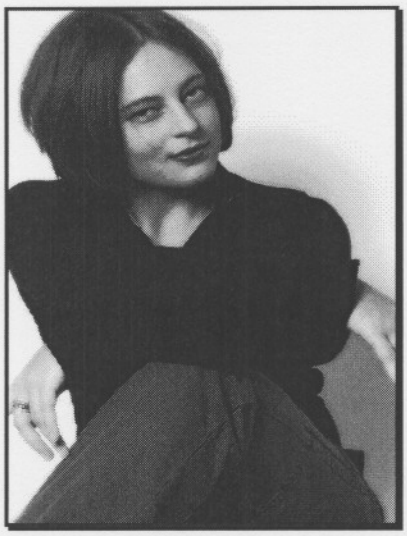

Jeanine Beneke

"Courage is reckoned the greatest of all virtues, because, unless a man has that virtue, he has no security for preserving any other."
[Samuel Johnson]

DECLARATION

The co-authors of the articles of this dissertation, Dr. Colette Underhay (supervisor), Dr. Alta E. Schutte (co-supervisor) and Prof. J. Hans de Ridder (assistant supervisor), hereby give permission to the candidate, Ms. Jeanine Beneke to include the two articles as part of a Masters dissertation. The contribution (advisory and supportive) of these co-authors was kept within reasonable limits, thereby enabling the candidate to submit this dissertation for examination purposes. This dissertation, therefore serves as fulfilment of the requirements for the M.A. degree in Biokinetics within the School of Biokinetics, Recreation and Sport Science in the Faculty of Health Sciences at the North-West University, Potchefstroom Campus.

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SUMMARY

Background

The prevalence of obesity in both the developed and developing world have increased, which leads to diverse health outcomes and is placing a heavy burden on the economy. Abdominal obesity proved to be one of the main features in predicting metabolic and cardiovascular disease (CVD) risk and may be the link that unifies the metabolic syndrome (MS) through pro-inflammatory pathways. While the pathogenesis of the MS and each of its components are complex and not well understood, abdominal obesity remains the mechanism that relates to increased lipolysis causing the liver to increase blood glucose and very low lipoprotein output. This in turns leads to raised blood glucose, triglycerides, low-density lipoprotein cholesterol (LDL-C), blood pressure and inflammatory markers (C-reactive protein, interleukin-6 and tumor necrosis factor-α) and decreased high-density lipoprotein cholesterol (HDL-C). Prevention of the metabolic syndrome and treatment of its main characteristics are now considered of utmost importance in order to combat the increased CVD risk and all-cause mortality. Decreasing sedentary behaviour through regular physical activity is a key element in successful treatment of obesity through an increase in energy expenditure, but the ability to decrease low-grade systemic inflammation may be an even greater outcome.

Aims

The aims of this study was firstly, to determine by means of a literature review, how obesity could be related to a state of chronic systemic inflammation (increased CRP and IL-6). Secondly to determine whether physical activity could serve as a suitable method to decrease inflammation associated with obesity and related disorders. Thirdly to determine if abdominal obesity is a predictor of the metabolic syndrome and CVD and finally, to determine if

measures of obesity can predict risk for the metabolic syndrome and CVD risk.

Methods

For this review study, a computer-assisted literature search were utilized to identify research published between 1990 and 2005. the following databases were utilized for the search: NEXUS, Science Direct, PubMed and Medline. Keywords related to obesity (abdominal obesity, overweight), metabolic syndrome (insulin resistance syndrome, dysmetabolic syndrome, syndrome X), cardiovascular disease (coronary heart disease, coronary artery disease), cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, physical activity), inflammatory markers (CRP, IL-6, chronic low-grade inflammation) and physical activity (fitness, exercise and training) were included as part of the search, including the references identified by previous reviewers (not identified as part of the computerized literature search).

Results and conclusions

- Several research studies concluded that obesity could be an inflammatory disorder due to low-grade systemic inflammation. Adipose tissue is known to be a sectretory organ producing cytokines, acute phase reactants and other circulating factors. The synthesis of adipose tissue TNF-α could induce the production of IL-6, CRP and other acute phase reactants. CRP is a acute phase reactant, synthesized primarily in hepatocytes and secreted by the liver in response to a variety of inflammatory cytokines of which IL-6 and TNF-α are mainly involved. CRP increases rapidly in response to trauma, inflammation and infection. Thus, enhanced levels of CRP can be used as a marker of inflammation.

- Several studies of large population cohorts provide evidence for an inverse, independent dose-response relation between plasma CRP concentration and level of physical activity in both men and women. Trends for decreased IL-6, TNF-α and CRP concentrations were linear

with increasing amounts of reported exercise in most of the research studies, physical activity proved effective in lowering measures of adiposity (BMI, WHR, WC and percentage body fat) and obesity related inflammatory markers (CRP & IL-6). Thereby indicating a potential anti-inflammatory effect.

- In the studies reviewed in this article abdominal obesity is identified as a predictor and independent risk factor for CVD in both men and women. High levels of deep abdominal fat have also been correlated with components of the metabolic syndrome, glucose intolerance, hyperinsulinemia, hypertension, diabetes, increases in plasma triglyceride levels and a decrease in HDL-C levels (dyslipidemia) in many of the studies. Prospective epidemiological studies have revealed that abdominal obesity (determined by WC and WHR) conveys an independent prediction of CVD risk and is more relevant compared to general obesity (determined by BMI).

- Abdominal fat has been linked to metabolic risk factors like high systolic blood pressure, atherogenic dyslipidemia, with increased serum TG and decreased HDL-C, and glucose intolerance. Although magnetic resonance imaging (MRI) and computerized tomography (CT) have been used successfully in many studies to measure adipose compartments of the abdomen (subcutaneous and visceral fat), anthropometrical measures like WHR and WC have been proven to be an effective measure in predicting the metabolic syndrome. WC has also been included in the metabolic syndrome definitions of the WHO, ATP III and new IDF.

Key words: Obesity, abdominal obesity, metabolic syndrome, inflammatory markers, cardiovascular disease, cardiovascular disease risk factors, physical activity.

OPSOMMING

Agtergrond

Die voorkoms van obesiteit het drasties gestyg in beide ontwikkelde- en ontwikkelende lande en daarmee saam die diverse gesondheidsuitkomste van obesiteit, wat gevolglik 'n verhoogde las op lande se ekonomie plaas. Abdominale obesiteit is een van die hoof faktore wat 'n rol speel in die voorkoms van metaboliese en kardiovaskulêre risiko's en mag die skakel wees wat die komponente van die metaboliese sindroom (MS) saamsnoer deur middel van inflammatoriese reaksies. Alhoewel die patogenese van die MS kompleks is en nie goed deur navorsers verstaan word nie, mag abdominale obesiteit die meganisme wees wat verband hou met verhoogde lipolise wat veroorsaak dat die lewer baie lae lipoproteïen uitsette het. Verhoogde lipolise veroorsaak 'n styging in bloed glukose, trigliseriede, lae-digtheid lipoproteïen cholesterol (LDL-C), bloeddruk en inflammatoriese merkers (C-reaktiewe proteïen, interleukien-6 en tumor nekrose faktor-α) en 'n verlaging in hoë-digtheid lipoproteïen cholesterol (HDL-C). Voorkoming van die MS en behandeling van onderlinge komponente van die sindroom word belangrik geag om kardiovaskulêre siektes (KVS) se risiko en mortaliteit teë te werk. Sedentêre gedrag moet gevolglik beperk word deur gereëlde deelname aan fisieke aktiwiteit. Dit is die sleutel tot die suksesvolle behandeling van obesiteit deur energie-verbruik te verhoog, maar die vermoë van fisieke aktiwiteit om lae-graadse sistemiese inflammasie te verminder mag selfs 'n belangriker uitkoms wees.

Doelstellings

Die doel van hierdie studie was eerstens, om deur middel van 'n navorsingsoorsig te bepaal of obesiteit verband hou met 'n toestand van chroniese sistemiese inflammasie (verhoogde CRP en IL-6). Tweedens om te bepaal of fisieke aktiwiteit as behandelingsmodaliteit kan dien om inflammasie

wat met obesiteit geassosieer word, te verminder. Derdens, om te bepaal of abdominale obesiteit as 'n voorspeller vir die metaboliese sindroom en KVS dien. Die laaste doelstelling van hierdie studie was om te bepaal of aanduiders van obesiteit, risiko vir die metaboliese sindroom en KVS kan voorspel.

Metode

Vir hierdie oorsig artikel is daar gebruik gemaak van 'n rekenaar-geassisteerde literatuursoektog. Die volgende databasisse is geraadpleeg: NEXUS, Science Direct, PubMed en Medline. Sleutelterme wat verwant is aan obesiteit (abdominale obesiteit, oorgewig), metaboliese sindroom (insulien weerstand sindroom, dismetaboliese sindroom, sindroom X), kardiovaskulêre siektes (koronêre hartsiektes, koronêre arteriële siektes), kardiovaskulêre risiko faktore (hipertensie, dislipidemia, diabetes mellitus, fisieke onaktiwiteit), inflammatoriese merkers (CRP, IL-6, chroniese lae-graadse inflammasie) en fisieke aktiwiteit (fiksheid en oefening) is in die soektog gebruik. Bronverwysings wat deur vorige navorsers geïdentifiseer is en nie deel gevorm het van die rekenaar-geassisteerde literatuursoektog nie, is ook ingesluit.

Resultate en gevolgtrekkings

- Verskeie navorsingstudies het bevind dat obesiteit as 'n inflammatoriese toetand beskou kan word, as gevolg van lae-graadse sistemiese inflammasie wat tydens obesiteit in die liggaam voorkom. Adipose / vet weefsel skei sitokiene af (akute fase reaktante en ander sirkulerende faktore). Die sintese van adipose weefsel TNF-α lei tot die produksie van IL-6, CRP en ander akute fase reaktante. CRP is 'n akute fase reaktant, wat primêr deur die hepatosiete in die lewer afgeskei word in respons op inflammatoriese sitokiene (IL-6 en TNF-α). CRP konsentrasies in die liggaam styg drasties in respons op trauma, inflammasie en infeksie. Gevolglik kan die verhoogde CRP

konsentrasies tydens obesiteit as aanduider dien dat obesiteit 'n chroniese lae-graadse inflammatoriese toestand is.

- Uit verskeie groot populasie studies is daar 'n omgekeerde onafhanklike dosis-respons verwantskap tussen plasma CRP konsentrasie en fisieke aktiwiteit deelname in beide mans en dames waargeneem. 'n Tendens dat IL-6, CRP en TNF-α konsentrasies afneem met 'n toename in fisieke aktiwiteit is in meeste studies waargeneem. Fisieke aktiwiteit blyk effektief te wees in die verlaging van aanduiders van obesiteit (BMI, WHR, WC en persentasie liggaamsvet) asook obesiteit verwante inflammatoriese merkers (CRP en IL-6). Gevolglik lei fisieke aktiwiteit tot 'n potensiële anti-inflammatoriese effek.

- In die navorsingsoorsig is bevind dat abdominale obesiteit 'n voorspeller en onafhanlike risiko faktor vir KVS is vir beide mans en vrouens. Groot hoeveelhede diep abdominale / viserale vet het ook positief gekorreleer met komponente van die metaboliese sindroom, glukose intolerasie, hiperinsulienemia, hipertensie, diabetes, toename in plasma trigliseried konsentrasie en 'n afname in HDL-C vlakke (dislipidemia). Verskeie epidemiologiese studies het tot die gevolgtrekking gekom dat abdominale obesiteit soos bepaal deur WC en WHR 'n onafhanklike voorspellller van KVS risiko is en meer relevant is as algemene obesiteit soos bepaal deur BMI.

- Abdominale obesiteit toon verbande met metaboliese sindroom risiko faktore soos hoë sistoliese bloeddruk, atherogeniese dislipidemia, verhoogde serum trigliseriede, 'n afname in HDL-C en glukose intoleransie. Alhoewel magnetiese resonans beelding (MRI) en gerekenariseerde tomografie (CT) in verskeie studies suksesvol aangewend is om adipose komponente van die abdomen (onderhuids en viseraal) te meet, is antropometriese metings soos WC en WHR ook

effektief om die metaboliese sindroom te voorspel. WC is ook ingesluit in die metaboliese sindroom definisies van die WHO, ATPIII en IDF.

Sleutel terme: Obesiteit, abdominale obesiteit, metaboliese sindroom, inflammatoriese merkers, kardiovaskulêre siektes, kardiovaskulêre siekte risiko's, fisieke aktiwiteit.

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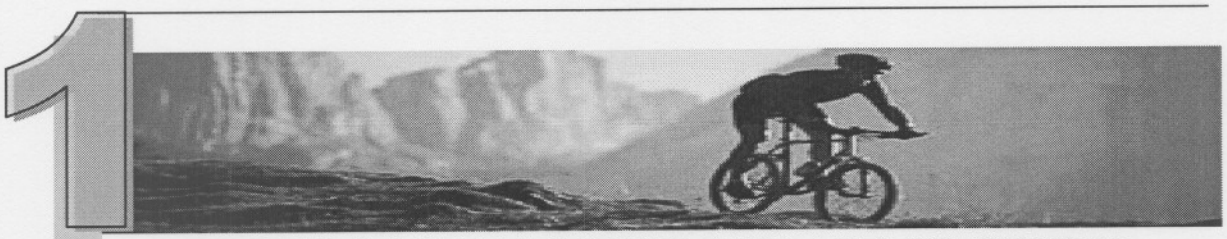
LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ACSM	American College of Sports Medicine
ATP	Adult Treatment Panel
BMI	Body mass index
CHD	Coronary heart disease
cm	Centimeter
cm^2	Centimeter squared
CRP	C-reactive protein
CT	Computerized resonance imaging
CVD	Cardiovascular disease
DEXA	Dual-Energy X-Ray Absorptiometry
EGIR	European Group for the study of Insulin Resistance
Fc	Constant fragment of an antibody molecule
Fat %	Percentage body fat
g/d	Gram per day
HDL-C	High-density lipoprotein cholesterol
HPFS	Health professionals' follow-up study
HRTN	Hormone replacement therapy non-users
HRT	Hormone replacement therapy users
IDF	International Diabetes Federation
IL-1	Interleukin-1
IL-1ra	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-18	Interleukin-18
IR	Insulin Resistance
ISBNPA	International Society of Behavioural Nutrition and Physical Activity
Kcal/d	Kilocalorie per day
kg	Kilogram

kg/m^2	Kilogram per meter square
LDL-C	Low-density lipoprotein cholesterol
mg/dL	Milligram per deciliter
mg/l	Milligram per liter
mmol/L	Millimole per liter
Mo	Months
mm Hg	Millimeters of mercury
MRI	Magnetic resonance imaging
m-RNA	Messenger ribonucleic acid
MS	Metabolic syndrome
NCD	Non-communicable disease
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Surveys
NHS	Nurses Health study
NRF	National Research Foundation
%	Percentage
% BF	Percentage body fat
PA	Physical activity
pg/ml	Picograms per millilitre
SAA	Serum amyloid protein A
STNFR	Soluble tumor necrosis factor-alpha receptor
SD / ±	Standard deviation
TNF-α	Tumor necrosis factor-alpha
TC	Total cholesterol
Visceral AT	Visceral adipose tissue
WC	Waist circumference
WHO	World health organization
WHR	Waist-to-hip ratio
Wk	Week
WSR	Waist-to-stature ratio
Yr	Year



1 PROBLEM STATEMENT AND AIM OF STUDY

INTRODUCTION

Atherosclerosis and coronary heart disease (CHD) are the leading causes of mortality in the Western world, and the incidence is projected to increase in the future (Boutin-Foster, 2005; Olson & Tsuyuki, 2003; Michaud *et al.,* 2001). While much of the cardiovascular risk attributable to obesity may be mediated through effects on blood pressure, lipids, and glucose tolerance, some of the risk may be mediated by inflammatory pathways (Rexrode *et al.,* 2003). According to the World Health Organization (WHO) (2003), there are more than 1 billion overweight adults, globally at least 300 million of them obese.

More facts from the WHO (2003) are that the obesity epidemic is not restricted to industrialized societies, but this increase is often faster in developing countries than in the developed world. In South Africa the Caucasian, Indian and coloured populations have high mortalities from CHD, cancer and stroke (Walker, 1996). Although the prevalence of obesity in South African populations is higher in black than in white women (Puoane *et al.,* 2002), it is

not clear why obesity is more common in African women. The Department of Health's Demographic and Health Survey of 1998 found women of all ages to be more obese than men, with the highest trend in women over the age of 65 years.

PROBLEM STATEMENT

The metabolic syndrome is associated with an increased risk of developing cardiovascular disease (CVD) and appears in individuals as a cluster of risk factors according to the National Cholesterol Education Program (NCEP) and Adult Treatment Panel III (ATP III) (2001). Das (2003) reported metabolic syndrome to be characterized by obesity, atherosclerosis, hyperlipidemias, essential hypertension, type 2 diabetes mellitus, and CHD. The utility of the metabolic syndrome in predicting risk for the incidence and mortality of cardiovascular disease and all-cause mortality needs to be better understood (Ford, 2004).

Obesity could be the central and causal component of metabolic syndrome. Research in the area of obesity has confirmed that obesity is a state of chronic inflammation, as indicated by increased plasma concentrations of C-reactive protein (CRP) (Yudkin *et al.,* 1999) and interleukin-6 (IL-6) (Mohamed-Ali *et al.,* 1997). Mohamed-Ali *et al.* (1997) also stated that adipocytes secrete IL-6, one of the major determinants of hepatic CRP production according to Papanicolaou *et al.* (1998).

Several factors play a major role in the inflammatory process. Rexrode *et al.* (2003) found both CRP and IL-6 levels to strongly correlate with Body Mass Index (BMI), not just at higher levels but also throughout the full spectrum of BMI. Another interesting but less investigated issue, is the relationship of abdominal obesity to CRP levels. Waist circumference (WC) also had a strong association with both inflammatory markers. Waist-to-hip ratio (WHR) had a weaker association in research by Rexrode *et al.* (2003), which is notable because stronger associations of WC, WHR and visceral fat have been shown

in South Asians, reported by Vikram *et al.* (2003). According to research findings by Slabbert (2004), percentage body fat, WC, WHR and BMI were all significantly correlated with CRP throughout the anthropometric spectrum. The latter was found to be the strongest predictor of elevated CRP concentrations amongst 19 to 60 year old black South African women.

The role of physical activity in the treatment and prevention of obesity is another key player in the inflammatory process. One of the important benefits of exercise is its ability to decrease systemic inflammation (Das, 2001), making exercise a favourable choice as part of an intervention program for obesity and therefore also the metabolic syndrome.

The contribution of this research will shed light on the role of physical activity transitions to traditional cardiac risk factors, but also alternative identified risk factors such as increased plasma CRP and IL-6. It will also highlight the role obesity plays in the development of the metabolic syndrome and other cardiovascular risk factors.

The research questions that will be answered in this research is firstly, to determine how obesity could be related to a state of chronic systemic inflammation (increased CRP and IL-6). Secondly, to determine whether physical activity could serve as a suitable method to decrease inflammation associated with obesity and related disorders. Thirdly, to determine if abdominal obesity is a predictor of the metabolic syndrome and cardiovascular disease. Finally, to determine if measures of adiposity can predict risk for the metabolic syndrome and CVD.

OBJECTIVES

The aims of this literature survey is:

- To determine if obesity is a state of systemic chronic low-grade inflammation.
- To determine if improved physical activity could serve as a suitable method of decreasing inflammation in obesity related disorders.
- To determine whether abdominal obesity is a predictor of the metabolic syndrome and cardiovascular disease.
- To determine if measures of adiposity serve as predictor of the metabolic syndrome and CVD.

HYPOTHESES

The study is based on the following hypotheses:

- Obesity is a systemic low-grade inflammatory condition.
- There is an anti-inflammatory action with increased physical activity projected by decreased plasma CRP and IL-6 concentrations.
- Abdominal obesity is a predictor of the metabolic syndrome and other risk factors for CVD.
- Anthropometrical measures of obesity are a suitable method for predicting the metabolic syndrome.

STRUCTURE OF THE DISSERTATION

Chapter 1	Introduction: Problem statement, objectives and hypotheses.
Chapter 2	Literature review (Article 1): Abdominal obesity as predictor of metabolic syndrome and other related risk factors for CVD.

Chapter 3	Research review (Article 2): The role of physical activity in the prevention and treatment of obesity as an inflammatory condition.
Chapter 4	Summary, conclusions and recommendations.
List of appendices	Instructions to Authors. Congress proceedings.

This dissertation is submitted in article format, as approved by the senate of the North-West University (Potchefstroom Campus). The articles have been submitted for publication in peer-reviewed journals (see Chapter 4). For the sake of uniformity in the dissertation, the articles are not given in the format according to the authors' instructions but are in the same format as the rest of the dissertation according to the guidelines of the North-West University (excluding the in-text references). The results and conclusions of the review articles in Chapters 2 & 3 will be presented and interpreted in each chapter respectively. The reference lists of Chapters 1 to 4 will be according to the guidelines of the North-West University. The instructions to authors of the journals to which the articles have been submitted are given in the list of appendices.

Parts of this dissertation were already presented at the "Fourth Annual Conference of the International Society of Behavioural Nutrition and Physical Activity (ISBNPA)" in Amsterdam, The Netherlands during June 2005 and the "11th South African Sports Medicine Congress" held during September 2005 in Johannesburg, South Africa.

The structure of the dissertation is shown in Figure 1.

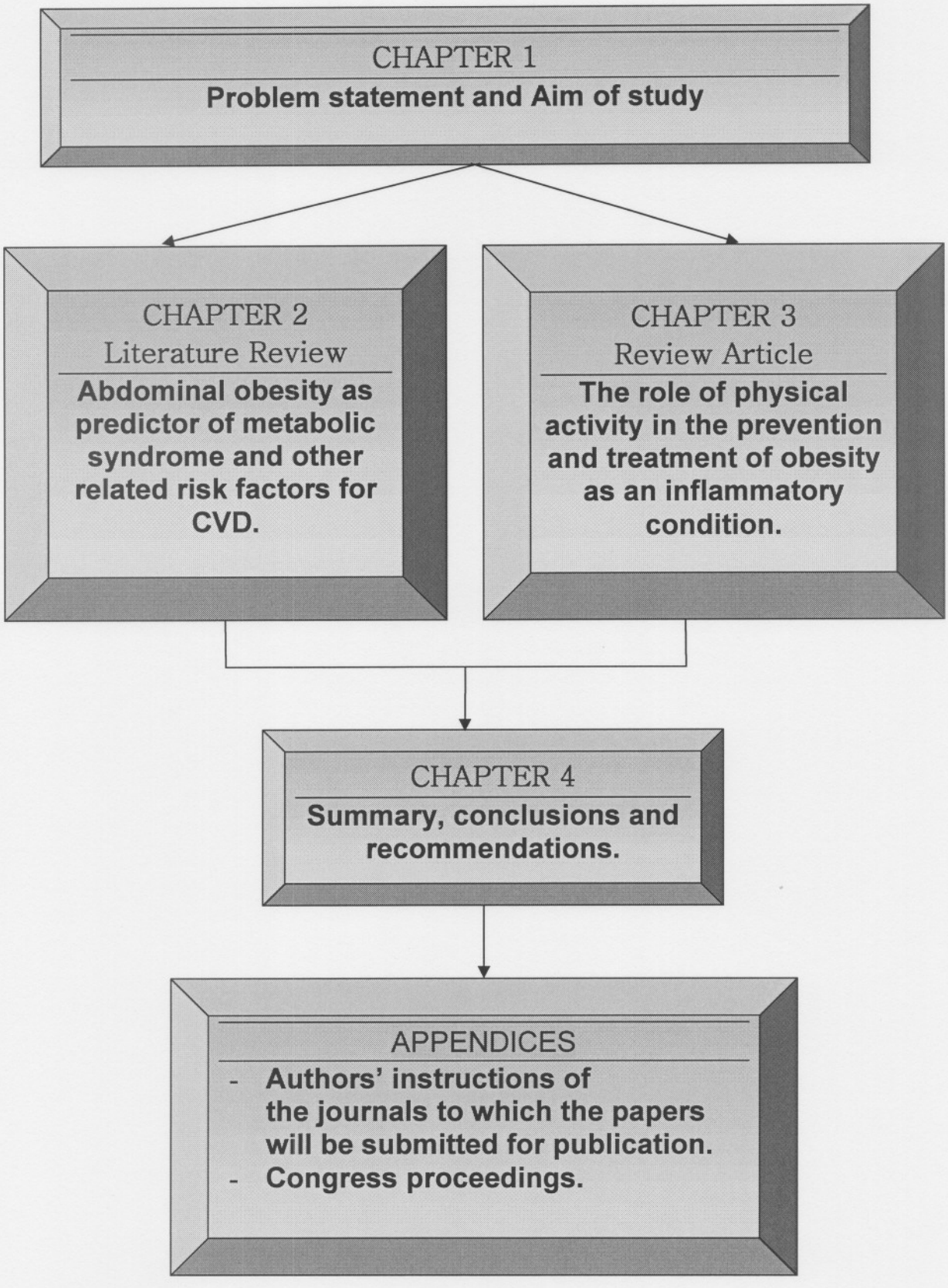


Figure 1: Structure of the dissertation

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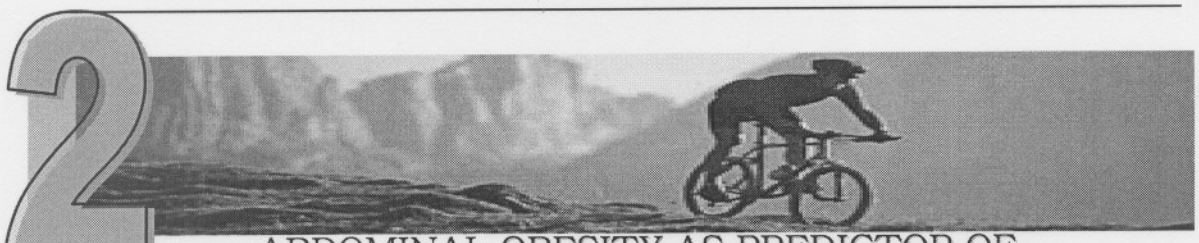

2 ABDOMINAL OBESITY AS PREDICTOR OF METABOLIC SYNDROME AND OTHER RELATED RISK FACTORS FOR CARDIOVASCULAR DISEASE *(LITERATURE REVIEW)*

Authors: Beneke, J., Underhay, C., Schutte, A.E. & De Ridder, J.H.

Key words: Body composition, obesity, metabolic syndrome, cardiovascular disease, cardiovascular disease risk factors.

ABSTRACT

Background: Multiple cardiovascular disease risk factors have been shown to have cumulative impact. A majority of people with the metabolic syndrome is overweight or obese and obesity is highly correlated with all of the components of the syndrome. Apart from abdominal obesity, the metabolic syndrome is characterized by hypertension, insulin resistance, atherogenic dyslipidemia, a prothrombotic state and a pro-inflammatory state. Increasing prevalence of adult obesity in developing countries is found to coincide with high prevalence of childhood undernutrition, resulting in metabolic alterations in all body tissues and body systems. Waist circumference (WC) is a preferable practical determinant of cardiovascular disease and metabolic risk as opposed to body mass index and other measures of body composition. **Aim:** Review to point out abdominal obesity as predictor of metabolic syndrome and other related risk factors for cardiovascular disease. **Methods:** NEXUS, Science Direct, PubMed and Medline were used collecting recent literature in the field. **Conclusion:** Cardiovascular disease remains the primary outcome of the metabolic syndrome. Abdominal obesity predicts and plays a central role in the pathogeneses of metabolic and cardiovascular risk.

INTRODUCTION

Obesity and early malnutrition has been significantly associated with chronic diseases (González-Barranco & Ríos-Torres, 2004; Sharma, 2003). Clinical and epidemiological studies indicated that obesity is strongly associated with all cardiovascular risk factors (Janssen, 2005; Grundy *et al.,* 2004a). An increase in the global epidemic of obesity (WHO, 2003), has led to increased metabolic syndrome prevalence (Eckel *et al.,* 2005).

Grundy *et al.* (2004b) confirmed cardiovascular disease (CVD) as a major clinical outcome of the metabolic syndrome. Six major components of the syndrome were identified: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance (glucose intolerance), a pro-inflammatory state, and a prothrombotic state. It should be noted however that although the metabolic syndrome is associated with obesity, not all obese individuals have this clustering of risk factors and that normal weight individuals can also be insulin resistant (Eckel *et al.,* 2005; You *et al.,* 2004).

Obesity is a problem reaching epic proportions in both the developed and developing world (Ali & Crowther, 2005; Yeater, 2000). In the United States alone, obesity has doubled from 15% to 30% in the last 3 decades (Flegal *et al.,* 2002).

Obesity is a serious health problem that reduces life expectancy by increasing one's risk of developing cardiovascular disease (CVD) (hypertension, type 2 diabetes, dyslipidemia), novel risk factors (inflammatory markers), insulin resistance, glucose intolerance, sleep apnea, gallbladder disease, obstructive pulmonary disease, osteoarthritis, and certain types of cancer (Kip *et al.,* 2004; Yeater, 2000; Grundy *et al.,* 1999; Heyward & Stolarczyk, 1996).

The purpose of this review is therefore to determine the role of obesity in identifying the metabolic syndrome and related coronary vascular disease and cardiovascular risk factors.

METHODS

For this literature review a computer-assisted literature search were used to identify research papers between 1990 and 2005. The following databases were utilized for the search: NEXUS, Science Direct, PubMed and Medline. Keywords related to body composition (Body Mass Index [BMI], waist circumference [WC], waist-to-hip ratio [WHR]), obesity (abdominal obesity, overweight), metabolic syndrome (insulin resistance syndrome, dysmetabolic syndrome, syndrome X), cardiovascular disease (coronary heart disease, coronary artery disease) and cardiovascular disease risk factors (hypertension, dyslipidemia, diabetes mellitus, physical inactivity, inflammatory markers) were conducted as part of the search, including references identified by previous reviewers (not identified as part of the computer-assisted search).

OBESITY

The increased health risks associated with obesity are related, not only to the total amount of body fat, but also to the way in which fat is distributed, especially in the abdominal region (visceral fat) (Heyward & Stolarczyk, 1996).

Visceral fat is adipose tissue within and around the organs in the thoracic (heart and lungs) and abdominal (liver and kidneys) cavities and is two to four times more sensitive to lipolytic stimuli than subcutaneous fat (Yeater, 2000). It should be noted that abdominal fat includes subcutaneous and visceral fat in the abdominal region (Heyward & Stolarczyk, 1996). Abdominal fat has been linked to metabolic risk factors like high systolic blood pressure, atherogenic dyslipidemia, with increased serum triglyceride and decreased HDL cholesterol (HDL-C), glucose intolerance, and abnormalities in the coagulation system, all factors that contribute to the coronary risk of an individual (Robinson & Graham, 2004; Vuori, 2004; Von Eyben *et al.*, 2003).

Obesity is commonly diagnosed by five anthropometric indices: Body Mass Index (BMI); percentage body fat (% body fat); waist circumference (WC); waist-to-hip ratio (WHR) and waist-to-stature ratio (WSR) (Cheng, 2004). Magnetic resonance imaging (MRI), dual energy x-ray absorptiometry (DEXA) and computerized tomography (CT) have been used successfully to measure adipose compartments of the abdomen (Hawes & Martin, 2001), but for practical purposes, using a tape measure is simple, easy to administer in epidemiological settings (Cheng, 2004).

Several definitions for obesity exist. Most definitions for obesity use weight and height tables such as BMI (weight/height squared), which is a measure of heaviness, and not fatness (Janssen, 2005). The BMI gained acceptance because in epidemiological studies it shows a moderate correlation with estimates of body fat (Hawes & Martin, 2001). BMI to define overweight and obesity however, does not quantify the magnitude or ratio of subcutaneous to visceral fat in a given individual (Kip *et al.,* 2004). According to Heyward & Stolarczyk (1996), obesity is better defined as an excessive amount of total body fat for a given weight. Abdominal obesity may be better diagnosed as a high waist-to-hip ratio (WHR) that can be because of excess of either subcutaneous or intra-abdominal fat (Von Eyben *et al.,* 2003). Measurement of WC as an important determinant of cardiovascular and metabolic risk is receiving increasing acceptance (Sharma, 2003; WHO, 1998).

Stunting

Early malnutrition has been found significantly associated with chronic diseases, the cardiovascular risk factors tend to track into adulthood when left untreated (González-Barranco & Ríos-Torres, 2004; Török *et al.,* 2001). Childhood stunting has been suggested as a factor contributing to high rates of adult obesity among South African women (Kruger *et al.,* 2004), although the precise relation between stunting and obesity is unknown. Kruger *et al.* (2004) suggested that stunted girls may be at risk of relatively greater fat deposition, especially in the abdominal area. Similarly, Sawaya *et al.* (2003) found stunted girls to have higher WHR presumably influencing risk for CVD.

Stunting is also related to the metabolic syndrome through obesity and relative weight gain in childhood carried over in adult life (Vanhala *et al.,* 1999).

Metabolic unhealthy lean individuals

Metabolically unhealthy normal weight individuals may represent one end of the metabolic syndrome spectrum. This additional patient group with insulin resistance in the absence of obesity (about 6% of the normal weight population) may have an increased risk of ischemic heart disease, compared to their metabolically healthy obese counterparts (St-Pierre *et al.,* 2005; Kip *et al.,* 2004; Park *et al.,* 2003; Ruderman *et al.,* 1998). In a review by Ruderman and colleagues (1998), these individuals may not be overweight or obese according to weight-height tables (BMI), but could be mildly obese especially around the midsection. Similarly, Kip *et al.* (2004) in a study of 780 women found that the metabolic syndrome and not BMI predict future cardiovascular risk in women.

METABOLIC SYNDROME

The metabolic syndrome is a common disorder that results from the increasing prevalence of obesity (Eckel *et al.,* 2005; WHO, 2000), although not the only associated factor of the disease (You *et al.,* 2004). The prevalence of the metabolic syndrome increases with age. The highest prevalence is observed in older persons, although frequency rises rapidly in middle age and parallels with the development of obesity in most populations (Grundy *et al.,* 2004b). Grundy *et al.* (2004a) identified 3 potential etiological categories of the metabolic syndrome: obesity and disorders of adipose tissue; insulin resistance; and a constellation of independent factors (molecules of hepatic vascular, and immunologic origin) that mediate specific components of the metabolic syndrome.

The metabolic syndrome comprises an array of cardiovascular disease risk factors such as abdominal obesity, dyslipidemia, hypertension, glucose

intolerance (or insulin resistance), pro-inflammatory state or prothrombotic state (Grundy *et al.,* 2004a; Pi-Sunyer, 2004; Robinson & Graham, 2004; Katzmarzyk *et al.,* 2003; NCEP, 2002).

The syndrome is defined by various organizations including the World Health Organization (WHO), but varies mainly by measure of obesity, detail and criteria (Eckel *et al.,* 2005; Carrol & Dudfield, 2004; Grundy *et al.,* 2004a). Currently the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATPIII) guidelines are the golden standard for clinical practice however, in the future, adding separate components from other definitions of the metabolic syndrome, may prove to be more clinically efficacious for determining CVD risk (Appel *et al.,* 2004). NCEP, ATPIII guidelines indicate that between 25% and 35% of adults in the United States have the metabolic syndrome, but many individuals are insulin resistant but do not meet the established criteria and may therefore go untreated (Cohn *et al.,* 2005). The latest diagnostic criteria for the metabolic syndrome according to NCEP, ATPIII and International Diabetes Federation (IDF) are shown in Table 1.

BMI and WHR is included in the World Health Organization (WHO) definition (BMI > 30 kg/m^2 / or WHR > 0.9 in men, > 0.85 in women), WC as indication for abdominal obesity is included in the ATPIII definition (men > 102 cm and women > 88 cm) (Grundy *et al.,* 2004a) and included in the European Group for the study of Insulin Resistance definition (EGIR), (WC of > 94 cm in men and > 80 cm in women) (Eckel *et al.,* 2005; Balkau & Charles, 1999). Finally, the International Diabetes Federation (IDF) has formulated new guidelines that take into account the differences in physical stature between different races (Table 2). Abdominal obesity is central to the IDF guidelines (see Table 1).

The American Diabetes Association has established a cut-off point of ≥ 100 mg/dL (5.6 mmol/L), above which persons have either pre-diabetes (impaired fasting glucose) or diabetes (Genuth *et al.,* 2003). Grundy *et al.* (2004b),

proposed that this new cut-off point should be applicable for identifying the lower boundary to define an elevated glucose as one criterion for the metabolic syndrome (Alberti *et al.,* 2005; De Simone, 2005).

It is evident that the many definitions of the metabolic syndrome in the literature create confusion, making it difficult to interpret and compare available research. However, literature is currently moving towards better clinical criteria for identification of those at risk for the metabolic syndrome as new ideas and findings emerge.

Table 1: Clinical criteria for the diagnosis of the Metabolic Syndrome

NCEP, ATP III Guidelines	IDF Guidelines
Three or more of the following indicate the metabolic syndrome: Central obesity WC ▪ Men >102 cm ▪ Women >88 cm Dyslipidemia ▪ TG ≥150 mg/dL (1.7 mmol/L) HDL-C ▪ Men <40 mg/dL (1.03 mmol/L) ▪ Women <50 mg/dL (1.29 mmol/L) Hypertension ▪ BP ≥130 / 85 mmHg Fasting glucose ▪ ≥110 mg/dL (6.1 mmol/L)	▪ Abdominal obesity defined by WC (Table 2) *Plus another two of the following:* Raised TG concentrations ▪ >150 mg/dL (1.7 mmol/L) Reduced HDL-C concentrations or specific treatment for this lipid abnormality ▪ Men <40 mg/dL (1.03 mmol/L) ▪ Women <50 mg/dL (1.29 mmol/L) Raised BP or treatment of previously diagnosed hypertension ▪ ≥130 / 85 mmHg Raised FPG concentrations or previously diagnosed type 2 Diabetes ▪ ≥100 mg/dL (5.6 mmol/L)

WC=Waist circumference; TG=Triglyceride; FPG=Fasting plasma glucose; HDL-C=High-density lipoprotein cholesterol; BP=Blood pressure; NCEP=National Cholesterol Education Program; ATP=Adult Treatment Panel; IDF=International Diabetes Federation.

Adapted from Alberti *et al.* (2005); Eckel *et al.* (2005); Grundy *et al.* (2004a) & Grundy *et al.* (2004b).

Table 2: Ethnic group-specific guidelines for waist circumference

Ethnic group	Gender	WC
European	**Male**	≥94 cm
	Female	≥80 cm
South Asian	**Male**	≥90 cm
	Female	≥80 cm
Chinese	**Male**	≥90 cm
	Female	≥80 cm
Japanese	**Male**	≥85 cm
	Female	≥90 cm

*** In future epidemiological studies of populations of European origin, prevalence should be given using both European and North American thresholds to allow better comparisons.**
*** There are not yet specific data available on the following populations: Ethnic South and Central Americans; Sub-Saharan Africans; Eastern Mediterranean and populations of the Arab world.**
WC=Waist circumference

Adapted from Alberti *et al.* (2005). (IDF definition of the metabolic syndrome.)

Obesity related mechanisms of the metabolic syndrome and CVD risk factors

Insulin resistance

Insulin resistance (IR) may be the major abnormality underlying most cases of the metabolic syndrome (Cohn *et al.,* 2005; Carr *et al.,* 2004; Grundy *et al.,* 2004b). According to Lerman *et al.* (2003) IR is not simply a problem of deficient glucose uptake in response to insulin, but is related to a multifaceted syndrome that increases significantly the risk of CVD.

The mechanism according to theory is that resistance to insulin-mediated glucose disposal provokes a compensatory hyperinsulinemia, which serves to

maintain glucose homeostasis (Cohn *et al.,* 2005). Hyperinsulinemia could however also serve as a marker of insulin resistance (Lerman *et al.,* 2003), but it remains unclear. Only after the pancreas is unable to meet increased insulin demand, such as in patients with longstanding IR, does glucose control become abnormal (Cohn *et al.,* 2005; Grundy *et al.,* 2004a; Fletcher & Lamendola, 2004). This is frequently manifested as glucose intolerance and is another emerging risk factor. When glucose intolerance evolves into diabetes-level hyperglycemia, elevated glucose constitutes a major, independent risk factor for CVD (Grundy *et al.,* 2004a).

IR is complicated by the fact that it is linked to obesity (Grundy *et al.,* 2004a). Central obesity, a common manifestation of obesity is more associated with insulin resistance, which appears to be the underlying cause of the metabolic syndrome and type 2 diabetes (Kip *et al.,* 2004).

Obesity and abnormal fat distribution

The most serious metabolic risks are associated with abdominal fat deposits (Nicklas *et al.,* 2005; Vuori, 2004). Brooks *et al.* (2000) stated that individuals with abdominal fat patterning have larger and perhaps a greater number of intra-abdominal fat cells. Studies indicate that adipocytes within the deep visceral compartments are more metabolically active than adipocytes within the superficial visceral compartment and thus a stronger predictor of insulin resistance (Wong *et al.,* 2003; Carey, 1997).

The most widely held view for this mechanism is that central obesity leads to IR by causing free fatty acid levels to increase in the portal and peripheral circulations (Ruderman *et al.,* 1998).

Hypertension

According to Vuori (2004) there are at least 600-million hypertension sufferers worldwide. Hypertension is estimated to cause 7.1 million deaths annually (Vuori, 2004). In obese adults alone, hypertension prevalence is 38.4% for men and 32.2% for women. This is markedly higher compared to leaner adults

with 18.2% and 16.5% for men and women respectively (BMI less than 25 kg/m^2) (Hirose *et al.,* 1998). Neck circumference as an index of upper body obesity correlated positively with blood pressure and other components of the metabolic syndrome in studies by Ben-Noun & Laor (2004; 2003) and Ben-Noun *et al.* (2001). Visceral fat however is of primary importance with regard to associated hypertension (Ding *et al.,* 2004; Anderson *et al.,* 1997).

Many investigators postulate that overweight leads to hypertension through excess fluid retention, cardiac output, or hormonal mechanisms (Landsberg, 2001; Hall *et al.,* 2001). Several mechanisms have been proposed to be the cause of these associations. Visceral fat may raise blood pressure by increasing sympathetic nervous system activity, enhancing renin-angiotensin system activation causing physical compression of the kidneys (Hall *et al.,* 2003). Alvarez *et al.* (2002) and Imazu (2002) indicated that visceral fat may increase sympathetic nervous system activity through associated insulin resistance. Visceral fat may cause greater activity of the renin-angiotensin system due to a higher expression of angiotensinogen in visceral fat compared with subcutaneous fat (Wajchenberg, 2000). Another mechanism is that visceral fat may raise intra-renal pressures by increasing intra-abdominal pressures and penetrating into the renal medullary sinuses (Hall *et al.,* 2003).

Findings by De Simone (2005) suggest that blood pressure is substantial for the development of preclinical CVD, and also that its effects is amplified by the presence of other metabolic risk factors.

Dyslipidemia

Obesity is associated with an increase in low-density lipoprotein cholesterol (LDL-C) particles and triglyceride levels (TG) and lower levels of high-density lipoprotein cholesterol (HDL-C) (NCEP, 2002). The combination of hypertriglyceridemia, low levels of HDL-C and preponderance of small, dense LDL-C particles have been named the 'atherogenic lipoprotein phenotype', 'atherogenic dyslipidemia' or 'lipid triad' (Grundy, 1998). Atherogenic dyslipidemia is associated with the central components of the metabolic

syndrome, namely impaired insulin-mediated glucose disposal (Howard *et al.,* 1998; Reaven *et al.,* 1993) and abdominal fat accumulation (Grundy, 1998; Sattar *et al.,* 1998).

According to Sharma (2003) lower levels of HDL-C and higher TG levels are more likely to be present when body fat is concentrated in the abdominal area compared to body fat that is concentrated in the lower body area. It has been proposed that an impaired systemic antilipolytic action of insulin and increased systemic free fatty acid flux underlie the association between intra-abdominal fat and insulin resistance (Abbasi *et al.,* 2000; Pescatello & van Heest, 2000; National Heart, Lung and Blood Institute, 1998; Despres, 1997; Bjorntorp, 1990). Intra-abdominal fat is relatively insensitive to insulin and has a high lipolytic activity, partly due to its complement of adrenergic receptors (National Heart, Lung and Blood Institute, 1998; Bjorntorp, 1993; Bjorntorp, 1990).

The often co-existent features of hyperinsulinemia and increased non-esterified free fatty acid levels affect several interconnected steps in lipoprotein metabolism (Laws, 1999). Both features appear to contribute to increased TG-enriched lipoproteins in the circulation (hypertriglyceridaemia) (Laws, 1999; Taskinen, 1995).

Hypertriglyceridaemia and hypercholesterolemia are risk factors for CVD (Dotevall *et al.,* 2005; Montalcini *et al.,* 2005; Walldius *et al.,* 2004). In the presence of hypertriglyceridaemia, a decrease in the cholesterol content of HDL-C results from decreases in the cholesteryl ester content of the lipoprotein core with variable increases in triglyceride making the particle small and dense (Brooks *et al.,* 2000; Murakami *et al.,* 1995). This change in lipoprotein composition also results in an increased clearance of HDL-C from the circulation (Brooks *et al.,* 2000). In addition to HDL-C, the composition of LDL-C is also modified in a similar way (De Graaf *et al.,* 1993; Manzato *et al.,* 1993). Small dense LDL-C might be more atherogenic than buoyant LDL-C because (1) its more toxic to the endothelium, (2) it is more able to transit

through the endothelial basement membrane, (3) it adheres well to glycosaminoglycans, (4) it has an increased susceptibility to oxidation, and (5) it is more selectively bound to scavenger receptors on monocyte-derived macrophages (Packard, 1996; Krauss, 1995). In some studies this alteration in LDL-C composition is an independent risk factor for CVD (Eckel *et al.*, 2005; Zambon *et al.*, 1999).

Therefore hypercholesterolemia due to high levels of LDL-C, hypertriglyceridemia often associated with low values of HDL-C and especially combined hyperlipidemias are all associated with increased risk of cardiovascular morbidity and mortality (Walldius *et al.*, 2004).

CARDIOVASCULAR DISEASE AND RELATED RISK FACTORS

Cardiovascular diseases (CVD) are the leading causes of death in western countries with staggering economical and human costs (Brooks *et al.*, 2000). According to Brooks *et al.* (2000) over 58 million people in the United States have one or more types of CVD. This includes 50 million with hypertension, 14 million with coronary heart disease (CHD) and 15 million with stroke.

One in five people presents with some form of CVD, this includes CHD, valvular heart disease, chronic heart failure, cardiomyopathy, congenital heart defects, stroke, hypertension, and peripheral vascular disease (Brooks *et al.*, 2000). Hyperinsulinemia, obesity, hypertension and dyslipidemia have been recognized as CVD risk factors in adults (Robinson & Graham, 2004; Naidoo, 2000).

Many studies have shown that patients diagnosed with the metabolic syndrome, by either the ATPIII or WHO definition (or by their modifications), have more prevalent CVD or are at greater risk of developing it (Scuteri *et al.*, 2005; Hunt *et al.*, 2004; Malik *et al.*, 2004; Ford, 2004). There are no doubts that when CVD risk factors cluster, risk of adverse events increase (De

Simone, 2005; Hanson *et al.,* 2002). According to Kahn *et al.* (2005) the increased CVD risk in patients with the metabolic syndrome ranged from 30% to 400%. Obesity and physical inactivity are considered particularly important as they directly affect other risk factors (Flegal *et al.,* 2002; Brooks *et al.,* 2000; Eckel & Krauss, 1998).

Other obesity related CVD risk factors

Diabetes

Dotevall *et al.* (2005); Lee *et al.* (2000); Malmberg *et al.* (2000) and Alberti & Zimmet (1998) indicated that diabetes mellitus patients are at increased risk of CVD. Globally around 4 million deaths are attributable to complications of diabetes (Vuori, 2004). An estimated projection of the global burden of diabetes for 2010 indicated by Amos *et al.* (1997) is 221 million (124 million in 2003).

In an editorial by Naidoo (2000) it is indicated that diabetic patients develop an earlier and more accelerated form of atherosclerosis. Women develop atherosclerosis more frequently than diabetic men and have higher mortality (Natalie *et al.,* 2000; Heyden *et al.,* 1980). Angina, myocardial infarction and sudden death are also more prevalent in women with diabetes, contributing to higher mortality in females. It is also well documented that ischemia is often silent in diabetic patients, particularly those with retinopathy and those taking insulin (Naidoo, 2000). Hyperglycemia in diabetes mellitus increases risk for CVD in several ways: (1) acute hyperglycemia leads to changes in lipid and coagulation factors, (2) chronic hyperglycemia is associated with glycosylation of proteins, renal damage and hypertension, (3) chronic hyperglycemia may have direct toxic effects on the vasculature (may accelerate atherosclerosis), (4) increased risk is associated with the metabolic syndrome (Naidoo, 2000).

Obesity (also related to the metabolic syndrome) is a major problem in this patient group (Fletcher & Lamendola, 2004; Grundy *et al.,* 2004a; Lerman, 2003; Sharma, 2003; Field *et al.,* 2001). Mild overweight, especially in the

presence of insulin resistance, increases the risk of diabetes (WHO, 2000). A majority of patients with type 2 diabetes are obese, approximately 85-96% in most population studies (Maggio & Pi-Sunyer, 2003). However, only 10% of obese patients are diabetic (Nadler *et al.,* 2000). According to Laäksonen *et al.* (2002) the WHO definition in which adiposity was defined by waist-hip ratio >0.9 or BMI of ≥30 kg/m^2 detected diabetes well, identifying 83% of prevalent and 67% of incident cases of diabetes, with a specificity of 0.78-0.80. The prevalence of obesity among adults with diabetes is associated with poorer control of blood glucose levels, blood pressure and cholesterol and a higher risk for both cardiovascular and microvascular disease (Flegal *et al.,* 2002).

Markers of inflammation

Previous researchers proposed that tumor necrosis factor-α (TNF- α), C-reactive protein (CRP) and interleukin-6 (IL-6) are involved in the pathobiology of obesity, insulin resistance and hyperinsulinemia, hypertension, dyslipidemia, atherosclerosis, type 2 diabetes and CVD, indicating that low-grade systemic inflammation plays a key role in these conditions and metabolic syndrome (Nicklas *et al.,* 2005; Das, 2002; Benjafield *et al.,* 2001; Pradhan *et al.,* 2001; Ridker *et al.,* 2000a; Ridker *et al.,* 2000b).

Hypertension is a central risk factor for cardiovascular events, but data suggest a link between blood pressure and vascular inflammation. Blake *et al.* (2003) in a study of blood pressure, CRP and future cardiovascular risk indicated that blood pressure and CRP might work as a tandem to increase cardiovascular risk. Hak *et al.* (1999) also found significant associations between blood pressure and CRP.

Chambers *et al.* (2001) reported elevated CRP concentrations in Asian Indians, closely associated with insulin resistance compared to Europeans. In the Framingham Offspring Study, Rutter *et al.* (2004) indicated that elevated CRP levels are related to insulin resistance and presence of the metabolic syndrome especially in women, both CRP and metabolic syndrome are independent predictors of new CVD events. CRP concentrations have been

demonstrated to be as strong as apolipoprotein B-100 levels and total cholesterol (TC) / HDL-C ratio in predicting the risk of cardiovascular events in women and even stronger than concentrations of TC, HDL-C, and homocysteine (Ridker *et al.*, 2000a).

Cardiorespiratory fitness has been shown to have a complimentary effect on CRP and IL-6 levels in most recent studies (Aronson *et al.*, 2004a; Pischon *et al.*, 2003; Church *et al.*, 2002; Meigs, 2002; Reaven, 2002; Geffken *et al.*, 2001). Enhanced fitness may have an anti-inflammatory role with improved insulin resistance that may be the mechanism for lowering CVD risk and type 2 diabetes mellitus (Aronson *et al.*, 2004b, Pischon *et al.*, 2003; Abramson & Vaccarino, 2002; La Monte *et al.*, 2002; Wannamethee *et al.*, 2002).

Physical inactivity

Low levels of physical activity and cardiorespiratory fitness predict development of the metabolic syndrome and CVD (Laäksonen *et al.*, 2002). Verdaet *et al.* (2004) found regular physical activity to be associated with reductions of several cardiovascular risk factors such as BMI, WHR and lipid profile. Risk of CVD is 30-50% lower in moderately active subjects compared to physically inactive subjects according to Vuori (2004). This association is seen across the lifespan (Thompson *et al.*, 2003; Kohl, 2001; Williams, 2001). Avoidance of a sedentary lifestyle is thus considered of paramount importance for prevention of obesity and associated health and CVD risks (WHO, 2000).

CONCLUSION

The importance of obesity in the pathobiology of the metabolic syndrome and cardiovascular risk is clear from the literature. Abdominal (visceral) measurements in the identification of obesity should be stressed to predict metabolic abnormalities and cardiovascular disease in children and adults. This will ensure early identification of those at risk and therefore guide the health professional to establish sufficient treatment and prevention by means of exercise and diet interventions. The use of IDF criteria for diagnosis of

metabolic syndrome and those of increased cardiovascular risk should be facilitated worldwide to improve comparison of data from research across the globe (Alberti *et al.*, 2005).

Multiple factors contribute to the pathogenesis of the metabolic syndrome but obesity and sedentary lifestyle remains the main risk factors (Vuori, 2004). CVD remains the primary clinical outcome of metabolic syndrome.

It is concluded that abdominal obesity (particularly in the visceral component) is a predictor of the metabolic syndrome and obesity related CVD risk factors. Many international studies have shown that there are differences in fat distribution especially abdominal fat patterning in different ethnic groups. This may explain the higher risk of certain ethnic groups for the development of metabolic syndrome and CVD risk factors than others

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3

THE ROLE OF PHYSICAL ACTIVITY IN THE PREVENTION AND TREATMENT OF OBESITY AS AN INFLAMMATORY CONDITION

(REVIEW ARTICLE)

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Key words: Obesity, inflammatory markers, physical activity.

ABSTRACT

Purpose: Review to point out the role of physical activity in prevention and treatment of obesity (as an inflammatory condition) and the metabolic syndrome. **Background:** Obesity has increased dramatically in the past decade and its consequences are a problem worldwide. Obesity is due to a complex interaction of genetics, diet, metabolism and physical activity levels and is strongly associated with low-grade systemic inflammation. Research reported abdominal adiposity to be strongly associated with C-reactive protein (CRP). CRP is an acute phase reactant and a marker for acute and chronic inflammation of diverse causes. Elevated CRP conditions can be ascribed to increased expression of interleukin-6 in adipose tissue. This could explain the increased risk of chronic diseases in the obese. **Method:** NEXUS, Science Direct, PubMed and Medline were used to collect recent research in the field. Observational and intervention studies published between 1995 and 2005 were included in this study. **Conclusions**: It is evident that low-grade, systemic inflammation occurs in obesity and that weight loss after intervention including physical activity may lower CHD risk. As shown by research, physical activity as a prospective predictor of inflammation is needed to establish the true anti-inflammatory role in CHD.

INTRODUCTION

Cross-sectional epidemiological studies and interventions have demonstrated the benefit of physical activity in the primary prevention of coronary heart disease, diabetes mellitus and hypertension (Grundy *et al.,* 2004). Most studies show an association between inactivity and these non-communicable diseases (NCD's), therefore the role of physical activity in the treatment and prevention of NCD's should not be underestimated (Grundy *et al.,* 2004; Sobngwi *et al.,* 2002; Grundy *et al.,* 1999; Leon, 1997). Improved functional capacity, flexibility, muscle strength and endurance are some of the main measurable outcomes of physical activity. Bouchard and Blair (1999) reported that regular physical activity plays a vital role in the regulation of energy balance. Physical activity also reduces the risk of being affected by the co-morbidities of obesity and results in lower all-cause and cardiovascular death rates (Bouchard & Blair, 1999).

Obesity is considered one of the cornerstone risk factors that cluster together when describing the metabolic syndrome (MS). According to Lam *et al.* (2003), most of the variables in the metabolic syndrome result from multiple factors linked by adiposity. These variables include hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C), hypertension, dysfibrinolysis, inflammation (associated with elevated C-reactive protein [CRP]), and/or elevated fasting insulin (Appel *et al.,* 2004).

Obesity-related inflammatory markers (CRP, Interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]) may be important mediators in the pathophysiology of coronary heart disease (CHD) and type 2 diabetes (Pischon *et al.,* 2003; Rexrode *et al.,* 2003). Significant inverse relationships between physical activity and these inflammatory markers (IL-6, TNF-α and CRP) have been identified by researchers, but they also suggested that the beneficial association could partially be due to less body fat (Aronson *et al.,* 2004a; Pischon *et al.,* 2003; Church *et al.,* 2002; La Monte *et al.,* 2002; Wannamethee *et al.,* 2002).

Although many studies have been done on physical activity and obesity, the purpose of this review however was to review existing literature to determine if physical activity plays a major role in the treatment and prevention of inflammation associated with obesity and related to the metabolic syndrome.

METHODS

For the review of this article, a computer-assisted literature search was utilized to identify research between 1995 and 2005. The following databases were used: NEXUS, Science Direct, PubMed and Medline. Keywords related to physical activity (fitness, exercise & training); obesity (overweight, body mass index, waist circumference & waist-to-hip ratio) and inflammatory markers (CRP, IL-6, chronic inflammation, low-grade inflammation) were conducted as part of the search, including the references identified by previous reviewers (not identified as part of the computerized literature search).

Since a general consensus already exists that obesity is related to the metabolic syndrome, this review article limited studies which focused on obesity as a state of chronic low-grade inflammation. A strong emphasis on the relationship between physical activity and CRP and IL-6 was made. A total of 39 studies were identified that met the above inclusion criteria. Of these, 13 studies demonstrated a relationship between obesity and inflammatory markers (Table 3), 15 studies identified the effects of decreased obesity by weight loss on systemic markers of inflammation (Table 4) and 16 studies showed an association between markers of inflammation and physical activity or fitness (Table 5). Studies listed include author group and year of publication, number of participants with mean age, BMI and other measures of obesity and the effect on inflammatory markers.

COMPONENTS OF THE METABOLIC SYNDROME

The Adult Treatment Panel (ATP III) identified 6 components of the metabolic syndrome that relate to CVD namely, abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance / glucose intolerance, pro-inflammatory state and prothrombotic state (Alberti *et al.,* 2005; Grundy *et al.,* 2004). Other criteria by the World Health organization (WHO) and American Association of Clinical Endocrinologists (AACE) require further oral glucose testing before the metabolic syndrome can be identified (see Table 1). Recently the International Diabetes Federation (IDF) proposed new guidelines for diagnosing the metabolic syndrome (Table 2). Central to the new IDF definition is abdominal obesity, identified by waist circumference (WC) and classified according to ethnicity (Alberti *et al.,* 2005).

Table 1: Clinical Criteria for Diagnosis of the Metabolic Syndrome

ATP III Criteria

Risk factor	*Defining Level*
Abdominal obesity, given as waist circumference:	
Men	>102 cm
Women	>88 cm
Triglycerides	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥ 85 mmHg
Fasting glucose	≥110 mg/dL
Any 3 of the above	

WHO Criteria

Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- Or for those with normal fasting glucose levels (< 110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Anti-hypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥150 mg/dL
- HDL-C <35 mg/dL in men <39 mg/dL in women
- BMI >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women

AACE Criteria

Risk factor	*Cut points*
Overweight/obesity	BMI ≥25 kg/m^2
Elevated triglycerides	≥150 mg/dL
Low HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Elevated blood pressure	≥130/85 mm Hg
2-Hour postglucose challenge	>140 mg/dL
Fasting glucose	Between 110 and 126 mg/dL

Other risk factors:

- Family history of type 2 diabetes, hypertension, or CVD
- Polycystic ovary syndrome
- Sedentary lifestyle
- Advancing age
- Ethnic groups having high risk for type 2 diabetes or CVD

ATP III: Adult Treatment Panel; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL-C: High density lipoprotein cholesterol; BMI: Body mass index; CVD: Coronary vascular disease

Cited by and adapted from Deen (2004), Grundy *et al.* (2004a).

Table 2: New IDF guidelines for diagnosis of the Metabolic Syndrome

IDF guidelines	Ethnic group-specific WC values		
	Ethnic group	**Gender**	**WC**
Abdominal obesity defined by WC	European		
		Male	= 94 cm
Plus another two of the following:		Female	= 80 cm
Raised TG concentrations or specific treatment for this lipid abnormality ▪ > 150 mg/dL (1.7 mmol/L)	South Asian	Male	= 90 cm
		Female	= 80 cm
	Chinese	Male	= 90 cm
		Female	= 80 cm
Reduced HDL concentrations or specific treatment for this lipid abnormality ▪ < 40 mg/dL (1.03 mmol/L) Males ▪ < 50 mg/dL (1.29 mmol/L) Females	Japanese	Male	= 85 cm
		Female	= 90 cm
	Ethnic South and Central American	Male	*
		Female	*
Raised BP or treatment of previously diagnosed hypertension ▪ ≥ 130 / 85 mmHg	Sub-Saharan African	Male	**
		Female	**
	Eastern Mediterranean Middle East	Male	**
		Female	**
Raised FPG concentration or previously diagnosed type 2 diabetes ▪ ≥ 100 mg/dL (5.6 mmol/L)			

BP=Blood pressure; WC=Waist circumference; TG=Triglyceride; FPG=Fasting plasma glucose; HDL=High-density lipoprotein; *Use South Asian recommendations until specific data are available; **Use European recommendations until specific data are available

Adapted from Alberti *et al.* (2005).

OBESITY AND THE METABOLIC SYNDROME

According to the WHO, obesity has reached epidemic proportions globally, with more than 1 billion overweight adults worldwide - at least 300 million of them obese (WHO, 2003). Obesity can be defined as a disease in which excess body fat has accumulated as a result of a positive energy balance to an extent that health may be adversely affected (ACSM, 2000; WHO, 1998).

Obesity proved to be one of the most essential features of the metabolic syndrome and may be the link that unifies the syndrome (Eckel *et al.,* 2005; Yudkin *et al.,* 2004; Anderson *et al.,* 2001; Yeater, 2000). Overweight and obesity lead to adverse metabolic effects on blood pressure, cholesterol, triglycerides and insulin resistance (WHO, 1998). Shen *et al.* (2003) proposed that obesity may share a synergistic physiologic pathway with insulin resistance, manifested by abnormal metabolism (Carr *et al.,* 2004; Kip *et al.,* 2004). In Figure 1 the pathophysiology of cardiovascular disease in the metabolic syndrome originating from central adiposity and innate immunity is illustrated (Reilly & Rader, 2003).

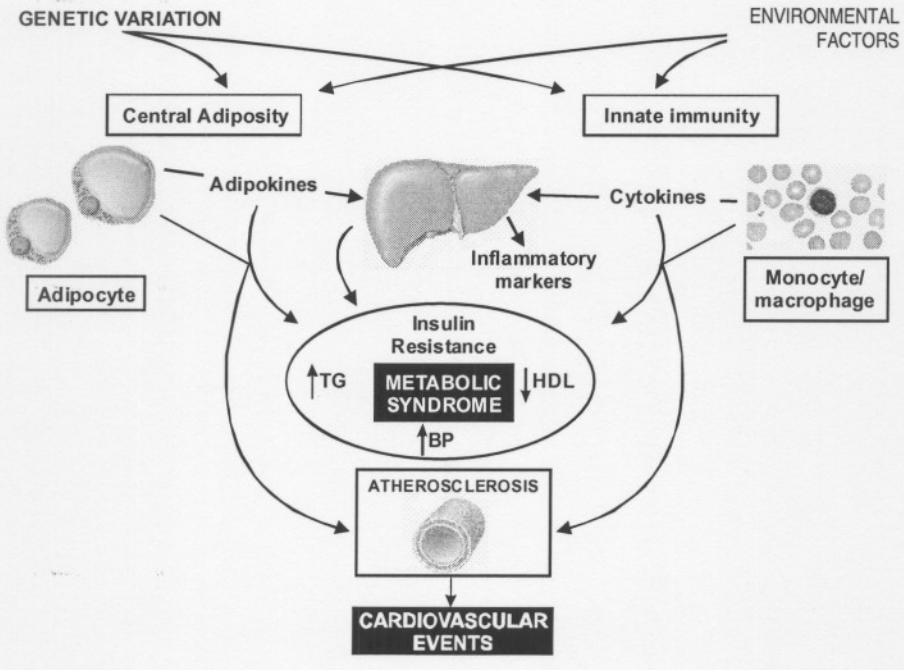

Figure 1: Pathophysiology of cardiovascular disease in the metabolic syndrome.
Adapted from Reilly and Rader (2003).

Interestingly, although most people with the metabolic syndrome are obese, some of them are of normal body weight. They do however have increased body fat, particularly around the midsection (Debè, 2002). Despres (1997) has shown that visceral fat accumulations greater than 130 cm^2 as measured by computerized tomography or magnetic resonance imaging are strongly associated with the metabolic syndrome. Relative weight gain and obesity as a child from about seven years, can predict the metabolic syndrome in adulthood (Vanhala *et al.,* 1999; Rudderman *et al.,* 1998). Therefore it is not surprising that obesity is a major target of prevention and treatment strategies, given the underlying role of altered adipose tissue metabolism in the metabolic syndrome (Robinson & Graham, 2004), which increases the morbidity and mortality risk of a person (Kip e*t al.,* 2004; Ford & Giles, 2003; Isomaa *et al.,* 2001).

A major challenge for metabolic research according to Reilly and Rader (2003) remains the identification of features of adiposity that best reflect increased risk of developing the metabolic syndrome.

OBESITY AS AN INFLAMMATORY CONDITION

Das (2001) proposed that obesity could be an inflammatory disorder due to low-grade systemic inflammation, this view is supported by a vast number of researchers (Dandona *et al.,* 2005; Dandona *et al.,* 2004; Nawrocki & Scherer, 2004; Ramos *et al.,* 2003; Weyer *et al.,* 2002). CRP is a highly conserved molecule and a member of the pentraxin family of proteins (Du Clos, 2000). CRP is an acute phase reactant, synthesized primarily in hepatocytes and secreted by the liver in response to a variety of inflammatory cytokines of which IL-6 and TNF-α are mainly involved. CRP increases rapidly in response to trauma, inflammation and infection and decreases just as rapidly with the resolution of the condition (Heilbronn & Clifton, 2002; Das, 2001). Thus, the measurement of CRP can be used to monitor inflammatory states. According to Das (2001), CRP has a role in the function of the innate immune system: it activates complement, binds to Fc (constant fragment of an antibody molecule) receptors and acts as an opsonin for various pathogens. Binding of CRP to Fc

receptors leads to the generation of pro-inflammatory cytokines. CRP can recognize self- and foreign molecules based on pattern recognition. Thus enhanced levels of CRP can be used as a marker of inflammation (Das, 2001).

Several markers of inflammation correlate with indirect measures of adiposity, especially fat distribution / patterning and insulin action. Providing a possible link between obesity and insulin resistance (Weyer *et al.,* 2002; Pannacciulli *et al.,* 2000). The synthesis of adipose tissue TNF-α could induce the production of IL-6, CRP and other acute phase reactants (Yudkin *et al.,* 1999), therefore contributing to the maintenance of a chronic low-grade inflammation state involved in the progression of obesity and its associated co-morbidities.

Many patients with the metabolic syndrome have a state of chronic low-grade inflammation indicated by high CRP levels, which may increase their risk for future adverse and cardiovascular events (Ford, 2003), even in apparently healthy individuals (Wang *et al.,* 2002).

Measures of adiposity

Clinically the prevalence of overweight and obesity is assessed by using body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters (kg/m^2) (Norton & Olds, 1996). Overweight as defined by the WHO is a BMI higher than 25 kg/m^2 and obesity as a BMI of higher than 30 kg/m^2 (Grundy *et al.,* 1999). It should be noted however that although BMI is widely used in the literature to measure degree of overweight and obesity, it is not a measure of fatness, but rather a measure of heaviness instead (Heyward & Wagner, 2004; WHO, 2000). For this reason many studies proposed that the definition of obesity based on height and weight need to be modified as cited by Ruderman *et al.* (1998). Waist-to-hip ratio (WHR), waist circumference (WC) and percentage body fat (% BF) could therefore be more accurate indicators of obesity. Increased WC is an indicator of abdominal obesity (Grundy *et al.,* 2004), and predicts greater cardiovascular risk (Charlton *et al.,* 2001; Grundy *et al.,* 1999).

Rexrode *et al.* (2003) found BMI and WC to be strongly correlated with CRP and IL-6. In particular, CRP and IL-6 as markers of inflammation will be considered in this review.

Relationship between CRP and measures of adiposity

In the literature search, 39 studies were identified which met the inclusion criteria. The studies are summarized in Tables 3-5. The studies were undertaken between 1998 and 2004. In Table 3, there were approximately 4254 participants, the majority being women. The ages varied from 14 to 63 years. Participants were mostly characterized as healthy. The mean BMI was 27.8 ± 6.5. All of the studies measured BMI in relationship to CRP. Six studies measured abdominal obesity by means of WC (Slabbert, 2004; Barinas-Mitchell *et al.,* 2001; Heilbronn *et al.,* 2001; Lemieux *et al.,* 2001; Vozarova *et al.,* 2001; Hak *et al.,* 1999). WHR was measured in 6 studies (Slabbert, 2004; Vikram *et al.,* 2003; Tchernof *et al.,* 2002; Ziccardi *et al.,* 2002; Barinas-Mitchell *et al.,* 2001; Chambers *et al.,* 2001). An indication of the relationship between % BF and markers of inflammation was given by 3 studies (Vikram *et al.,* 2003; Weyer *et al.,* 2002; Barinas-Mitchell *et al.,* 2001). All of the above found a positive relationship between markers of inflammation (CRP and IL-6), total obesity (BMI) and abdominal obesity (WC and WHR).

Evidence is strong that circulating levels of inflammatory markers are elevated with total and abdominal obesity (see Table 3). This is possibly owing to a higher secretion rate of cytokines by adipose tissue in obese people (Nicklas *et al.,* 2005). The relationship between CRP and abdominal obesity showed strong associations with WC, WHR and visceral fat as reported by Vikram *et al.* (2003), Lemieux *et al.* (2001) and Slabbert (2004). Elevated CRP levels have been cross-sectionally associated with proxy indicators of elevated body fatness (body weight and BMI) and positive associations between fat-free mass, total fat mass and the intra-abdominal adipose tissue area were indicated (Tchernof *et al.,* 2002). In studies by Saijo *et al.* (2004) and Forouhi *et al.* (2001) the amount

of visceral fat was a better determinant of CRP levels than other levels of obesity, including fat mass. The location of the body fat, independent of the total amount, is therefore an important factor affecting chronic inflammation. There is some evidence from observational studies involving both men and women, that in addition to total body fat, visceral or abdominal body fat (measured by WC and WHR) may be an independent predictor of inflammatory markers (Saijo *et al.,* 2004; Sites *et al.,* 2002; Ziccardi *et al.,* 2002; Forouhi *et al.,* 2001; Lemieux *et al.,* 2001; Bertin *et al.,* 2000; Barinas-Mitchell *et al.,* 2001).

Adipose tissue is known to be a secretory organ producing cytokines, acute phase reactants and other circulating factors (Kershaw & Flier, 2004; Trayhurn & Wood, 2004; Ouchi *et al.,* 2003; Wong *et al.,* 2003). These "adipokines" are mostly not produced by the adipocyte itself but by the infiltration of macrophages into the adipocytes (Fain *et al.,* 2004; Weisberg *et al.,* 2003). Research by Yudkin *et al.* (1999) suggests that the cytokines, arising in part from adipose tissue, might be partly responsible for the metabolic, hemodynamic, and hemostatic abnormalities that cluster with insulin resistance. One of the determinants of CRP is IL-6, which is secreted by adipocytes (Papanicolaou *et al.,* 1998; Mohamed-Ali *et al.,* 1997). In vivo release of IL-6 and TNF-soluble receptors from subcutaneous abdominal adipose tissue has been shown to correlate with BMI and body-fat proportion (Mohamed-Ali *et al.,* 1999; Yudkin *et al.,* 1999). In one in-vitro study TNF-α release from abdominal subcutaneous adipose tissue was 7.5 fold higher in tissue from obese (BMI 30-40 kg/m^2) than lean (BMI < 25 kg/m^2) subjects (Kern *et al.,* 1995). Ouchi and associates (2003) reported not only that CRP is expressed in adipose tissue, but also that CRP and adiponectin mRNA levels are highly inversely related. (Adiponectin is a protein with anti-inflammatory properties.) Thus, both in vivo and in vitro studies confirm that adipose tissue expression and release of cytokines are elevated in people with a higher adipose mass.

It is however interesting that most studies related to body composition in particular, did not measure abdominal obesity, but only BMI (Vikram *et al.,* 2003; Weyer *et al.,* 2002). Strong associations of CRP and BMI were found in

obese individuals (Aronson *et al.,* 2004b; Rexrode *et al.,* 2003; Ridker, 2003; Vikram *et al.,* 2003; Lemieux *et al.,* 2001; Hak *et al.,* 1999), but many studies do not differentiate between android and gynoid type obesity (abdominal obesity). This complicates the interpretation of the CRP relationship to abdominal obesity and could lead to confusing assumptions in this regard. The relationship between CRP and BMI in the normal weight range has not been well characterized (Rexrode *et al.,* 2003). Rexrode and associates (2003) could not determine whether obesity causes elevated CRP levels directly, or whether higher CRP levels are a marker of other intermediate conditions such as atherosclerosis or insulin resistance which influence the underlying burden of inflammation among overweight and obese individuals.

The contribution of the association between abdominal obesity and metabolic risk remains the subject of considerable debate (Frayne, 2000). There are however studies that indicate that adipocytes within the deep visceral compartment are more metabolically active than adipocytes within the superficial visceral compartment and thus a stronger predictor of insulin resistance (Wong *et al.,* 2003; Carey, 1997).

Table 3: Summary of published data on the relationship between obesity and inflammatory markers.

Author group and year of publication	Participants (n) and age (yr)	Mean BMI (kg/m^2), WC (cm), and WHR	Effects on inflammatory markers by measure of obesity
Research on CRP:			
Heilbronn *et al*,. 2001	83 healthy obese women Age 48.0±0.9	BMI 33.8 ± 0.4 WC 98.3 ± 1.0 WHR 0.83 ± 0.01	↑CRP ↑BMI ↑WC
Lemieux *et al.*, 2001	159 adult men Age 22 to 63	BMI 30.3 ± 3.9 WC 101.0 ± 9.3	↑CRP ↑BMI ↑WC ↑visceral AT
Hak *et al.*, 1999	186 healthy women Age 50.9±2.3	BMI 24.9±4.0 WC 81.5±9.5 WHR 0.77±0.05	↑CRP ↑BMI ↑WC
Aronson *et al.*, 2004a	892 subjects Age 50±10 63% Males	BMI 28.2±4.9	↑CRP ↑BMI
Vikram *et al.*, 2003	332 male * Age 18.2±2.3 46 female * Age 16.9 ± 2.0	BMI 20.1 ± 3.3 BMI 19.9 ± 3.3	↑CRP ↑BMI ↑Fat% ↑WHR
Weyer *et al.*, 2002	32 males and females $ Age 18 and 43	BMI 20.2 ± 55.8	↑CRP ↑BMI ↑Fat%
Chambers *et al.*, 2001	507 # Subjects Age 49.4 ± 6.5 518 * Subjects Age 49.0 ± 6.9	BMI 26.7 ± 4.0# WHR 0.93 ± 0.07# BMI 26.9 ± 3.5 * WHR 0.97 ± 0.07 *	↑CRP in * ↑CRP ↑BMI ↑WHR
Rutter *et al.*, 2004	1681 women 1356 men Mean age 54	BMI 26 ± 5 women WC 34 ± 5 BMI 28 ± 4 men WC 39 ± 4	↑CRP with increased features of the metabolic syndrome
Barinas-Mitchell *et al.*, 2001 Healthy Women Study	101 HRT Age 59.5 ± 2.1 106 HRTN Age 59.3 ± 1.8	BMI 26.8 ± 4.5 (HRT) WHR 0.79 ± 0.07 BMI 28.0 ± 6.1 (HRTN) WHR 0.79 ± 0.09	↑CRP ↑BMI ↑WC ↑WHR ↑Fat%
Tchernof *et al.*, 2002	61 obese women Age 56.4 ± 5.2	BMI 35.6 ± 5.0	↑CRP ↑BMI ↑WHR
Research on IL-6:			
Vozarova *et al.*, 2001	58 men and women without diabetes $ Age 30 ± 7	BMI 32.5 ± 6.5 WC 104.14 ± 15.24	↑IL-6 ↑Fat% ↑WC
Ziccardi *et al.*, 2002	56 obese women Age 35.3 ± 4.8	BMI 37.2 ± 2.2 WHR 0.84 ± 0.06	↑IL-6 ↑WHR

Note: ↑ = increased, BMI = mean body mass index WHR = waist-hip-ratio WC = waist circumference ± standard error of the mean, CRP = C-reactive protein, IL = interleukin, Visceral AT = Visceral adipose tissue, HRT = Hormone replacement therapy users, HRTN = Hormone replacement therapy non users, # Caucasian, * Asian Indians, $ Pima Indians

Table 4: Summary of published data on the effects of decreased obesity (by weight loss and/or physical activity) on systemic markers of inflammation

Author group and year of publication	Participants and mean BMI, kg/m^2	Intervention for decreasing obesity	Duration	Magnitude of weight loss	Effects on inflammatory markers
Intense, short-term dietary restrictions					
Xydakis *et al.*, 2004	40 obese adults with metabolic syndrome BMI 38.9 ± 1.0	600-800 kcal/d very-low-calorie diet	4-6wk	7.0% of weight	CRP↓14% No change in TNF-α
Heilbronn *et al.*, 2001	83 obese women BMI 33.8 ± 0.4	Low-fat (15%), 1260 kcal/d	12 wk	7.9kg	CRP↓26%
Gallistl *et al.*, 2001	49 obese children BMI 26.7 ± 1.4	908-1194 kcal/d energy-restricted diet	3 wk	5.2% of BMI, 3.1% of fat mass	IL-6 ↓ 49%
Bastard *et al.*, 2000a	14 obese women BMI 39.5 ± 1.1	941 kcal/d very-low-calorie diet	3 wk	5.3% of BMI 8.5% of fat mass	IL-6 ↓ 17% no change in CRP, TNF- α
Bastard *et al.*, 2000b	17 obese women BMI 39.9 ± 1.6	941 kcal/d very-low-calorie diet	3 wk	5.0% of fat mass	sTNFR1 ↓ 8% no change in sTNFR2
Long-term behavioural changes					
Marfella *et al.*, 2004	67 obese pre-menopausal women BMI 36.5 ± 1.8	1300 kcal/d energy-restricted diet, increased exercise	12 mo	13.4% of weight	CRP ↓ 44%; IL-6 ↓ 62%; TNF- α ↓31%; IL-18 ↓ 30%
Seshadri *et al.*, 2004	78 obese adults, 86% with diabetes or metabolic syndrome BMI 43.5 ± 1.3	≤ 30g/d low-carbohydrate diet, or	6 mo	8.5kg	CRP ↓ 12%
		500kcal/d deficit energy-restricted diet	6 mo	3.5kg	CRP ↓ 7%
Monzillo *et al.*, 2003	24 obese healthy and diabetic adults BMI 36.7 ± 0.9	500kcal/d deficit energy-restricted diet and moderate-intensity exercise	26 wk	7.0 % of weight	IL-6 ↓ 41%; no change in TNF- α
Bruun *et al.*, 2003	19 obese men BMI 38.7 ± 0.7	1000-1480 kcal/d energy restricted diet	16 wk	14.7% of weight	IL-6 ↓ 24%; TNF- α ↓ 29%; IL-8 ↓ 30%
Tchernof *et al.*, 2002	25 obese post menopausal women BMI 35.2 ± 1.0	1200 kcal/d American Heart Association Step II diet	14 mo	15.6% of weight, 25% of fat mass, 36,4% of visceral fat	IL-6 ↓ 24%; TNF- α ↓ 29%; IL-8 ↓ 30% CRP ↓ 32%
Ziccardi *et al.*, 2002	56 obese women BMI 37.2 ± 2.2	1300 kcal/d energy-restricted diet, increased exercise	12 mo	12.6% of BMI	IL-6 ↓ 47%; TNF α - ↓ 31%;
Esposito *et al.*, 2002	40 obese women BMI 36.4 ± 2.0	1300 kcal/d energy-restricted diet	12 mo	12.4% of BMI	IL-18 ↓ 41%

Table 4: Summary of published data on the effects of decreased obesity (by weight loss and/or physical activity) on systemic markers of inflammation (continue)

Author group and year of publication	Participants and mean BMI, kg/m^2	Intervention for decreasing obesity	Duration	Magnitude of weight loss	Effects on inflammatory markers
Dandona *et al.*, 1998 **Randomized, controlled trials:** Intervention group (versus control group)	38 obese women BMI 35.7 ± 0.9	925-1150 kcal/d energy-restricted diet and increased aerobic exercise	1-2 yr	12.3% of weight	TNF- α ↓ 24%
Esposito *et al.*, 2003	120 obese women BMI 35.0 ± 2.3 (v. BMI 34.7 ± 2.4)	1300-1500 kcal/d energy-restricted Mediterranean-style American Heart Association Step 1 diet (v. normal diet)	2 yr	14.7% of weight (v. 3.2% of weight)	CRP ↓ 34%; IL-6 ↓ 33% (v. no changes in CRP, IL-6)
Nicklas *et al.*, 2004	316 older adults BMI 34.5 ± 5.4 (v. BMI 34.2 ± 5.0)	Behavioural counselling to achieve and keep a 5% weight loss (v. normal diet)	18 mo	5.1% of weight (v. 1.8% of weight)	CRP ↓ 3%; IL-6 ↓ 11%; sTNFR1 ↓ 2%; no change in TNF- α (v. no changes)

Note: ↓ = decreased, BMI = mean body mass index ± standard error of the mean, CRP = C-reactive protein, IL = interleukin, TNF = tumour necrosis factor, sTNFR = soluble TNF- α receptor, yr = year, mo = month.

Table 5: Summary of published data on associations between systemic markers of inflammation and physical activity

Author group and year of publication (study name)	No of participants (sex ratio)	Age, yr	Association between physical activity and inflammatory markers	Independent of obesity?
Colbert *et al.*, 2004 (Health, Aging and Body Composition Study)	3075 (49% male)	70 - 79	↑min/wk exercise Ψ ↓ CRP, IL-6, TNF α - ↑ non-exercise PA Ψ ↓ CRP, IL-6	Yes, for IL-6 only
Albert *et al.*, 2004 (Pravastatin Inflammation/CRP Evaluation [PRINCE])	2833 (61% male)	60 ± 12	↑ frequency of PA Ψ ↓ CRP in men only; no PA-CRP relationship in women	Yes
Jankord & Jemiolo, 2004	12 men	60 - 74	Very active Ψ ↓ IL-6; less active Ψ ↑ IL-10	Not assessed
Pischon *et al.*, 2003 (HPFS and NHSII)	HPFS: 405 men NHS: 454 women	40 - 75 25 - 42	↑ metabolic equivalent-hours/wk Ψ ↓ CRP, IL-6, sTNFR1, sTNFR2	No
Reuben *et al.*, 2003 (MacArthur Studies of Successful Aging)	870 (47% male)	70 - 79	↑ recreational activity Ψ ↓ CRP, IL-6 ↑ house or yard work Ψ ↓ CRP, IL-6	Yes
King *et al.*, 2003 (NHANES III)	4072 (50% male)	>17	Jogging or aerobic dancing >12 time/mo protective for CRP	Yes
Rawson *et al.*, 2003	109 (57% male)	49 ± 12	CRP not related to current physical activity or to physical activity during previous year	No
Wannamethee *et al.*, 2002 (British Regional Heart Study)	3810 men	60 -79	↑ volume of PA Ψ ↓ CRP (no PA Ψ 2.29 mg/L; vigorous PA Ψ 1.54mg/L	Yes
Church *et al.*, 2002 (Aerobics Center Longitudinal Study)	722 men	51 ±10	↑ cardiorespiratory fitness Ψ ↓ CRP	Yes
Abramson & Vaccarino, 2002 (NHANES III)	3638 (51% male)	>40	More frequent exercise Ψ ↓ CRP	Yes
Geffken *et al.*, 2001 (Cardiovascular Health Study)	5888 (42% male)	≥65	↑ kcal/wk of physical activity Ψ ↓ CRP	Yes
Taaffe *et al.*, 2000 (MacArthur Studies of Successful Aging)	880 (47% male)	70 -79	↑ h/yr moderate-strenuous PA Ψ ↓ CRP, IL-6	Yes
Milani *et al.*, 2004	227 (71% male)	65.3 ± 11	↑ Cardiorespiratory fitness ⇒ ↓CRP	Yes
Aronson *et al.*, 2004a	892 (63 % male)	50 ± 9	↑ Level of fitness ⇒ ↓CRP	Yes
Verdaet *et al.*, 2004	892 men	35 - 59	No association between leisure time PA and CRP if corrected for BMI	Yes
La Monte *et al.*, 2002	135 (100% female)	55 ± 11	↑ Cardiorespiratory fitness ⇒ ↓CRP	Yes

Note: ↑ = increased, Ψ led to, HPFS = Health Professionals' Follow-up Study, NHANES III = Third National Health and Nutrition Examination Survey, NHS II = Nurses' Health Study II, PA = physical activity; other symbols and abbreviations as defined in Table 4

THE INFLUENCE OF PHYSICAL ACTIVITY AND WEIGHT LOSS ON SYSTEMIC INFLAMMATORY MARKERS ASSOCIATED WITH OBESITY

The etiology of obesity represents a complex interaction of genetics, diet, metabolism and physical activity levels (Das, 2001). Diet and physical activity play very significant roles in the prevalence of obesity. In addition to the consumption of high-energy food, physical activity is a key factor in the energy balance equation (Epstein *et al.,* 2000). Epstein *et al.* (2000) reported that decreasing sedentary behaviour is a key ingredient in the successful treatment of obesity.

Weight loss and inflammatory markers associated with obesity

Evidence from intervention studies showed that weight loss leads to a reduction in the state of chronic systemic inflammation, which is associated with increased adipose tissue mass in overweight and obese subjects (summarized in Table 4). Weight loss by means of dietary restriction (short term) (5 studies), long term behavioural changes (8 studies) and randomized controlled trails (2 studies) are summarized. Intense short term dietary restrictions of 3-12 weeks were indicated. Of the 5 studies summarized, 2 studies led to decreased CRP (Xydakis *et al.,* 2004; Heilbronn *et al.,* 2001). Two studies showed decreased IL-6 (Gallistl *et al.,* 2001; Bastard *et al.,* 2000a). No change was found in TNF-α (Xydakis *et al.,* 2004; Bastard *et al.,* 2000a), CRP (Bastard *et al.,* 2000a) and sTNFR2 (Bastard *et al.,* 2000b). Long term behavioural changes indicated significant reductions in CRP in 4 of the studies, reductions in IL-6 and TNF-α in 5 studies and reduced IL-18 and IL-8 was both found in 2 studies.

Several markers of inflammation, including CRP, IL-6, TNF-α and TNF-α receptors are reduced after weight loss achieved through short-term intense dietary restriction (Xydakis *et al.,* 2004; Gallistl *et al.,* 2001; Heilbronn *et al.,* 2001; Bastard *et al.,* 2000a; Bastard *et al.,* 2000b). Most of the dietary weight-loss studies showed the magnitude of decrease in inflammatory markers to be linearly related to the amount of weight lost. An example is when CRP

concentrations were reduced from 3.1 ± 0.7 mg/l to 1.6 ± 0.8 mg/l in a study of postmenopausal women after a 14 month individualized weight-loss program by Tchernof and co-authors (2002). The reductions in CRP correlated with changes in body weight and fat mass. Decreases in CRP, IL-6 and TNF-α in a group of pre-menopausal women after 10% weight reduction correlated with changes in BMI but were more strongly related to changes in waist-hip-ratio (Marfella *et al.*, 2004; Ziccardi *et al.*, 2002). In other studies, weight loss reduced CRP levels from 5.0 ± 0.5 mg/l to 4.3 ± 0.5 mg/l in women with metabolic syndrome (Xydakis *et al.*, 2004), and IL-6 concentrations from 2.75 ± 1.51 to 2.3 ± 0.91 pg/ml in women with insulin resistance (Monzillo *et al.*, 2003). Heilbronn *et al.* (2001) reported that CRP values decreased 26% with a 19% weight-loss, and decreased 32% - 34% with a 15% - 16% weight-loss (Esposito *et al.*, 2003; Tchernof *et al.*, 2002).

The results of this review suggest that there may be a dose-response effect between the degree of weight loss and its capacity to attenuate chronic inflammation. Longitudinal studies are needed to determine whether a reduced incidence of cardiovascular disease and diabetes is associated with the decline in CRP concentrations seen with weight loss (Nicklas *et al.*, 2005).

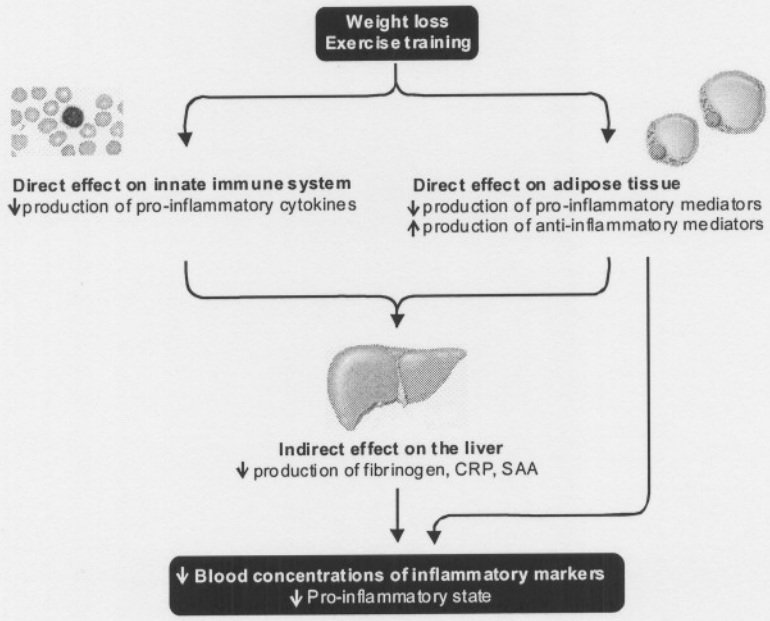

Figure 2: Mechanisms by which weight loss and exercise training reduce chronic low-grade inflammation

Adapted from Nicklas *et al.* (2005).

Mechanism of effect (Nicklas *et al.,* 2005): One of the postulated mechanisms by which weight loss reduces circulating markers of inflammation is through a decrease in adipose-tissue cytokine production (Nicklas *et al.,* 2005). In Figure 2 the possible mechanisms by which weight loss and exercise training reduce sources of inflammation that lead to chronic activation of a pro-inflammatory state are illustrated. According to Nicklas *et al.* (2005) weight loss and increased activity affect the immune system by reducing the number of mononuclear cells in the peripheral blood, which are a source of pro-inflammatory cytokines (such IL-6 and TNF-α and its receptors). A reduction in adipose tissue would not only reduce the volume of adipocytes and pre-adipocytes, but also decrease the number of endothelial cells and macrophages that reside there. These cells produce many pro-inflammatory mediators such as CRP, serum amyloid protein A (SAA) and cytokines. Weight loss and exercise may also increase the expression of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (IL-1ra) in cells. The resulting circulatory changes could, in turn, cause the liver to contribute by decreasing its production of fibrinogen and other pro-inflammatory mediators.

Grundy *et al.* (2004) reported that physical activity is a modality associated with successful weight reduction, particularly for weight maintenance. The studies in Table 3 revealed that dietary weight loss and exercise are likely more effective than weight reduction alone in reducing inflammation.

Physical activity associations with CRP, IL-6 and obesity

Physical activity proved effective in lowering measures of adiposity (BMI, WHR, WC and percentage body fat) (Milani *et al.,* 2004; Verdaet *et al.,* 2004; Pischon *et al.,* 2003; Tchernof *et al.,* 2002) and obesity related inflammatory markers (CRP & IL-6) (Aronson *et al.,* 2004a; Aronson *et al.,* 2004b; Church *et al.,* 2002). Thereby indicating a potential anti-inflammatory effect of physical activity (Wannamethee *et al.,* 2002; La Monte *et al.,* 2002). According to Aronson *et al.* (2004a) the importance of physical activity in improving the pro-inflammatory state associated with the metabolic syndrome needs to be emphasized because it could be more efficient than the use of medication.

A summary of 16 published studies on the associations between systemic markers of inflammation and physical activity is shown in Table 5. Physical activity and fitness demonstrated an inverse relationship with CRP and IL-6 in 12 of the studies. Most studies kept the significant inverse relationship between physical activity and CRP / IL-6 even when corrected for obesity (by measure of BMI or WC). Two studies found no association between physical activity and CRP (Verdaet *et al.,* 2004; Rawson *et al.,* 2003).

Increased leisure time physical activity (recreational, house and yard work) indicated reductions in CRP and IL-6 in a study by Reuben *et al.* (2003), and this association was independent of obesity. However, Verdaet *et al.* (2004) found no association between physical activity and inflammatory markers when CRP was corrected for BMI. Increased frequency, volume and intensity (moderate to strenuous) of physical activity and increased level of cardiorespiratory fitness showed an inverse relationship with CRP and IL-6 (Albert *et al.,* 2004; Aronson *et al.,* 2004a; Milani *et al.,* 2004; Wannamethee *et*

al., 2002; Abramson & Vaccarino 2002; Church *et al.,* 2002; La Monte *et al.,* 2002; Geffken *et al.,* 2001; Taaffe *et al.,* 2000). These studies were all independent of obesity. Clearly, evidence for an inverse, independent dose-response relation between CRP concentration and level of physical activity in both men and women are provided. This relation did not seem to alter with age as is evident in studies by Colbert *et al.* (2004) and Geffken *et al.* (2001).

Pischon *et al.* (2003) assessed physical activity by metabolic equivalent-hours per week and found reductions in CRP and IL-6, dependent of obesity, in 405 men and 454 women (Health Professionals' Follow-up Study and Nurses' Health Study II). Trends for decreased concentrations of inflammatory markers were linear with increasing amounts of reported exercise (Nicklas *et al.,* 2005).

The health and cardiovascular benefits from enhanced fitness may have an anti-inflammatory mechanism and may at least be short-term effects mediated through the already mentioned mechanisms (Wannamethee *et al.,* 2002; La Monte *et al.,* 2002).

CONCLUSION

Data from several large population-based cohorts showed an inverse association between markers of systemic inflammation and physical activity or fitness status. Small-scale intervention studies also proved that exercise training diminishes inflammation associated with obesity. To date, data from randomized controlled trials designed to definitively test the effects of weight loss or exercise training, or both, on inflammation are limited. Future studies are required to define the amount of weight loss needed for clinically meaningful reductions of inflammation. In addition, controlled studies are necessary to clarify the effect of exercise training on chronic systemic inflammation. The mechanisms by which weight loss and increased physical activity reduce inflammation have yet to be elucidated.

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SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

This dissertation is submitted in article format, as approved by the Senate of the North-West University (Potchefstroom Campus) and therefore, includes one literature review article (Chapter 2) and one research review article (Chapter 3) which have been submitted to peer-reviewed journals. Chapter 2 is a literature review according to the example and format set by leading reviewers in the field (see Eckel *et al.,* 2005; Ali & Crowther, 2005; Das, 2001). This chapter will be in the form of a review article on obesity as a predictor of metabolic syndrome and other related risk factors for cardiovascular disease by Beneke, J., Underhay, C., Schutte, A.E., & De Ridder, J.H. and have been submitted for publication in Obesity Research. Chapter 3 consist of a research review entitled "The role of physical activity in the prevention and treatment of obesity as an inflammatory condition" by Beneke, J., Underhay, C., Schutte, A.E., & De Ridder, J.H. and have been submitted for publication in Preventive Medicine.

SUMMARY

Obesity is a problem reaching epidemic proportions in both the developed and developing world (Ali & Crowther, 2005; Yeater, 2000). According to the WHO

(2003), there are more than 1 billion overweight adults, globally at least 300 million of them obese. In the United States alone, obesity has doubled from 15% to 30% in the last 3 decades (Flegal *et al.,* 2002).

Obesity can be defined as a disease in which excess body fat has accumulated as a result of a positive energy balance to an extend that health may be adversely affected (ACSM, 2000; WHO, 1998). Obesity is a serious health problem that reduces life expectancy by increasing one's risk of developing CVD (hypertension, type 2 diabetes, dyslipidemia), novel risk factors (inflammatory markers), insulin resistance, glucose intolerance, sleep apnea, gallbladder disease, obstructive pulmonary disease, osteoarthritis, and certain types of cancer (Kip *et al.,* 2004; Yeater, 2000; Grundy *et al.,* 1999; Heyward & Stolarczyk, 1996).

Obesity also proved to be one of the most essential features of the metabolic syndrome and may be the link that unifies the syndrome (Eckel *et al.,* 2005; Yudkin *et al.,* 2004; Anderson *et al.,* 2001; Yeater, 2000). According to Lam *et al.* (2003), most of the variables in the metabolic syndrome results from multiple factors linked by adiposity. These variables include hypertriglyceridemia, low HDL-C, hypertension, dysfibrinolysis, inflammation (associated with elevated CRP), and/or elevated fasting insulin (Appel *et al.,* 2004).

Das (2001) proposed that obesity could be an inflammatory disorder due to low-grade systemic inflammation, this view is supported by a vast number of researchers (Dandona *et al.,* 2005; Nawrocki & Scherer, 2004; Dandona *et al.,* 2004; Ramos *et al.,* 2003; Weyer *et al.,* 2002). Obesity-related inflammatory markers (CRP, IL-6 and TNF-α) may be important mediators in the pathophysiology of CVD, CHD and type 2 diabetes (Pischon *et al.,* 2003; Rexrode *et al.,* 2003).

A major challenge for metabolic research according to Reilly and Rader (2003) remains the identification of features of adiposity that best reflect increased risk of developing the metabolic syndrome.

Relative weight gain and obesity as a child from about seven years, can predict the metabolic syndrome in adulthood (Vanhala *et al.,* 1999; Rudderman *et al.,* 1998). Therefore it is not surprising that obesity is a major target of prevention and treatment strategies, given the underlying role of altered adipose tissue metabolism in the metabolic syndrome (Robinson & Graham, 2004), which increases the morbidity and mortality risk of a person (Kip *et al.,* 2004; Ford & Giles, 2003; Isomaa *et al.,* 2001).

Cross-sectional epidemiological studies and interventions have demonstrated the benefit of physical activity in the primary prevention of coronary heart disease, diabetes mellitus and hypertension. Most studies show an association between inactivity and these non-communicable diseases (NCD's) therefore the role of physical activity in the treatment and prevention of NCD's should not be underestimated (Grundy *et al.,* 2004a; Sobngwi *et al.,* 2002; Grundy *et al.,* 1999; Leon, 1997).

In chapter 2 (Article 1) obesity as predictor of metabolic syndrome and other related risk factors for CVD was investigated by a literature review. Available studies (intervention, observational and review articles) on the topic from 1990 – 2005 were included in this study. Firstly the health risks associated with obesity and especially abdominal obesity was discussed. The increased health risks associated with obesity are related, not only to the amount of body fat, but also to the way in which fat is distributed, especially in the abdominal region (visceral fat) (Heyward & Stolarczyk, 1996). Abdominal fat has been linked to metabolic risk factors like high systolic blood pressure, atherogenic dyslipidemia, with increased serum triglyceride and decreased HDL-C, glucose intolerance and abnormalities in the coagulation system, all factors that contribute to the coronary risk of an individual.

Secondly, the metabolic syndrome were discussed. The metabolic syndrome comprises an array of cardiovascular disease risk factors such as abdominal obesity, dyslipidemia, hypertension, glucose intolerance (or insulin resistance), pro-inflammatory state or prothrombotic state (Grundy *et al.,* 2004a; Pi-Sunyer, 2004; Robinson & Graham, 2004; Katzmarzyk *et al.,* 2003; NCEP, 2001). Obesity as a predictor of the metabolic syndrome was also discussed. The syndrome is defined by various organizations including WHO, NCEP ATPIII and IDF, but varies mainly by measure of obesity, detail and criteria (Alberti *et al.,* 2005; Eckel *et al.*, 2005; Carrol & Dudfield, 2004; Grundy *et al.*, 2004a). The underlying mechanisms of the metabolic syndrome, insulin resistance, obesity and abnormal fat distribution, hypertension and dyslipidemia were also discussed.

CVD as a leading cause of death in western countries were also highlighted. According to Brooks *et al.* (2000) one in five people presents with some form of CVD, this includes CHD, valvular heart disease, chronic heart failure, cardiomyopathy, stroke, hypertension and peripheral vascular disease. Hyperinsulinemia, hypertension and diabetes, which are all associated with obesity have been recognized as CVD risk factors (Grundy *et al.,* 2004a; Robinson & Graham, 2004; Lerman *et al.,* 2003; Sawaya *et al.*, 2003; Naidoo, 2000).

Finally, diabetes, markers of inflammation (TNF-α, CRP, IL-6) and physical inactivity as obesity related risk factors for CVD were discussed. A majority of patients with type 2 diabetes are obese, 85-96% in most population studies according to Maggio and Pi-Sunyer, (2003). Diabetes mellitus and hyperglycemia increases risks for CVD in several ways: (1) acute hyperglycemia leads to changes in lipid and coagulation factors, (2) chronic hyperglycemia is associated with glycosylation of proteins, renal damage and hypertension, (3) chronic hyperglycemia may have direct toxic effects on the vasculature (may accelerate atherosclerosis), (4) increased risk for CVD is associated with the metabolic syndrome (Naidoo, 2000).

Previous researchers proposed that TNF-α, CRP and IL-6 are involved in the pathology of obesity, insulin resistance and hyperinsulinemia, hypertension, dyslipidemia, atherosclerosis, type 2 diabetes and CVD, indicating that low-grade systemic inflammation play a key role in these conditions and metabolic syndrome (Nicklas *et al.,* 2005; Das, 2002; Benjafield *et al.,* 2001; Pradhan *et al.,* 2001; Ridker *et al.,* 2000a; Ridker *et al.,* 2000b).

Physical inactivity or low levels of physical activity and cardiorespiratory fitness predict development of the metabolic syndrome and CVD. Risk of CVD is 30-50% lower in moderately inactive subjects according to Vuori (2004). Verdaet *et al.* (2004) found regular physical activity to be associated with reductions of several cardiovascular risk factors such as BMI, WHR and lipid profile. Avoidance of a sedentary lifestyle is thus considered of paramount importance for prevention of obesity and related CVD risks. Cardiorespiratory fitness also has been shown to have a favorable effect on CRP and IL-6 levels in most recent studies (Aronson *et al.,* 2004a; Pischon *et al.,* 2003; Church *et al.,* 2002; Meigs, 2002; Reaven, 2002; Geffken *et al.,* 2001).

Therefore enhanced fitness may have an anti-inflammatory role with improved insulin resistance that may be the mechanism for lowering type 2 diabetes and CVD (Aronson *et al.,* 2004b; Pichon *et al.,* 2003; Abramson & Vaccarino, 2002; Wannamethee *et al.,* 2002).

In chapter 3 (Article 2) the role of physical activity in the prevention and treatment of obesity as an inflammatory condition was investigated. Firstly, the relationship between obesity and the metabolic syndrome is discussed. Obesity proved to be one of the most essential features of the metabolic syndrome (Eckel *et al.,* 2005; Yudkin *et al.,* 2004; Anderson *et al.,* 2001; Yeater, 2000). Overweight and obesity lead to adverse metabolic effects on blood pressure, cholesterol, triglycerides and insulin resistance (WHO, 1998). Many people with the metabolic syndrome have an increased body fat, particularly around the midsection (Debé, 2002). Then obesity as an inflammatory condition was discussed. Several researchers proposed that

obesity could be an inflammatory disorder due to low-grade systemic inflammation (Dandona *et al.,* 2005; Ramos *et al.,* 2003; Weyer *et al.,* 2002). CRP is an acute phase reactant and is directly associated with obesity (Heilbronn & Clifton, 2002; Das, 2001). Several markers of inflammation (CRP and IL-6) correlate with indirect measures of adiposity, especially abdominal fat distribution and insulin action, providing a possible link between obesity and insulin resistance (Rexrode *et al.,* 2003; Weyer *et al.,* 2002; Pannacciulli *et al.,* 2001).

The influence of physical activity and weight loss on systemic inflammatory markers associated with obesity were summarized and discussed. Evidence from intervention studies showed that weight loss leads to a reduction in the state of chronic systemic inflammation, which is associated with increased adipose tissue mass in overweight and obese subjects (Xydakis *et al.,* 2004; Gallistl *et al.,* 2001; Heilbronn *et al.,* 2001; Bastard *et al.,* 2000a; Bastard *et al,* 2000b). The postulated mechanisms by which weight loss reduces circulatory markers of inflammation were also highlighted (Nicklas *et al.,* 2005).

Physical activity proved effective in lowering measures of adiposity (BMI, WHR, WC and percentage body fat) (Milani *et al.,* 2004; Verdaet *et al.,* 2004; Pischon *et al.,* 2003; Tchernof *et al.,* 2002) and obesity related inflammatory markers (CRP & IL-6) (Aronson *et al.,* 2004a; Aronson *et al.,* 2004b; Church *et al.,* 2002). Thereby indicating a potential anti-inflammatory effect of physical activity (Wannamethee *et al.,* 2002; La Monte *et al.,* 2002). According to Aronson *et al.* (2004a) the importance of physical activity in improving the pro-inflammatory state associated with the metabolic syndrome need to be emphasized because it could be more efficient than the use of medication. A summary of published research on the associations between systemic markers of inflammation and physical activity is shown in Article 2, Table 5. Increased frequency, volume and intensity (moderate to strenuous) of physical activity and increased level of cardiorespiratory fitness showed an inverse relationship with CRP and IL-6 (Alberti *et al.,* 2004; Aronson *et al.,* 2004a; Milani *et al.,* 2004; Wannamethee *et al.,* 2002; Abramson *et al.,* 2002). Trends

for decreased concentrations of inflammatory markers were linear with increasing amounts of reported exercise.

However, in a study done by Abramson and Vaccarino (2002), it was observed that physical activity was associated with lower levels of inflammation even after adjustment for measures of general obesity (BMI) and central obesity (WHR). Therefore it is unlikely that the association between physical activity and inflammation is mediated entirely by reductions in obesity.

Strenuous physical activity can lead to muscle damage and thereby increase inflammation (Pyne, 1994). Although physical activity increases oxidative metabolism and thereby induces oxidative stress, there is also evidence from several studies that adapting to long-term exercise or physical training can significantly elevate antioxidant defences (Leeuwenbergh & Heinecke, 2001; Alessio & Blasi, 1997).

CONCLUSION

The conclusions of this study are based on the hypotheses that were set in chapter 1 of this dissertation.

Hypothesis 1

Obesity is a systemic low-grade inflammatory condition.

In chapter 3 (Article 2), several research studies concluded that obesity could be an inflammatory disorder due to low-grade systemic inflammation. CRP is an acute phase reactant, synthesized primarily in hepatocytes and secreted by the liver in response to a variety of inflammatory cytokines of which IL-6

and TNF-α are mainly involved. CRP increases rapidly in response to trauma, inflammation and infection. Thus, enhanced levels of CRP can be used as a marker of inflammation.

Adipose tissue is known to be a sectretory organ producing cytokines, acute phase reactants and other circulating factors. These 'adipokines' is mostly not produced by the adipocyte itself by the infiltration of macrophages into the adipocytes.

The synthesis of adipose tissue TNF-α could induce the production of IL-6, CRP and other acute phase reactants, therefore contributing to the maintenance of a chronic low-grade inflammation state involved in the progression of obesity and its associated co-morbidities. Evidence from research studies is strong that circulating levels of inflammatory markers are elevated with total and abdominal obesity and that the location of the body fat, independent of the total amount, is therefore an important factor affecting chronic inflammation. There is some evidence from observational studies involving both men and women that abdominal body fat (measured by WC and WHR) may be an independent predictor of inflammatory markers.

Hypothesis 1 is therefore accepted.

Hypothesis 2

There is an anti-inflammatory action with increased physical activity.

Several studies of large population cohorts provide evidence for an inverse, independent dose-response relation between plasma CRP concentration and level of physical activity in both men and women. Trends for decreased IL-6, TNF-α and CRP concentrations were linear with increasing amounts of reported exercise in most of the research studies. Physical activity proved

effective in lowering measures of adiposity (BMI, WHR, WC and percentage body fat) and obesity related inflammatory markers (CRP & IL-6).

One of the postulated mechanisms by which physical activity reduces circulating markers of inflammation is through a decrease in adipose tissue cytokine production. Physical activity and the associated weight loss that is induced affect the immune system by reducing the number of mononuclear cells in the peripheral blood, which are a source of pro-inflammatory cytokines (such as IL-6 and TNF-α and its receptors). A reduction in adipose tissue would not only reduce the volume of adipocytes and pre-adipocytes, but also decrease the number of endothelial cells and macrophages that reside there. These cells produce many pro-inflammatory mediators such as CRP, serum amyloid protein (SAA) and cytokines. Physical activity may also increase the expression of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist (IL-Ira) in cells. The resulting circulating changes could in turn, cause the liver to contribute by decreasing its production of fibrinogen and other pro-inflammatory mediators.

Thereby indicating a potential anti-inflammatory effect. Therefore Hypothesis 2 is accepted.

Hypothesis 3

Abdominal obesity is a predictor of the metabolic syndrome and other risk factors for CVD.

In the studies reviewed in this article abdominal obesity is identified as a predictor and independent risk factor for CVD in both men and women. High levels of deep abdominal fat have also been correlated with components of the metabolic syndrome. Glucose intolerance, hyperinsulinemia, hypertension, diabetes, increases in plasma triglyceride levels and a decrease in HDL levels

(dyslipidemia) in many of the studies. Prospective epidemiological studies have revealed that abdominal obesity (determined by WC and WHR) conveys an independent prediction of CVD risk and is more relevant compared to general obesity (determined by BMI). Many international studies have shown that there are differences in fat distribution especially abdominal fat patterning in different ethnic groups. This may explain the higher risk of certain ethnic groups for the development of metabolic syndrome and CVD risk factors than others.

Hypothesis 3 is therefore accepted based on the research findings.

Hypothesis 4

Anthropometrical measures of obesity are a suitable method for predicting the metabolic syndrome.

In the studies included in this review obesity is commonly diagnosed by five anthropometrical indices, namely, BMI, % body fat, WC, WHR and Waist-to-stature ratio (WSR).

Abdominal fat has been linked to metabolic risk factors like high systolic blood pressure, atherogenic dyslipidemia, with increased serum TG and decreased HDL-C, and glucose intolerance. Although magnetic resonance imaging (MRI) and computerized tomography (CT) have been used successfully in many studies to measure adipose compartments of the abdomen (subcutaneous and visceral fat), anthropometrical measures like WHR and WC have been proven to be an effective measure in predicting the metabolic syndrome. WC has also been included in the metabolic syndrome definitions of the WHO, ATP III and new IDF.

Hypothesis 4 is therefore accepted.

RECOMMENDATIONS

The results of this dissertation will be made available to health professionals internationally through publication in peer-reviewed journals and presentations at conferences.

Parts of this dissertation were already presented at the "Fourth Annual Conference of the International Society of Behavioural Nutrition and Physical Activity (ISBNPA)" in Amsterdam, The Netherlands during June 2005 and the "11th South African Sports Medicine Congress" held during September 2005 in Johannesburg, South Africa.

- With new data emerging on the metabolic syndrome topic, the use of a unified definition is lacking. Thus, it becomes clear that the many definitions of the metabolic syndrome in the literature create confusion, making the interpretation and comparison of data complicated. The use of a gold standard definition or guidelines will make it easier to draw definite conclusions.

- Ethnic group-specific values for WC are available for Europeans, Asians, Americans, Japanese and Chinese. Future studies should steer towards specific data to identify cut-off values for Africans and African sub-populations in diagnosis of the metabolic syndrome.

- Limited data are available on the prevalence of the metabolic syndrome (as a whole) among Africans. Epidemiological studies are needed to determine the relationship between obesity, metabolic syndrome and CVD in various African populations.

- HIV and AIDS have become an interesting factor that should not be underestimated. The relationship between HIV, metabolic abnormalities and CVD is a new possibility to be explored in Africa.

- Many research exist on the individual components of the metabolic syndrome and the effect of exercise on these components. To date, limited data on the metabolic syndrome per se exist. African specific data on the effect of physical activity on diagnosed metabolic syndrome are much needed.

- Investigation into the acute versus chronic effect of physical activity and fitness on obesity related chronic low-grade inflammation is needed. This will assist researchers to understand the dose response relationship that is needed for treatment of low-grade inflammation. From research it is evident that treatment of the metabolic syndrome includes lifestyle modification and exercise. More research should however be devoted to understanding the physical activity guidelines on the treatment of the metabolic syndrome.

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- Correct format (word counts, 1.5-spaced throughout but table single-spaced, references checked)
- Title Page complete with brief and informative title
- Structured Abstract (Objectives, Methods, Results, and Conclusions), followed by keywords
- Introduction with clear explanation of manuscript's novelty and importance
- Methods, Results, Discussion, And Conclusions main sections
- Acknowledgments
- Reference list (alphabetical order)
- Tables (begin each on a separate page)
- Figure legends (all listed on a separate page)
- Gender-neutral language
- Relevant financial relationships noted
- Precis (last unnumbered page)

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