
The Metabolic Syndrome and associated components among African women

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Afrikaanse titel en opsomming

Die Metabooliese Sindroom en geassosieerde komponente in swart Suid-Afrikaanse vroue

Die metabooliese sindroom (MS) is wêreldwyd 'n ernstige probleem. Dit verwys na 'n groep faktore wat die risiko vir kardiovaskulêresiektes verhoog. Sommige van die faktore (hipertensie, diabetes en obesiteit in vrouens) is algemeen in swart populasies. Die doel van hierdie studie was dus om die insidensie van die MS faktore in swart Suid-Afrikaanse vroue te bepaal, volgens die NCEP ATP III (National Cholesterol Education Program's Adult Treatment Panel) definisie. 'n Verdere doelwit was om moontlike interverwantskappe te bepaal tussen die obesiteits- of insulienweerstand komponent en ander MS komponente, asook met kardiovaskulêre veranderlikes soos angiotensien II (Ang II) en endotelien-1 (ET-1). Die studiegroep het uit 101 swart Suid-Afrikaanse vroue (ouderdom: 20-50 jaar) bestaan wat aan die POWIRS (Profile of Obese Women with Insulin Resistance Syndrome) projek deelgeneem het. Bloeddruk (BD) is met 'n Finometer-apparaat geneem. Antropometriese metings is ook geneem. Vastende glukose, lipiede, Ang II en ET-1 waardes is vanaf bloedmonsters bepaal. Die studiegroep is geklasifiseer volgens die hoeveelheid ATP III MS kriteria teenwoordig. Geen MS kriteria is in 20 van die deelnemers geïdentifiseer, 46 het slegs een kriterium gehad en 35 het twee of meer kriteria gehad. Die laasgenoemde groep se liggaamsmassa indeks (LMI), middelomtrek, BD, glukose en trigliseriede waardes was betekenisvol hoër ($p \leq 0.05$) en die HDL cholesterol (HDL-C) betekenisvol laer ($p \leq 0.05$) as die ander groepe. Met meervoudige regressie analiese het diastoliese BD (DBD) en arteriële meegewendheid 'n assosiasie getoon met middelomtrek en LMI in meeste groepe. In die groep met een MS kriterium het Ang II en ET-1 'n assosiasie getoon met insulienweerstand en HDL-C het 'n assosiasie getoon met middelomtrek en LMI. HDL-C was ook betekenisvol laer ($p \leq 0.05$) in hierdie groep as in die groep met geen MS kriteria en dit was ook die enigste betekenisvolle verskil tussen die groepe. Die gevolgtrekking word dus gemaak dat abdominale obesiteit (middelomtrek) moontlik 'n belangrike rol speel tydens die ontwikkeling van die MS omdat dit betekenisvol geassosieerd was met vaskulêre komplikasies (DBD en arteriële meegewendheid). Verder is dit ook moontlik dat Ang II, ET-1 en HDL-C ook betrokke is tydens die ontwikkelingsfases van die MS by jonger swart Suid-Afrikaanse vroue.

Summary

The metabolic syndrome (MS) and its components have become a serious problem worldwide. The MS describes a cluster of risk factors related to cardiovascular disease. Some of these factors (hypertension, diabetes and obesity in women) have been found to be common among Africans. Therefore, the aim of this study was firstly to determine the incidence of the MS components among African women, using the NCEP ATP III (National Cholesterol Education Program's Adult Treatment Panel) definition. Further objectives were to determine possible interrelationships between the obesity or the insulin resistance (IR) component and other MS components and with other related cardiovascular variables such as angiotensin II (Ang II) and endothelin-1 (ET-1). The subject group consisted of 101 African women (age: 20-50 yrs) that participated in the POWIRS (Profile of Obese Women with Insulin Resistance Syndrome) project. Blood pressure (BP) was taken with a Finometer device. Anthropometric measurements were also taken. Fasting glucose, lipids, Ang II and ET-1 values were obtained from blood samples. The subject group was classified according to the number of ATP III MS criteria present. None of the MS components were identified in 20 subjects, 46 presented one component and 35 had two or more of the components. The latter group showed significantly higher ($p \leq 0.05$) body mass index (BMI), waist circumference (WC), BP, glucose and triglyceride values and a significantly lower ($p \leq 0.05$) HDL cholesterol (HDL-C) value than the other groups. In the multiple regression analyses, diastolic BP (DBP) and arterial compliance were associated with WC and BMI in most groups. In the group with one MS criterion, Ang II and ET-1 were associated with IR. HDL-C was associated with WC and BMI in this group. HDL-C was also significantly lower ($p \leq 0.05$) in this group than in the group with no MS components and this was the only significant difference found between these two groups. It is concluded that abdominal obesity (WC) may play an important role in the development of the MS as it showed significant associations with vascular complications (DBP and arterial compliance). It was further found that Ang II, ET-1 and HDL-C could also be involved in the developmental stages of the MS among younger African women.

Preface

For the purpose of this study, the article format is used and, therefore, Chapter 3 is a manuscript in the form of an article as required by the regulations of the North-West University. The manuscript was submitted to the *Journal of Diabetes and its Complications* and all references are cited according to the instructions for authors of the journal and the full reference list appears at the end of the manuscript. This reference style is used in all the chapters of this dissertation. A short background of the appropriate literature is given in the introduction section of the manuscript (Chapter 3), but Chapter 2 is an extensive assessment of the relevant literature regarding the metabolic syndrome and its associated components among African women. In this study black African women are referred to simply as African women and white women are referred to as Caucasian women. Chapter 1 is an introductory chapter in which the motivation for the study is discussed. In Chapter 4 a short summary of the main findings of the study is given, the study limitations are discussed and recommendations for future studies are made. The supervisor and co-supervisor are named in the manuscript as co-authors and during the study they acted in their specific roles of supervisor and co-supervisor. They also gave consent that the manuscript could be used as part of this dissertation. The specific contribution of each author during the study is given on the following page.

Authors' contributions

The contribution of each author in the study is set out in the following table:

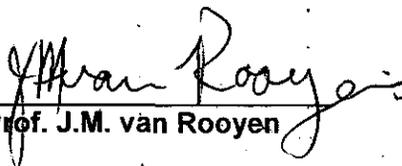
Name of author	Role in the study
Ms. J. Kotze	Responsible for the literature searches, statistical analyses, planning and design of the manuscript, interpretation of results and the writing of the manuscript.
Dr. A.E. Schutte (<i>Physiologist</i>)	Supervisor. Supervised the writing of the manuscript, responsible for initial planning and design of the study and gave guidance in the interpretation of data and results.
Prof. J.M. van Rooyen (<i>Physiologist</i>)	Co-supervisor. Supervised the writing of the manuscript, assisted with the planning of the manuscript and was involved in the interpretation of results.

The following is a statement from the co-authors confirming their individual roles in the study and giving their permission that the article may form part of this dissertation.

I declare that I have approved the above-mentioned article, that my role in this study, as indicated above, is representative of my actual contribution and that I hereby give my consent that it may be published as part of the M.Sc. dissertation of Jolene Kotze.



 Dr. A.E. Schutte



 Prof. J.M. van Rooyen

Abbreviations

ACE	-	Angiotensin converting enzyme
Ang II	-	Angiotensin II
ANP	-	Atrial natriuretic peptide
AT ₁	-	Angiotensin type 1 receptor
AT ₂	-	Angiotensin type 2 receptor
ATP III	-	Third Adult Treatment Panel
BMI	-	Body mass index
BP	-	Blood pressure
C	-	Arterial compliance
CAD/CHD	-	Coronary artery disease/Coronary heart disease
CO	-	Cardiac output
CVD	-	Cardiovascular disease
CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
ESH	-	European Society of Hypertension
ET-1	-	Endothelin-1
HDL-C	-	High density lipoprotein cholesterol
HIV/AIDS	-	Human immunodeficiency virus/Acquired immunodeficiency syndrome
HOMA	-	Homeostasis model assessment
HR	-	Heart rate
IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerance
IR	-	Insulin resistance
LDL-C	-	Low density lipoprotein cholesterol
MS	-	Metabolic syndrome
NCD	-	Non-communicable diseases/disorders
NCEP	-	National Cholesterol Education Program
NHANES	-	National Health and Nutrition Examination Survey
NO	-	Nitric Oxide
OGTT	-	Oral glucose tolerance test
POWIRS	-	Profile of Obese Women with Insulin Resistance Syndrome
RAS	-	Renin-angiotensin system

SA	-	South Africa
SBP	-	Systolic blood pressure
SNS	-	Sympathetic nervous system
SSA	-	Sub-Saharan Africa
SV	-	Stroke volume
TGF- β_1	-	Transforming growth factor beta-1
TNF- α	-	Tumor necrosis factor α
TPR	-	Total peripheral resistance
UK	-	United Kingdom
US/USA	-	United States/United States of America
VEGF	-	Vascular endothelial cell growth factor
VLDL-C	-	Very low density lipoprotein cholesterol
WC	-	Waist circumference
WHO	-	World Health Organisation
WHR	-	Waist-to-hip ratio

All abbreviations are indicated and explained where they first appear in the text, whereafter only the abbreviation is used.

1

Introduction

1. Background and motivation

The purpose of this dissertation is to report on the metabolic syndrome (MS) components and associated variables among African women. The MS and associated components are discussed with the focus on obesity, insulin resistance (IR) and cardiovascular disease (CVD) like hypertension as integrated features of the MS. Selected cardiovascular variables [*systolic blood pressure (SBP)*, *diastolic blood pressure (DBP)*, *cardiac output (CO)*, *stroke volume (SV)*, *heart rate (HR)*, *total peripheral resistance (TPR)* and *arterial compliance*, *angiotensin II (Ang II)* and *endothelin-1 (ET-1)*] are considered with regard to obesity [*waist circumference* and *body mass index (BMI)*], cardiovascular health and the MS among younger African women. In this chapter, motivations are provided regarding the specific concerns of the MS for the health of African women and the possible involvement of associated cardiovascular variables in the development of the MS, particularly in obesity, IR and CVD. The study includes a manuscript in a publication format with a detailed outline of the aims and objectives, a short literature review, the results of the study and discussion of the findings and conclusions. In this chapter, an overview is provided concerning the motivations, reasons, goals and objectives of the study.

2. The metabolic syndrome

The NCEP ATP III (*National Cholesterol Education Program's Third Adult Treatment Panel*) uses the term MS to describe the clustering of multiple risk factors for CVD (1,2). The MS increases the mortality risk from CVD and all causes (3). The main abnormalities that comprise the MS are obesity, hypertension, IR and dyslipidemia (4,5). The use of different definitions to classify the MS has made it complicated to generate prevalence estimates (3). Nonetheless, it is estimated that the prevalence of the MS is very common in Westernised societies like the United States (US), affecting between 25% and 35% of the population (4).

Ford and Giles (3), using US NHANES III (*the Third National Health and Nutrition Examination Survey 1988-1994*) data, found that the prevalence of the MS in the overall sample was similar using two different definitions of the MS [ATP III = 23.9% and *World Health Organisation (WHO)* = 25.1%], although the estimates differed substantially for some of the ethnic subgroups within the sample. In other developing countries like Mexico, the prevalence of the MS has also been found to be high, with a rate of 13.6% when using the WHO definition and a rate of 26.6% when using the definition of the ATP III (6).

2.1 Components of the metabolic syndrome

Worldwide it is estimated that CVD is responsible for 30% of annual deaths (7) and in the US it is estimated that 60 million Americans have one or more CVD (8). It is generally thought that CVD is more common in industrialised countries, but 80% of CVD-related deaths occur in low-to-middle income countries (7) and at present, developing countries contribute a larger share to the global CVD burden than developed countries (9). The African population of the North West Province of South Africa (SA) is an example of a population where urbanisation is related to hypertension, and it has been shown that newcomers to urban areas that live in informal settlements have elevated blood pressure (BP) levels (10).

The rising prevalence of the MS could in part be a consequence of the global obesity problem (1). Obesity presents a serious health problem for developed countries like the US (11), but the prevalence of obesity is now also rapidly increasing in developing countries all over the world (12,13). Data from the NHANES III study revealed that an estimated 97.1 million American adults have a BMI greater or equal to 25 kg/m² (14). The latest NHANES data showed that in 1999, 34% of American adults were overweight and 27% were obese (13,15). The problem with obesity is that it is associated with many negative health outcomes and social disabilities (16). It is not simply a cosmetic problem, but represents an unhealthy state currently accepted as an illness (17) associated with mortality from CVD such as heart failure (18). Obesity may account for as much as 65% to 75% of human essential hypertension and it is important to establish and clarify the mechanisms that link obesity and hypertension (19).

The ATP III definition of the MS was chosen as the appropriate definition to determine the incidence of the MS components in the current subject group of younger African women. As shown in the above literature, obesity and hypertension rates are high among Africans. Abdominal obesity, as reflected by waist circumference in the ATP III definition reflects the high priority given to abdominal obesity by the ATP III and the ATP III further also considers CVD as the primary outcome of MS (1). The ATP III definition also only requires readily available variables to identify individuals with the MS (20).

2.2 Ethnicity and gender

Non-Caucasian ethnicity is often recognised as a factor that increases the likelihood for development of the MS (21). CVD is the leading cause of death among African Americans (22) and high rates of hypertension are found among them (23,24). Hypertension rates vary within African American groups and those at greatest risk are likely to be older, less educated, overweight, physically inactive and diabetic (25). In SA, hypertension rates have also been found to be very high among Africans (10,26).

Diabetes has also reached epidemic proportions across the world and a strong association exists between diabetes and CVD prevalence (in the US 60–75% of diabetic patients die due to CVD); diabetes is, therefore, in itself a significant and independent risk factor for the development of CVD (27). In SA, the rapid migration of Africans to urban centres has led to increases in the prevalence of obesity, hypertension and diabetes and this pattern of increasing risk factors with urbanisation is likely to affect most of sub-Saharan Africa (22). In most ethnic groups diabetes is more prevalent among women than men and it seems that the protective effect of female sex hormones against CVD is negated by diabetes in premenopausal women (27).

The BMI of 50.7% of American women participating in the NHANES III study was greater or equal to 25kg/m² (14). Obesity affects a higher percentage of women than men, and African American women are at especially high risk (15). It is estimated that approximately 38% of African American women have a BMI greater than 30 kg/m² compared to 23% of Caucasian women (22). Obesity influences the health of

both African and Caucasian women, but the obesity-related risks for African women could be higher because of the presence of multiple risk factors (28).

There is also a very high prevalence of obesity among African women in SA. In the THUSA (*Transition and Health during Urbanisation of South Africans*) study, done among the African population of the North West Province of SA, it was found that 25.2% of the women were overweight and 28.6% were obese (29). A study conducted in a disadvantaged population from mixed ancestry in SA found that half of the middle-aged women studied were obese and a rising BMI trend was seen (30). Using data from the 1998 *Demographic and Health Survey*, Puoane and co-authors (31) found higher levels of obesity among the urban African women group than among the other population groups studied.

African women were therefore chosen as the subject group of this study because of the high prevalence rates of obesity, hypertension and diabetes found among them as indicated in the above literature.

2.3 The role of angiotensin II and endothelin-1

CVD has more serious health consequences for Africans than Caucasians, but the underlying racial mechanisms for this are at present still unclear, although differences in the function of the renin-angiotensin system (RAS) have been suggested (24). To maintain CVD processes and progression, activation of G-protein coupled receptors in response to vasoconstrictor peptides like Ang II or ET-1 and the resulting intracellular processes are essential (18). The RAS plays an important role in BP regulation, but it is also a key factor involved in CVD (18,32). Increased production of Ang II and/or enhanced Ang II activity is often associated with several cardiovascular risk factors (18,33). Elevated levels of RAS components may also play a role in other diseases like diabetes (32,34). Evidence also suggests a role for the local adipose tissue RAS in obesity-associated MS (35). Ang II can stimulate the release of the vasoconstrictor ET-1, which could be related to the mechanisms obesity-related hypertension (36).

ET-1 could play a role in energy metabolism via adipose tissue factors like resistin and leptin (37) and this suggests a role for ET-1 in obesity (18). It has been found that ET-1 levels are increased in hypertensive Africans compared with Caucasians

with hypertension (38). The elements of hypertension often have endothelial dysfunction in common (39). In CVD, dilatation is reduced and constriction is enhanced via the release of constrictor factors like ET-1 from the defective endothelium (40).

The above literature indicates that obesity and hypertension could be linked via several hormonal mechanisms. High rates of obesity and CVD are common in populations of African ancestry, especially women. For this reason it is important to explore the possible role of hormonal systems such as the RAS and ET-1 during the MS among African women.

The underlying structure among the MS risk factors reveals that it is often primarily represented by the obesity and IR factors, followed by the lipid factor and lastly the BP factor (41). BP generally forms a separate factor from other components of the MS (i.e. IR) during factor analyses and this raises uncertainty over the extent to which it should be included in the MS (42).

Hormonal systems like the RAS are associated with obesity (35,43,44) on the one hand and CVD such as hypertension (18,32) on the other. It is, therefore, of interest to explore Ang II as a possible link between the obesity and BP factors of the MS among Africans, because it is known that the RAS plays an important role during the development of hypertension in this subject group (24,45). It has been shown that Ang II is involved in both salt-sensitive hypertension and IR (46), which are both common disorders among Africans. Physiological differences in sodium handling have been implicated in racial differences in hypertension between Africans and Caucasians (22).

3. Aims

The aims of the study are:

- To determine the incidence of the ATP III MS components and other associated cardiovascular variables such as Ang II and ET-1 among the African women that participated in the POWIRS (*Profile of Obese Women with Insulin Resistance Syndrome*) study.

- To describe how these variables contribute to the obesity (waist circumference and BMI) and the IR component of the MS and to identify specifically which of these variable(s) are the strongest contributors to either the obesity or the IR component of the MS in order to determine whether obesity or IR is the major contributor to the development of the MS in this study of younger African women.

4. Structure and outline of the study

- **Title**

**The Metabolic Syndrome and associated components
among African women**

- **Chapter 1 – Introduction**

Background, motivation, aims and outline of the study is given.

- **Chapter 2 – Literature review**

The MS (obesity, IR, dyslipidemia and CVD or hypertension) is discussed.

- **Chapter 3 – Article**

Title

**Interrelationships between Metabolic Syndrome components
associated with cardiovascular variables.**

Main aim

The aim of this study is to determine the incidence of the MS components among African women according the ATP III definition. Further objectives are to determine interrelationships between the obesity or the IR component and other MS components, as well as with the other related cardiovascular variables such as Ang II and ET-1.

Specific objectives

- a. To determine cardiovascular parameters including SBP, DBP, CO, SV, HR, TPR and arterial compliance. To measure weight, height and waist circumference and to calculate BMI. To determine fasting glucose, high-density lipoprotein cholesterol (HDL-C), triglyceride, Ang II and ET-1 concentrations.
 - b. To classify the subjects into three groups according to the number of ATP III MS criteria present (No MS criteria, one MS criterion and two or more MS criteria).
 - c. To determine the incidence of the MS components and associated variables in the different groups. To determine the mean value with 95% confidence intervals for each of the variables and to determine significant differences for all the variables between the groups. To examine and compare these values with the cut-points of the ATP III, in order to establish which of the ATP III MS features may play a role during the development of MS in this study group.
 - d. To do multiple regression analyses with waist circumference, BMI and IR as dependent variables with independent variables to discover possible interrelationships between the MS components. To determine which of these variable(s) are the strongest contributors to the obesity and IR components of the MS in order to establish whether obesity or IR is the major contributor to the development of the MS in the study group.
- **Chapter 4 – General findings and final comments**

Summary of the main findings is given; final comments and recommendations for future studies are made.

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Literature review

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Health in Africa

A literature review is presented here, detailing the issues surrounding the metabolic syndrome (MS) and its components, as well as the possible involvement of other cardiovascular variables, such as angiotensin II (Ang II) and endothelin-1 (ET-1) in the development of the MS among African women.

In South Africa (SA), literature regarding these issues among Africans is limited. According to Yusuf *et al.* (1), cardiovascular disease (CVD) data from Sub-Saharan African (SSA) countries are inadequate because only 1.1% of all deaths are registered with a central agency. Where possible reference has been made to studies done among populations in SA, but in order to clarify certain concepts, it has been necessary to discuss them as they relate to the African American, Caucasian American and the Caucasian population of SA, because more research has been done among these populations. Health research among Africans is greatly needed and is, therefore, of high importance. Reddy and Yusuf (2) comment that the emerging CVD epidemic in developing countries has attracted little public health response, even within the countries themselves.

The abnormalities of the MS are very rare in hunter-gatherer, less Westernised societies that follow a more traditional lifestyle and for this reason these abnormalities are often referred to as '*diseases of civilisation*' (3). During the 20th century, many countries experienced a transition in societal structures, economics, politics, education and home environments, which has led to a shift from agricultural and rural societies to industrial and urban societies and more recently a further shift to information-based societies (1). Often referred to as the modern epidemiological transition, this shift represents a decline in deaths attributable to infectious diseases and an increase in deaths due to chronic lifestyle diseases (2).

Formerly in SA, the most common cause of death was attributable to infections like malaria and tuberculosis. Up until the 1970's, Africans who reached the age of 50 years had a longer life expectancy than Caucasians because of the low prevalence of chronic lifestyle diseases. This is no longer the case due to a rise in communicable diseases like HIV/AIDS and non-communicable disorders (NCD), including obesity in women, hypertension, stroke, diabetes and cancer (4).

CVD is regarded as the leading cause of death in most regions around the world, except in SSA, but it is anticipated that CVD will overtake infectious disease as the leading cause of death within a few years (5). Mortality due to CVD is projected to rise at an alarming rate in developing countries and with a simultaneous decline in infectious and nutritional disorders (competing causes of death), the proportional burden due to CVD and other chronic lifestyle diseases will increase even further (2). Over the next decade communicable diseases will remain the main health problem in SSA, but the prevalence of NCD is increasing rapidly, particularly in the urban areas (6). Developing countries should expect to experience the burden of both pre-transitional and post-transitional diseases for some time to come, which could result in inadequate attention to both disease categories (2). In SA, the rapid migration of Africans to urban centres has led to increases in poverty, obesity, hypertension and diabetes and this pattern of increasing risk factors with urbanisation is likely to affect most of SSA (1). The poor health status of Africans can be attributed to the fact that SA as a country is suffering from a triple burden of disease related to poverty and infection (HIV/AIDS), from violence-related injuries and lifestyle-related NCD which are consequences of the rapid urbanisation rates (7). The African population of the North West Province of SA is an example of a population where urbanisation is related to hypertension and it has been shown that newcomers to the urban areas that live in informal settlements have elevated blood pressure (BP) levels (8).

CVD is responsible for an estimated 30% of all deaths each year worldwide and it is said that the world is currently in the midst of a cardiovascular pandemic (5). It is the leading cause of death in the United States (US) and it is estimated that 60 million Americans have one or more CVD (3). Although it has previously been more typical in affluent societies, 80% of CVD-related deaths now occur in low-to-middle income countries (5). It is often not realised that the developing countries contribute a larger share to the global CVD burden than developed countries (2). In developing countries, research is needed to guide improvements of resources and to direct and evaluate preventative measures with regard to NCD (6), because the medical and socio-economic consequences of the projected increases in the CVD burden will be disastrous for these countries (2).

The metabolic syndrome

1. Conceptualising the metabolic syndrome

The MS describes the clustering of risk factors for CVD (9). The NCEP ATP III (*National Cholesterol Education Program's Third Adult Treatment Panel*) identifies CVD as the primary outcome of MS (10). People with the MS are, therefore, at an increased risk for CVD and are also at risk for increased mortality from CVD as well as from all causes (11). The ATP III uses the term MS to describe this clustering of risk factors (10). Others use terms such as syndrome X and insulin resistance syndrome to describe the cluster (12,10). The latter term emphasises the central role of insulin resistance (IR) and compensatory hyperinsulinemia as the underlying defect in the pathogenesis of the syndrome (13). The term central adiposity syndrome has also been proposed by some to support the idea that obesity is the major cause of the syndrome (14). The main abnormalities that comprise the MS include obesity, IR, dyslipidemia and hypertension (12,14).

The conceptual importance of diagnosing the MS is to show that these abnormalities are more likely to occur together than alone (15). A study exploring the underlying structure among the MS risk factors found that it was primarily represented by the IR and obesity factors, followed by the lipid factor and lastly the BP factor (16). BP generally forms a separate factor from other components of the MS (i.e. IR) during factor analyses and this raises uncertainty over the extent to which it should be included in the MS (17).

2. Diagnoses and prevalence of the metabolic syndrome

Different definitions with different criteria can be used to diagnose the MS. Here a comparison is made between the definitions of the ATP III and that of the *World Health Organisation* (WHO) (10,18):

Table I. Definitions of the metabolic syndrome.

	ATP III	WHO
Fasting glucose [Hyperglycemia]	(1) IFG ≥ 6.1 mmol/L	IFG ≥ 6.1 mmol/L &/or IGT ≥ 7.8 mmol/L
Insulin resistance	-	Diabetes or $\geq 4^{\text{th}}$ quartile HOMA-IR*
Obesity	(2) Waist circumference > 88 cm	BMI ≥ 30 kg/m ² or WHR > 0.85
Blood pressure [Hypertension]	(3) SBP ≥ 130 &/or DBP ≥ 85 or treated	SBP ≥ 140 &/or DBP ≥ 90 or treated
Dyslipidemia [Hypertriglyceridemia; Low HDL-C]	(4) Triglycerides ≥ 1.69 mmol/L; (5) HDL-C < 1.29 mmol/L	Triglycerides ≥ 1.69 mmol/L and/or HDL-C < 1.0 mmol/L
Microalbuminuria	-	AER ≥ 20 mg/min or albumin-to-creatinine ratio $20 \geq$ mg/g
Diagnosis	When 3 or more of the 5 criteria are identified	IR or IFG/IGT and 2 other risk factors are required

ATP III, Adult Treatment Panel; WHO, World Health Organisation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; *HOMA, homeostasis model assessment; BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; AER, albumin excretion rate; IR, insulin resistance.

*HOMA-IR: [Calculated homeostasis model assessment (HOMA-IR = fasting insulin ($\mu\text{U/mL}$) x fasting plasma glucose (mmol/L)/22.5]

Although the importance of the MS has been established, it remains difficult to identify individuals with the syndrome (13). The use of many definitions, instead of a routine and standard definition, has made it complicated to generate estimates of the MS for research purposes and health care allocation (11). Nonetheless, the prevalence of the MS is common in Westernised societies like the US, and it has been estimated that it affects 25–35% of the population (12). In developing countries like Mexico, the prevalence of the MS is also high, with a rate of 13.6% when using the WHO definition and a rate of 26.6% when using the definition of the ATP III (19).

When using and interpreting the different definitions of the MS the following aspects should be considered:

ATP III

- ◆ The primary outcome of the syndrome according to the ATP III is CVD (10).
- ◆ The ATP III definition requires only readily available variables to make a diagnosis (9).
- ◆ Inclusion of abdominal obesity as reflected by waist circumference reflects the high priority given to it by the ATP III (10).
- ◆ The cut-points of the ATP III are less strict than those usually required to classify a categorical risk factor, because multiple marginal risk factors can represent a significant increased risk for CVD (10).
- ◆ The ATP III definition does not include a direct way to identify subjects with IR (11). Although explicit IR is not required for diagnosis, most subjects that meet the ATP III criteria will have IR (10). The ATP III criteria are to some degree associated with IR and therefore should result in the identification of subjects who are likely to have IR (11).
- ◆ The presence of diabetes does not exclude diagnosis of the MS according to the ATP III definition (10).

WHO

- The WHO guideline group also identifies CVD as the main outcome of the MS (10).
- The WHO criteria for central obesity (Table I) could result in higher prevalence estimates of WHO defined MS than ATP III defined MS within the same population (11).
- The WHO definition requires the presence of diabetes, impaired glucose tolerance (IGT) or IR and two other risk factors to make a diagnosis. IGT requires an oral glucose tolerance test (OGTT), which is the standard method for identifying subjects at increased risk for diabetes in clinical research, but it is not routinely used in clinical practice because it is inconvenient and costly (9). A possible disadvantage of the definition is that special glucose testing beyond the clinical routine may be needed for diagnosis (10).
- IR is a required component for diagnosis but the presence of diabetes does not exclude diagnosis (10). The precise measurement of IR requires an insulin clamp

study (9). By including IR explicitly, the WHO definition identifies subjects with the MS more directly than the ATP III definition (11).

- The hypertension criteria differ between the definitions (Table I) and the higher WHO threshold could lead to the inclusion of MS subjects who are particularly at high risk for CVD (11). This is reflected in the different strategies of the two definitions. The ATP III definition has a clinical strategy of reducing the population burden of CVD, while the WHO definition has a more pathophysiological approach (9). The WHO criteria are valuable in research, where the ATP III criteria are useful in clinically diagnosing the MS (20).

Other aspects to consider

- **Ethnicity:** Ford and Giles (11), using US NHANES III (*the Third National Health and Nutrition Examination Survey*) data, found that the prevalence of the MS in the overall sample studied was similar using the two different definitions (ATP III = 23.9% and WHO = 25.1%), but the estimates differed markedly for some ethnic subgroups within the sample. In the same study it was reported that 80–90% of the participants who were classified as having the MS under one definition only needed one additional criterion to meet the demands of the other definition as well. As mentioned earlier, the prevalence of the MS is high in developing countries like Mexico, but prevalence estimates differ depending on the definition used, for example, the WHO definition gives a rate of 13.61% and the definition of the ATP III yields a rate of 26.6% (19).
- **Genetics and age:** Genetics and age are also important risk factors for the development of the MS (21). With advancing age more of the MS criteria become apparent. Many studies have demonstrated that the prevalence of the MS rises with advancing age (10). Advancing age is considered a major and independent risk factor for CVD (18). Weight tends to increase and physical activity decreases as people become older (13). Each risk factor of the MS is subject to regulation via genetic/acquired factors, which leads to variability in the expression of risk factors, i.e. lipoprotein metabolism is influenced by genetic variation and accordingly the resulting dyslipidemias in response to obesity and/or IR vary considerably. This principle applies to factors such as BP regulation as well (10).

3. Components and risk factors of the metabolic syndrome

The ATP III presents the components of the MS in a particular combination of what is termed underlying, major and emerging risk factors as follows (10):

- **Underlying risk factors:** Obesity (particularly abdominal obesity), physical inactivity and an atherogenic diet.
- **Major risk factors:** Smoking, hypertension, elevated low density lipoprotein cholesterol (LDL-C), low high density lipoprotein cholesterol (HDL-C), family history of premature coronary heart disease (CHD) and ageing.
- **Emerging risk factors:** Elevated triglycerides, small and dense LDL-C, glucose intolerance, a pro-inflammatory and prothrombotic state.

Hereafter follows a discussion of some of the components of the MS that are relevant to the present study.

3.1 Obesity and body composition

The ATP III considers obesity an underlying risk factor for CVD and others term obesity as a metabolic risk factor (10). Here a discussion is provided concerning the classification, prevalence, health risks and aetiology of obesity, as well as the role of adipose tissue in the MS.

3.1.1 Classifying overweight and obesity

To understand statistics related to overweight and obesity, it is important to know what is meant by these terms and how they are defined. Obesity generally refers to a condition of excessive fat accumulation to the extent that health and well-being are affected (22). Obesity is defined as an abnormal increase in body fat, which is not necessarily an increase in body weight and for adult men and women with an average weight, the percentage of body fat is around 15–20% and 25–30% respectively (23). Although it is possible to measure body fat in various ways, including skinfold thickness and bio-electrical impedance (23), most studies use certain markers for fatness like the body mass index (BMI) because it is difficult to measure body fat content (24). In the scientific literature, BMI is commonly used to describe weight for height stature and general obesity (25), whereas waist-to-hip ratio (WHR) and waist circumference is often used as an indicator of abdominal obesity (26).

3.1.1.1 Body mass index

For population studies, WHO defines cut-off values for obesity based on the BMI or the quetelet index, calculated by dividing weight in kilograms by the square of the height in metres: $[\text{weight (kg)}/\text{height (m}^2\text{)}]$ (22,27,28). According to WHO, a person is overweight if his/her BMI $\geq 25 \text{ kg/m}^2$ and obese if his/her BMI $\geq 30 \text{ kg/m}^2$ (27). A BMI that exceeds 25 kg/m^2 can already be associated with negative health consequences, but it is practice to consider a BMI greater than 30 kg/m^2 as the cut-off value, which is that point at which fat accumulation is a major health hazard (29).

It should always be kept in mind that BMI is an approximation that does not always express the exact degree of fatness or obesity of an individual (23). The BMI is a useful tool for population studies even though some ethnic groups require different threshold values (24). The relationship between body fat percentage and BMI differs between ethnic groups and as a consequence, cut-off points for overweight and obesity based on BMI need to be ethnicity specific (22). Using a BMI $\geq 25 \text{ kg/m}^2$ to identify subjects at increased risk to have the MS could be too high for ethnic groups where the prevalence of IR and hyperinsulinemia is also common (13).

Obesity prevalence estimates vary based on which BMI cut-off points are used, for instance, the criteria proposed by WHO or those of the US Dietary Guidelines for Americans (25). The lack of consistent published data using standardised BMI diagnostic criteria and the use of poorly standardised reference populations make it difficult to estimate the total burden of diseases associated with obesity (28). Adapting BMI cut-off point values can have important consequences for prevalence data in some populations, as the prevalence of obesity can dramatically increase or decrease accordingly (22). Another reason why using BMI alone may be insufficient to monitor the rising prevalence of obesity is because increased body fat appears to be matched by a reduction in fat free mass due to decreased physical activity (23).

3.1.1.2 Waist circumference and waist-to-hip ratio

Fat distribution can be assessed by measuring the circumference of the waist and hips to obtain the WHR, although waist circumference alone is an adequate marker of intra-abdominal fat content (24). It seems that measurement of waist circumference is a relatively good indicator of health (23) and being obese with a large waist circumference represents a greater risk to health as to being obese with a

smaller waist circumference (24). Studies have shown that in women already at increased health risk due to a high BMI, further measurement of WC may help to identify CVD risk (30). Cut-off values for WHR are based on studies done among Caucasians in the US and may, therefore, not be entirely appropriate for all ethnic groups (31).

Many studies have shown that abdominal obesity in women as indicated by a WHR > 0.80 and/or a waist circumference > 80cm is very common in populations of African ancestry (31). A waist circumference \geq 88cm is the proposed cut-off point for identifying an increased risk for obesity co-morbidities in women (23). In a study by Okosun *et al.* (32), it was shown that African ethnicity is associated with the clustering of the multiple risk factors of the MS and IR. In the study, waist circumference appeared to be a good marker for the clustering of the MS risk factors studied, and accordingly it was suggested that waist circumference could be used as a clinical variable when assessing CVD risk in this population (32).

As it has been demonstrated that waist circumference is a sensitive measure and predictor of abdominal obesity in African American women and is a better predictor of NCD risk factor prevalence than WHR in other African populations, it is the recommended measure when determining abdominal obesity among the African population in SA (31). It has further been shown that among a group of hypertensive African women in SA, central obesity measures (waist circumference) were more strongly associated with MS components than BMI (33). These aspects further highlight the motivation for choosing the ATP III definition of the MS for the current study among African women as this definition gives a high priority to abdominal obesity as represented by waist circumference (Table I).

In a study by Kip *et al.* (34), it was found that in women with suspected myocardial ischemia, the presence of the MS was more predictive of future CVD risk than BMI alone, therefore it was recommended to evaluate metabolic status according to ATP III criteria (which includes waist circumference rather than BMI), to reduce manifestations of the MS (through treatment of modifiable risk factors like weight loss) and ultimately CVD risk (34). It is, therefore, important to diagnose the MS in individuals in order to reduce their risk for ultimately developing CVD.

3.1.2 Prevalence and trends of obesity

Since the earliest era's, up until quite recently, daily human life revolved around the struggle of actively hunting and gathering of food for survival. Today diseases such as obesity threaten the survival of modern man. This situation is the result of a lifestyle characterised by large amounts of readily available, attractive food and little need for physical activity (29).

3.1.2.1 Obesity – a global problem

Obesity is a major health problem in the US (35) and other countries all over the world and the prevalence of obesity is continuing to rise (22). Obesity has become a common disorder that affects more than one third of American adults (36). It is steadily becoming the biggest health problem in the developed world and this pattern of rising obesity rates is now also occurring in developing countries around the world (29). Obesity is as much an issue for low-income countries as it is for more affluent countries (5). In European countries, obesity rates are also high (23). In the United Kingdom (UK), 20 years ago 6% of men and 8% of women had a BMI greater than 30 kg/m² and in 1997 the figures had risen to 17% and 20% respectively (24).

From prospective cohort studies and national statistics data, Allison *et al.* (35) estimated the annual number of obesity-related deaths among American adults between 280 000 and 325 000 and more than 80% of these deaths occurred in individuals with a BMI greater than 30 kg/m². An estimated 400 000 Americans die each year from smoking-related diseases and in the future, mortality due to obesity is expected to exceed that of smoking because smoking rates are decreasing significantly (29). Obesity costs are enormous and it is an economic burden to individuals and health care systems (23). Obesity and inactivity represent a major but avoidable contribution to the cost of illness in the US and other countries where modern lifestyles with sedentary occupations have replaced physical labour (37). It is estimated that 29% of adults do not participate in any physical activity and another 46% do not achieve the recommended physical activity level, therefore, around 60% of the world population are insufficiently active (5).

3.1.2.2 Ethnicity and gender

Obesity affects a higher percentage of women than men, and African American women are at especially high risk (38). Approximately 38% of African American women have a BMI $> 30 \text{ kg/m}^2$ compared to 23% of Caucasian American women (1). In a prospective cohort study among female registered nurses participating in the *Nurses' Health Study*, Rextrode *et al.* (39) found that both obesity and weight gain in women are important risk factors for ischemic and total stroke. Obesity appears to have qualitatively similar health consequences for African and Caucasian women, but the obesity risks for African women may be enhanced by the presence of multiple risk factors, it is therefore the strength of the association to certain disease risks that differ in particular (40). This is another reason why African women were chosen as the subject group for this study.

3.1.3 Obesity and other metabolic syndrome components: health consequences and risks

Obesity affects many aspects of a woman's life by increasing risk for heart disease, diabetes, breast cancer and infertility (41). Obesity is not simply a single disease, but consists of a variety of conditions resulting from different mechanisms which are associated with various types and degrees of risks (42).

The exact relationship between body weight and overall mortality remains a controversial subject despite considerable investigation (43). Increased body weight is associated with an increased mortality rate due to many diseases, like heart disease, diabetes, gallbladder disease and cancer (44). A BMI of 30 kg/m^2 is associated with a 1.5 to 2 fold increase in premature mortality risk when compared to a BMI of $20\text{-}25 \text{ kg/m}^2$ (24). A study among middle-aged women by Manson *et al.* (43), using data from the prospective *Nurses' Health Study*, found that body weight and mortality from all causes were directly related. Some studies have found an association between weight fluctuation and cardiovascular mortality or other cardiac risk factors (23).

The MS describes a cluster of related components namely, obesity, IR, dyslipidemia, and hypertension, which increase the risk for CVD (45). It has further been linked with diseases such as polycystic ovary syndrome (symptoms driven by IR), non-

alcoholic steatohepatitis (a common cause for abnormal liver function and fatty liver disease) (29), cholesterol gallstones, asthma, sleep disturbances and certain cancers (10). The MS exerts these effects through different risk factors and different mechanisms (21). The rising prevalence of the MS could be a consequence of the global obesity problem (10) discussed in the above paragraphs.

3.1.3.1 Obesity and cardiovascular disease

According to Pearson (46), hypertension is a global problem that contributes significantly to mortality worldwide. Epidemiologic studies show that up to 50% of obese individuals (as defined by a BMI > 27 kg/m²) have concomitant hypertension (36), therefore, overweight, obesity and inactivity are serious contributing factors to the current global hypertension burden (5). The fact that there is a link between obesity and hypertension, referred to as obesity-related hypertension, has been recognised since the early 1900's (47). It is important to discover the mechanisms of obesity-related hypertension, especially because obesity is a growing concern in countries all over the world (48). The aetiology of obesity-related hypertension is likely to be complex and multi-factorial (47) and the mechanism probably includes activation of the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS), IR, abnormal renal sodium handling and possibly also leptin resistance and natriuretic peptide down-regulation (36). Obesity can, therefore, cause CVD via several clinical consequences. Although numerous risk factors can influence cardiovascular events, obesity is a modifiable risk factor of major concern (45). Obesity causes physiologic cardiovascular changes that can lead to many pathological states such as high BP and lipid abnormalities (44), which could contribute to the development of the MS.

Role of ethnicity in cardiovascular disease: CVD is the leading cause of death among African Americans (1) and very high rates of hypertension are found among them (49-52). It develops at an earlier age and causes more severe target organ damage in Africans than in Caucasians, but the underlying mechanisms for racial differences in hypertension remain unclear (50), but are likely to involve complex interactions between environmental responses to diet, stress and a possible genetic or physiological difference in various systems such as the RAS and SNS (1;36) as discussed hereafter. Salt-sensitive hypertension is more common and has more severe consequences in urban Africans than Caucasians and increased renal sodium reabsorption, slower and incomplete sodium excretion could all contribute to the

development of high BP in Africans (53). It must be noted that hypertension rates vary within African American groups and those at greatest risk are more likely to be those who are older, less educated, overweight, physically inactive and those who have diabetes (51). In SA, hypertension rates are also very high among Africans (8,54) and abnormal sodium transport as a possible underlying mechanism has been suspected (55).

Obesity and the cardiovascular system (volume-loading hypertension):

Functional and structural abnormalities in the vasculature of obese individuals could potentially lead to the development of hypertension (47). During obesity, a high intra-vascular volume leads to an increased cardiac output (CO) with an inappropriately normal total peripheral resistance (TPR) (56). Heart rate (HR) remains unchanged, therefore, the increased CO in response to elevated metabolic needs and elevated intra-vascular volume mainly occurs through increased stroke volume (SV) (36,56). Over time secondary changes occur within the cardiovascular system (CVS) that return CO to almost normal by increases in TPR. This increase is mainly responsible for further elevations in BP and the progression of the developing hypertensive state (56).

Hypertension is characterised by an altered systemic haemodynamic balance and particularly an increased TPR (57). Hypertension is associated with many adverse morphologic and functional changes in the CVS, including alterations in the mechanical properties of the vasculature and the development of endothelial dysfunction (58). Abdominal obesity is associated with reduced aortic distensibility and is often accompanied by structural changes in peripheral resistance vessels that influence vascular responsiveness (36). In CVD such as hypertension dilatation is reduced and constriction is enhanced (59). Obesity and hypertension exert a double burden on the heart that results in pathologic cardiac changes such as hypertrophy, which seriously increases the risk for CVD (36).

The role of sodium retention during obesity and volume-loading hypertension, as well as explanations of the above cardiovascular variables is provided under the blood pressure section later in this chapter.

3.1.3.2 Obesity, insulin resistance and diabetes

IR is a central feature of the MS (9). Obesity is related to IR and IR in turn is linked to many of the conditions associated with obesity (9,14). Diabetes and obesity rates have increased in the US over the past decade and are continuing to increase (60). Worldwide, diabetes has reached epidemic proportions (21). Most patients with diabetes are overweight and more than half are obese and in many cases, diabetes exists because of obesity and it generally disappears with weight loss (29). A strong association also exists between the prevalence of diabetes and CVD. In the US, 60–75% of diabetic patients die due to CVD and diabetes is, therefore, in itself a significant, independent risk factor for the development of CVD (21).

Role of ethnicity and gender in diabetes: In most ethnic groups diabetes is more prevalent among women than men and it seems that the protective effect of female sex hormones against CVD is negated by diabetes in premenopausal women (21). African Americans have a larger diabetes risk than Caucasians, when comparing them at low BMI values, probably due to the greater impact of abdominal obesity in Africans at low BMI values. At higher BMI values, the diabetes risk between the two groups is more equal (61.).

3.1.3.3. Secondary symptoms, impaired quality of life and other negative obesity consequences

Obesity is not only associated with increased risk for chronic diseases but also with secondary symptoms and impairment of quality of life (28). Impaired psychosocial function manifests as social isolation, loss of job mobility, increased employee absenteeism and economic and social discrimination (44). Being significantly overweight or obese can lead to symptoms like lower back pain, which in turn can lead to hindrance in the performance of basic daily activities, absence from work and medical consultation, which seriously impairs general quality of life (28). Respiratory diseases like obstructive sleep apnea, obesity-hypoventilation syndrome and asthma have been noted in people with central obesity (29). Other abnormalities that are common in obese women include gout and reproductive abnormalities (44).

3.1.4 The aetiology and pathophysiology of obesity

The specific underlying causes of adult weight gain remain uncertain (62), but the following are some factors that could contribute to the development of obesity:

- ♦ **Energy balance:** During the development of obesity there must be a state of positive energy balance (24). Most often it is the energy intake that is high in obese people, but in certain cases a decrease in energy expenditure can also contribute to obesity (23). In terms of energy balance, obesity can only develop when energy intake exceeds energy expenditure for an extended period of time (24). A small and persistent discrepancy between energy intake and expenditure is all that is needed to induce progressive weight gain (23,24). Metabolic factors that can influence weight gain include metabolic rate, physical inactivity, IR, SNS activity and leptin concentrations (23). Some of these will be discussed later in this review.
- ♦ **Genetics:** Although inappropriate dietary intake and low physical activity are the main causes of obesity, inherited factors can influence these environmental factors (24). Genetic influences predispose certain individuals to obesity (63). Studies in twins and families show that as much as 80% of the variance in BMI is due to genetic factors and the heritability of body fat distribution, physical activity, metabolic rate and other aspects of feeding behaviour is estimated to be around 30–40% (23).
- ♦ **Gender:** Obesity affects a higher percentage of women than men and African American women are at especially high risk (38). Hormonal fluctuations (menstrual cycle, pregnancy, menopause and hormone therapies) uniquely predispose women to excess weight gain which may help to explain the gender difference in the prevalence of obesity (41).
- ♦ **Ethnicity:** Obesity rates are found to be high among African Americans (52) but African American women present some of the highest obesity rates in the US and consequently they suffer an excess burden of obesity-related diseases (64). No clear mechanism for excess obesity among African women can be identified, but environmental factors such as diet and lifestyle, together with metabolic and genetic factors could all potentially play a role and need to be considered (40). African American women are faced with distinct physiological, nutritional, societal, cultural and environmental factors that promote weight gain and prevent

weight loss and researchers need to understand these unique problems in order to develop strategies to improve the health of low-income, urban, African American women (64). A study of the social desirability of normal and overweight African American and Caucasian women reported that Caucasian normal-weight women received a higher desirability rating than Caucasian overweight women, but for African women the desirability ratings did not differ (65). In SA, the prevalence of obesity among African women is also very high and a reason could be that culturally these women see obesity with less disfavour than Caucasian women (66). In this population, heaviness is a sign of well-being and even the community health educators are often obese themselves (67).

- **The environment:** The human body has excellent physiological mechanisms to defend against weight loss, but only weak mechanisms to defend against weight gain when food is abundant (68). Humans generally display an asymmetrical pattern of weight regulation where weight reduction is strongly defended but weight gain is not (69). A possible cause of the current obesity epidemic is that the environment promotes excessive food consumption but discourages physical activity (63,68).
- **Socio-economic status:** In most countries obesity rates are higher among the lower socio-economic groups. This is also the case in the UK (24). In the US, a high prevalence of obesity is found among low-income women (70). In developing countries like SA, BMI and income are positively associated, probably because as income increases due to urbanisation, so does the intake of fat and animal-protein foods (66). In an environment that promotes consumption, the body lacks a strong enough mechanism to reduce body weight, therefore, a positive energy balance is tolerated (69). In lower socio-economic status groups obesity is viewed with less disfavour which could contribute to higher obesity rates (66).
- **Lifestyle:** In SA, among the disadvantaged communities, rising BMI trends may be explained by factors associated with urbanisation such as reduced physical activity and increasing availability of energy-dense food (71). Physical inactivity could be a major factor contributing to obesity in African women, as was found in the THUSA (*Transition and Health during Urbanisation of South Africans*) study (66). A sedentary lifestyle does not down-regulate food intake, because energy expenditure is only loosely coupled to energy intake (69). Over-nutrition is common among adult women in SA and it is influenced by factors like age, level

of education, ethnicity and area of residence (26). The obesity problem presents an important challenge for low-income countries because the structure of diet and physical activity is changing, especially in urban areas (72).

- ♦ **Eating behaviour:** It has been found that eating behaviour plays an important role during the development of obesity in adults, because behaviour like the lack of restraint is associated with weight gain and a higher BMI (62). Eating behaviour may, therefore, increase the prevalence of obesity (38). Eating is a behaviour that is subject to conscious control and self-imposed control of food intake should be considered together with biological and environmental factors to explain the development of obesity (69). Eating beyond satiation could contribute to the development of obesity because obese individuals could lack the inhibitory feedback that signals the end of a meal (38). Behaviours that protect against obesity include control of portion size, consumption of a low-fat and low-energy dense diet and regular physical activity, though it is difficult adopting and maintaining these behaviours in the current environment (68).

3.1.5 Adipose tissue, fat distribution and the metabolic syndrome

Fat is a normal component of the human body that is stored in adipose tissue (22). Fat cells or adipocytes represent the major component of adipose tissue (45). Adipocytes are found in subcutaneous and visceral depots of white and brown adipose tissue, in organ capsules and in close proximity to blood vessels and lymph nodes (73). Adipose tissue is considered to be a dynamic organ on its own (74) and the following are some functions of adipose tissue:

- **Energy provision:** White adipose tissue stores energy in lipid form (73) and accordingly the principle function of the adipocyte is the provision of energy substrate through lipolysis (75). Mobilisation of lipids by lipolysis is tightly controlled by the SNS and insulin and, therefore, IR can change the balance between lipolysis and fat storage, which can then lead to elevated levels of plasma free fatty acids (73). A discussion of the role of lipids and fatty acids in the MS is given later in this chapter.

Adults do not have notable depots of the thermogenic brown adipose tissue, primarily responsible for heat production, but some can be found dispersed within white adipose tissue (73).

- **Adipokine secretion:** Adipose tissue is a dynamic endocrine organ that secretes a number of factors (collectively called adipokines) that contribute to vascular and systemic inflammation (73,74,76). Several of these adipokines are involved directly or indirectly in the development of hypertension, endothelial dysfunction, IR and vascular remodelling (74). Adipose tissue mass increases because of increases in adipocyte volume which is the result of increased lipid storage (73). Adipokine secretion increases as adiposity increases and many adipokines are preferentially expressed in visceral adipose tissue (74).
- **Secretion of vasoactive substances:** Adipocytes contain a fully functional local RAS and also components of the endothelin system (45). The high expression of components of the RAS, such as angiotensinogen in visceral adipose tissue suggests a role for the RAS components in conditions where visceral adipose tissue is present (86). The activity of renin which mediates the formation of Ang 1 from angiotensinogen is increased in the plasma of obese subjects, suggesting that obesity systemically activates the RAS, therefore, inhibition of the RAS markedly improves morbidity and survival. Activation of ET-1 also occurs in the adipose tissue and CVS of obese subjects. Increased body fat mass will lead to increases in the expression and activity of these and other vasoactive systems (45).

3.1.5.1 Effects of abdominal obesity on components of the metabolic syndrome

When looking at the effects of obesity on health, it is especially abdominal obesity that correlates with metabolic risk factors which presents as an increased waist circumference (10). Abnormalities associated with obesity are much more pronounced in central obesity (upper body, male-type, android, splanchnic, visceral, abdominal or intra-abdominal obesity) than in peripheral (lower body, female-type, genoid, gluteofemoral or subcutaneous obesity) (23).

Insulin resistance: It is not only the magnitude of fat mass, but especially the distribution of fat that determines the development of obesity-related conditions such as IR (14). Nieves *et al.* (14) reported that intra-abdominal fat is a more important determinant of insulin sensitivity than subcutaneous fat. According to Reaven (15), abdominal obesity is not a manifestation of IR, but is a factor that could promote the degree of IR beyond the effect of generalised obesity, although the association between IR and abdominal obesity compared to generalised obesity could be exaggerated.

Cardiovascular disease and hypertension: Upper body fat distribution is an independent risk factor for the development of CVD such as hypertension and other metabolic abnormalities (24,47). Hypertension and central obesity are two conditions closely linked, though the exact mechanisms responsible for obesity-related hypertension are still unclear (57,77).

3.1.5.2 Effects of endocrine abnormalities on components of the metabolic syndrome

Obesity could represent a low-grade systemic inflammatory disease as levels of C-reactive protein (CRP), interleukin-6, tumor necrosis factor alpha (TNF- α), and leptin are elevated during obesity and these substances are known markers of inflammation associated with CVD risk and mortality (76). Several different vasoactive proteins derived from adipocytes play an important role in cardiovascular homeostasis and are likely to contribute to the cardiovascular complications associated with obesity (45). Adipose tissue contributes to the risk factor cluster of the MS and CVD through effects on leptin, adiponectin, angiotensinogen, plasminogen activator inhibitor (PAI-1) and fatty acids among others (10,78). For this reason the ATP III describes the MS as a clustering of metabolic complications of obesity (10).

a. Leptin

Leptin derives its name from the Greek word 'leptos', which means thin in English, due to its ability to induce weight loss in mice (23). It is a neuro-endocrine hormone (52) primarily synthesised by adipocytes (45). Leptin seems to be a key element in the long-term regulation of food intake and body weight homeostasis (79). Plasma leptin concentrations are approximately three times higher in women than in men of similar age and BMI (23,52). There is a paradoxical over-expression of the leptin gene in practically all obese humans (23) and the obesity state is associated with high plasma leptin levels (36,48), possibly attributable to leptin resistance (23,52). Leptin may also provide a link between obesity and hypertension (52), because leptin-induced increases in BP could be mediated via increased SNS activity (80,81). The exact role of leptin in obesity-related hypertension remains undefined (52). Apart from leptin's anorectic effect and its stimulating effect on energy expenditure, it also affects several neuro-endocrine mechanisms (23). For example, ET-1 stimulates leptin production and secretion from adipocytes (45,82) and in turn ET-1

production can be induced in endothelial cells by leptin, suggesting a synergic regulation between these two proteins (45).

b. Adiponectin

Adiponectin is a plasma protein synthesised and secreted by adipose tissue with anti-inflammatory and anti-atherogenic properties (21). It is an important insulin-sensitising adipokine that is down-regulated in IR and obesity (83). Adiponectin is reduced in the plasma of obese subjects and it is, therefore, possible that low circulating adiponectin levels could serve as an indicator of vascular injury in conditions such as IR and diabetes, because adiponectin also has the potential to inhibit the proliferation of vascular smooth muscle cells (45). Adiponectin gene expression is reversibly down-regulated by insulin and TNF- α which suggests that adiponectin is a selectively controlled modulator of insulin (83). Lower plasma adiponectin levels have also been documented in subjects with MS and coronary artery disease (CAD) (21).

c. Resistin (“Resistance to insulin”)

The adipokine resistin could be involved in adipocyte-induced IR (73) and because of this implication it could potentially link obesity to IR and diabetes (84). Resistin levels are increased in obesity and its effects on glucose metabolism oppose those of insulin, but resistin levels are not uniquely controlled in obesity (45). TNF- α is a negative regulator of resistin gene expression (84) and ET-1 inhibits basal and hormonal stimulation of resistin by insulin from adipocytes (45,82). It is possible that resistin secretion is regulated in a similar manner to other adipokines like leptin, therefore, vascular factors like ET-1 could potentially regulate whole body energy metabolism via adipokines like resistin and leptin (82). This suggests yet another pathogenic role for ET-1 in obesity (45).

d. Angiotensin II

Since the discovery of the local adipose tissue RAS much research has been undertaken exploring the involvement of this system in the pathophysiology of several metabolic diseases and obesity-associated disturbances (73,85). The possible deteriorating metabolic effects of the adipose tissue RAS appear to be more pronounced in pathophysiological situations such as obesity and hypertension (73). Adipocytes express many components of the RAS including angiotensinogen, AT₁-

receptors and angiotensinogen converting enzyme (ACE) (75). A study by Giacchetti *et al.* (86) demonstrated the presence of these components in human visceral and subcutaneous adipose tissue, but angiotensinogen levels in particular are higher in visceral compared to subcutaneous adipose tissue (73). The high expression of these RAS components in visceral adipose tissue suggests a role in conditions where visceral adiposity is present (86). A detailed discussion of the possible role of the RAS during the metabolic syndrome is given later in this chapter.

e. Natriuretic peptides in obesity

Natriuretic peptides are important regulators of volume homeostasis and arterial BP, but abnormal states like obesity are associated with suppressed natriuretic peptide activity, which contributes to sodium retention and hypertension (36). Atrial natriuretic peptides (ANP), mostly localised in the heart, provide a potent defence mechanism against volume overload, but ANP receptors are also found in brain areas involved in body fluid volume and BP regulation. Ang II, also an important body fluid regulator, generally antagonises the actions of ANP (87).

f. C-reactive protein, plasminogen activator inhibitor and fibrinogen

Obesity is a state characterised by high levels of CRP, PAI-1 and fibrinogen levels (10). PAI-1 levels are increased during obesity and PAI-1 functions as the main inhibitor of the fibrinolytic system (88). Obesity can contribute to elevated CRP and fibrinogen levels, because the release of adipokines elicits CRP and fibrinogen levels to rise and in this way the inflammatory and pro-thrombotic states could metabolically be linked (10). A study by Skurk *et al.* (88) showed that Ang II and its metabolites are able to increase PAI-1 levels in adipose tissue, which further supports a possible link between the RAS and fibrinolytic systems. It is possible that PAI-1 could be involved in CHD because in addition to obesity, hyperglycemia, Ang II and very low density lipoprotein cholesterol (VLDL-C) can all contribute to elevated PAI-1 and together with diabetes it could contribute to a prothrombotic and atherosclerotic state (74).

3.2 Insulin resistance

3.2.1 Defining insulin resistance

Dietary carbohydrates are converted to glucose by enzymatic action in the gastro-intestinal tract. During the first 2 hours after digestion glucose is absorbed rapidly and this leads to an elevated plasma glucose concentration, which (together with other gastro-intestinal hormone signals) stimulates pancreatic insulin secretion, resulting in an acute rise in plasma insulin concentration. When tissues resist insulin-mediated glucose uptake, IR occurs and sites that can develop IR include skeletal muscle, peripheral tissues, adipose tissues, liver and endothelial cells (3).

When peripheral tissues become insulin resistant, glucose levels do not necessarily rise pathologically at first, because the pancreas secretes additional insulin that maintains normal blood glucose levels, which is defined as compensatory hyperinsulinemia (3). Hyperinsulinemia, therefore, maintains plasma glucose concentration at a relatively constant level, despite impaired insulin action (48). Glucose levels also depend on other aspects such as insulin secretory capacity and not only on insulin sensitivity and such variations also need to be considered as causes of the MS (10). IR as such should be defined as the diminished early action of insulin in the situation where insulin is not deficient (89).

Glucose tolerance: Long term IR can lead to the development of IGT or glucose intolerance (10). When the pancreas fails to maintain normal blood glucose levels, IGT or type 2 diabetes results (3). In subjects with normal plasma fasting glucose concentration (< 6.11 mmol/L), a plasma glucose concentration 2 hours after a 75g oral glucose load (OGTT) greater than 11.1 mmol/L indicates diabetes and a concentration greater than 7.77 mmol/L indicates IGT (90). The ATP III does not include OGTT as a criterion for MS diagnosis because of the inconvenience and cost thereof in normal clinical practice (10).

Fasting glucose: Fasting plasma glucose concentration is a less sensitive manner to estimate the presence or absence of IR and a fasting glucose concentration less than 6.11 mmol/L does not mean that the person is insulin sensitive. Subjects with a fasting plasma glucose concentration between 6.11–6.99 mmol/L (the latter

diagnostic of type 2 diabetes) are classified as having impaired fasting glucose (IFG) and are likely to have IR and hyperinsulinemia (90).

3.2.2 Insulin resistance and components of the metabolic syndrome

The ATP III classifies IR as an emerging risk factor because the underlying mechanisms that link IR to CVD are still uncertain (10). The association of obesity with CHD, hypertension and diabetes is often characterised by IR and the resultant hyperinsulinemia has been shown to predict the above conditions independently (90). IR is not a disease but a physiological change that increases the risk to develop the abnormalities of the MS and not all persons with IR will develop the entire cluster of abnormalities associated with the MS (15). The majority of people with the MS have IR and it is strongly correlated with CVD risk (10). It has been documented that there is a relationship between insulin levels and factors of the MS like BP, independent of obesity, therefore, obesity is not necessarily a direct cause of the MS (12). Some researchers place a higher priority on insulin than on obesity as a possible cause of the MS, because it is argued that insulin and hyperinsulinemia directly cause other metabolic risk factors (10). It is important to note that IR and the MS are not synonymous (15) despite the fact that many studies have shown that IR often precedes many of the other manifestations of the syndrome (12).

Obesity and diet: IR is linked to obesity and, therefore, it is difficult to discover a unique role for insulin in the pathophysiology of the MS independent of the effects of obesity (10), but it is important to note that not all overweight and obese subjects are insulin resistant and not all persons with IR are overweight or obese (15). Still, the dissociation of obesity and IR in the MS is difficult because weight gain enhances IR and in this way promotes other factors of the MS (10). It seems that selective IR rather than just hyperinsulinemia is more likely to be a metabolic link between obesity and hypertension and this means that although insulin might have an impaired ability to cause whole body glucose uptake in an individual, some of the other actions of insulin remain preserved (47).

Roberts *et al.* (12) showed that high-fat and refined-carbohydrate diets can induce features of the MS in rats and diet-induced IR precedes other MS complications. The insulin response upon carbohydrate metabolism depends on the glycemic index and the glycemic load (glycemic index x carbohydrate content per serving size) thereof

and ingestion of high glycemic index load meals can promote some of the dietary causes of IR such as chronic elevated glucose, insulin, VLDL-C and fatty acid concentrations (3).

Cardiovascular disease and hypertension: Many studies have demonstrated a significant association between IR and hypertension, independent of other factors like obesity and it is this finding that underlies the hypothesis that IR could be central to the cluster of abnormalities of the MS (91). Insulin shows many pro-hypertensive actions, including activation of renal sodium reabsorption, activation of the SNS and stimulation of vascular smooth muscle growth (92). Insulin can raise BP via several mechanisms (10). Insulin stimulates vasodilatation effects which should protect against the development of arterial hypertension, but it could be argued that if the vasculature becomes resistant to insulin, IR could be responsible for the development and maintenance of hypertension (93). Insulin affects TPR via its vasodilator properties, but in obesity these effects are blunted leading to increases in vascular resistance (36).

Insulin could also sustain hypertension directly via activation of the SNS, which acts on the vasculature, heart and kidneys. It has been shown that there is a characteristic decrease in arterial wall elasticity in hypertensive patients with IR, which suggests a complex interaction between insulin sensitivity, hypertension and endothelial function (93). Evidence also suggests that high BP is one of the factors that can contribute to the development of IR (92). Increasing evidence also suggests a relationship between IR and cardiovascular morbidity and mortality (93). It seems that hypertension promotes IR and hypertension in turn is promoted by IR (92). The presence or absence of hypertension is not a strong predictor of IR because only 50% of hypertensive subjects have IR or hyperinsulinemia (15,90), but this should not detract from the fact that in 50% of the hypertensive cases, IR is present and it is these subjects that are at highest risk for CHD (15).

Diabetes: Most people with the MS have IR which also implies an increased risk for diabetes and if diabetes develops, this will increase the risk for CVD sharply (10). It is possible that the MS could be a good predictor of diabetes because IR often precedes the onset of diabetes (9).

3.2.3 Insulin resistance, blood pressure and ethnicity

Hypertension and diabetes rates are higher among African Americans and consequently they also suffer from a higher prevalence of CVD (94). A study by Ferrannini *et al.* (95) demonstrated that in normotensive, non-diabetic, Caucasian Europeans BP is inversely related to insulin sensitivity and directly related to fasting plasma insulin levels. The relationship between insulin sensitivity and BP is well documented in European and Hispanic Americans, but the relationship is weak or absent in the African American population (93). On the other hand, a study by Mgonda *et al.* (91) indicated a strong association between insulin sensitivity and BP among normal weight, untreated urban Africans in Tanzania. Possible factors related to such ethnic disparities include genetic variance, racial differences in hypertension and IR pathogenesis, or the fact that the combination of obesity, diabetes and hypertension are more common among Africans could play a role (93). Associations between BP and IR are sometimes challenged because the association is often weak and it depends and varies according to other characteristics (i.e. ethnicity) of the subject group and it is confounded by factors like age (95). A recent study by Saad *et al.* (96) again demonstrated an association between IR and BP in non-diabetic Caucasian subjects, but the association was not found for African Americans. The study by Osei (93) raised the possibility that the greater IR often seen in Africans is more likely due to impaired insulin clearance than hypersecretion.

When exploring the underlying structure among the MS risk factors, it is often found that the syndrome is primarily represented by the IR and obesity factors, followed by the lipid factor and lastly the BP factor (16). BP generally forms a separate factor from the other components of the MS (i.e. IR) during factor analyses and this raises uncertainty over the extent to which it should be included in the MS (17).

3.3 Dyslipidemia

Dietary lipids consist mainly of triglycerides or simply called fats and they are also the major metabolic energy storage in humans (97). Triglycerides are formed from fatty acids (a lipid subclass) and a glycerol group (a carbohydrate) (98). Triglycerides are transported in the circulation by proteins and as a compound they are known as lipoproteins (97). Lipid abnormalities of the MS include increased triglycerides, total cholesterol, small LDL-C, VLDL-C, remnant lipoproteins, apolipoprotein B (apo-B) and decreased HDL-C levels (all of which have been shown to be atherogenic) (10,21,90).

Dyslipidemia in obesity: Obesity is associated with the dyslipidemia seen in the MS (14). Central fat distribution suggests a relatively unfavourable lipid and BP profile, because the endocrine abnormalities associated with the MS result in lipid accumulation that is more pronounced in intra-abdominal than in the subcutaneous fat (23). In centrally obese subjects it is possible to detect an atherogenic lipid profile together with a prothrombotic and hypofibrinolytic pattern (57). There could be ethnic differences in lipid metabolism between African American and Caucasian women, which could result in an increased synthesis of fat in adipose tissue leading to a higher prevalence of obesity in African American women (99). Important racial differences between Africans and Caucasians are higher BP and HDL-C levels as well as a lower triglyceride levels in Africans (100). Studies have shown lower triglyceride levels among African American women compared to Caucasian American women (101) and this has also been found when comparing obese African and obese Caucasian women in SA, which is partly the result of a possible reduced clearance by adipose tissue (102).

Dyslipidemia in diabetes: IR is associated with the dyslipidemia seen in the MS (14). Lipid abnormalities are a major problem in patients with diabetes and at every cholesterol level diabetic subjects have a 2 to 3 fold higher CVD risk than non-diabetic subjects (21). Plasma LDL-C concentrations do not differ between diabetic and non-diabetic subjects (21). The LDL in diabetic subjects has an altered composition as it is smaller, denser and highly oxidised, with an increased concentration of apo-B that is considered to be highly atherogenic (21,29).

Dyslipidemia in cardiovascular disease and hypertension: Elevated triglyceride levels are usually accompanied by low HDL-C levels (18). Both high triglyceride levels and low HDL-C levels are risk factors for CHD, but it seems that the ratio of their plasma concentrations (triglyceride-to-HDL-C) could be an even better predictor of CHD (90). Hyperlipidemia in hypertension is characterised by an increased number of apoB-lipoproteins and a decreased LDL-C level or a decreased LDL-apoB ratio (89). It has been reported that apo-B is significantly associated with CHD in women (103) and the combination of hyperinsulinemia, high apo-B, and small, dense LDL-C is associated with a 20-fold increase in the risk of CHD (29). A study by Jagla and Schrezenmeir (104) demonstrated that in subjects with the MS, postprandial triglyceride levels lead to increased ET-1 and insulin levels. In another study by Piatti *et al.* (105) it was shown that triglycerides are independently correlated with ET-1 in subjects with the MS. In hypercholesterolemic subjects, ET-1 activity is enhanced, which suggests an increased ET-1 production in these subjects that could participate in the pathophysiology of CVD characteristic in these subjects (106).

Fatty acids: Fatty acid levels are elevated in subjects who are abdominally obese (78) and abdominal or central obesity is a principle feature of the MS (29). Fatty acids increase vascular reactivity and enhance the proliferation and migration of vascular smooth muscle cells (78). Increased fatty acid levels are a possible mechanism for SNS activation in obesity and increased neurovascular tone (48,107). Activation of the SNS plays an important role in the pathogenesis of CVD including hypertension (108). Fatty acids can act directly on the vasomotor centres of the brain or indirectly through afferent pathways from the liver to increase sympathetic activity in obesity (48).

The MS pathogenic process probably involves the effects of an increased free fatty acid load on the hepatic uptake of insulin, leading to systemic hyperinsulinemia and hyperlipidemia, skeletal muscle IR and eventual pancreatic beta cell failure (29,78). When insulin resistant muscle is overloaded with lipids, excess could be diverted to the liver, promoting fatty liver and atherogenic dyslipidemia (10). When considering the role of insulin in CVD, insulin's stimulatory affect on glucose uptake as well as its role in the regulation of lipolysis need to be considered. Insulin lowers plasma fatty acid levels because it is involved in triglyceride storage and inhibits triglyceride breakdown in adipose tissue, therefore defects in fatty acid suppression by insulin could be involved in the lipid risk factors for CVD (109). Fatty acids could also affect BP by inhibiting nitric oxide (NO) production, thereby impairing dilatation and

favouring constriction. Many fatty acid effects are mediated through oxidative stress and oxidative stress is implicated in the pathogenesis of IR, hypertension, vascular remodelling and other vascular complications (78).

3.4 Cardiovascular function and blood pressure

Elevated BP and decreased arterial compliance is considered to be a metabolic risk factor because it is strongly associated with obesity, is common in people with IR and is considered to be multifactorial in origin (10).

3.4.1 Defining blood pressure

The *European Society of Hypertension* (ESH) considers BP values of 140-159/90-99 mmHg as mild hypertension, 160-179/100-109 mmHg as moderate hypertension and values greater than 180/110 mmHg as severe hypertension (110).

The classification of the severity of hypertension has for decades been based on DBP values, but SBP is by no means less important. Isolated systolic hypertension shows a marked increase in the risk for CVD. Control of SBP is achieved much less often than control of DBP, but treatment of SBP greatly reduces cardiovascular complications when compared to a similar or greater degree of reduction in DBP. (111)

Technically, BP refers to the force exerted by blood against any unit area of a vessel wall expressed in millimetres of mercury (mmHg). When measuring BP, two values are recorded: the systolic pressure is the BP against the vessel walls when the heart contracts and the diastolic pressure is the BP against the vessel walls when the heart relaxes (between heartbeats) (112). The total volume of blood forced from each ventricle to the circulation when the heart contracts is known as the SV expressed in millilitres (mL) and multiplying the SV with the HR (in beats/minute) yields the CO expressed in litre/minute (L/min) which is the volume of blood pumped by each ventricle in a minute. Resistance against blood flow through the CVS (determined by vessel radius) is known as the TPR and together with CO it is the other important factor when determining mean arterial BP ($BP = CO \times TPR$) (98.). The total volume of blood that can be stored in a given portion of the circulation as BP rises is known as the vascular compliance and it is calculated by dividing the increase in volume by

the increase in pressure and is expressed in mL/mmHg (56). According to O'Rourke (113), compliance is an absolute term which relates the absolute diameter and volume change of arteries to changes in pressure, therefore, it is lowest in larger arteries and highest in smaller arteries. A decreased arterial compliance is also associated with some metabolic syndrome risk factors (10).

3.4.2 The endothelium

Endothelial cells form the inner lining of arterial and venous blood vessels (45). The endothelium is considered to be an important functional unit that controls the tone of the underlying vascular smooth muscle mainly through the production of vasodilator mediators and in most vascular diseases the vasodilator function of the endothelium is impaired (114). Other functions of the endothelium include regulation of vascular growth, vasomotion, platelet function, plasma coagulation and immunologic and inflammatory responses via the release of vasoactive and trophic substances such as prostacyclin, endothelium-derived relaxing factor or NO, Ang II and ET-1 (45). Impaired endothelial function is characterised by decreased levels of vasodilator substances like NO and prostacyclin (or a decreased sensitivity of the vascular smooth muscle to these substances), increased production and release of reactive oxygen species or endoperoxides and increased levels of vasoconstrictor substances like ET-1 (114).

The endothelium and disease

Cardiovascular disease: In subjects with a high risk to develop CVD, endothelial dysfunction is seen before the development of clinically manifested vascular disease. (21). Although BP is a critical element of hypertension, many other interrelated risk factors such as hypercholesterolemia, IR and vascular dysfunction contribute to form a complex syndrome of hypertension and these factors often precede the actual elevation in BP (115). Endothelial dysfunction may be an important contributing factor to obesity-related hypertension and an early marker of cardiovascular damage associated with obese-hypertensive states (57). Blood flow and shear stress trigger the endothelium to release dilators such as NO and constrictors such as ET-1, but in CVD such as hypertension, flow-induced dilatation is reduced and constriction is enhanced (59). Endothelium-dependent vasodilatation is also defective in obese subjects (45) as well as in subjects with IR (13).

Insulin resistance and diabetes: Even though the aetiology of hypertension is multi-factorial, evidence for a causal link between IR and hypertension is growing (21). IR with central fat distribution is often associated with the MS, which combines glucose intolerance, hypertension, hyperlipidemia and abdominal obesity (23). Hypertension and diabetes are two diseases that generally co-exist and the prevalence of hypertension in diabetic patients (40–50%) is considerably higher when compared to non-diabetics (20%) (21). Cardiovascular risk factors cluster in obese individuals and IR emerges as a common denominator within the cluster (78). In addition to insulin's role in glucose metabolism, it also regulates steps involved in lipid, protein, platelet, fibrinolytic and endothelial metabolism (89). IR is a major factor in the development of endothelial dysfunction but the exact mechanisms that lead to accelerated development of CVD in diabetic patients is not completely understood (21). Insulin reaches target cells through the intact endothelium which also synthesises prostacyclin which may have insulin-potentiating effects, therefore, the mechanism of the role of IR in CVD could in part be attributable to endothelial dysfunction (89).

3.4.3 Endothelin

Endothelins are peptides synthesised and released by vascular endothelial cells (45,116). Based on structure and receptor affinity, three endothelin isoforms can be identified. ET-1 binds to ET_A-receptors and ETB₂-receptors expressed on vascular smooth muscle cells and ETB₁-receptors expressed on endothelial cells. ET_A and ETB₂ stimulation induces smooth muscle contraction and proliferation, whereas ETB₁ receptor stimulation induces relaxation (116).

ET-1 synthesis is stimulated by the major signals of cardiovascular stress, including the vasoactive agents such as Ang II, norepinephrine, bradykinin, cytokines and other factors like mechanical stress (117). It is a 21 amino acid peptide with potent vasoconstrictor, positive inotropic, metabolic and mitogenic properties (82,118), stimulating the synthesis and secretion of several vasoactive molecules (119). ET-1 plays an important role in maintaining peripheral vascular tone and systemic BP (116). ET-1 can lead to sustained BP elevation resulting from an increase in TPR (120). Of particular importance to the current study is that certain hypertensive groups could have ET-1 dependent hypertension, including Africans and those with IR and/or obesity-associated hypertension among others (117). Increased ET-1 levels have been reported in disease states such as obesity, diabetes and congestive

heart disease and could possibly be a contributor to the pathology of these diseases (82).

Role of endothelin-1 in disease

Cardiovascular disease: ET-1 is possibly involved in the development of various CVD associated with vasoconstriction (116). It may, therefore, play an important role in the pathogenesis of hypertension (119). Activation of the ET-1 system can potentially contribute to elevated BP and hypertension in centrally obese subjects (45), but the specific mechanisms responsible for elevated plasma ET-1 levels in central obese subjects remains unknown (57). Although the exact role of ET-1 in obesity is not clear, experimental obesity demonstrates an increased ET-1 level in the CVS of normotensive and hypertensive animals (45). Increased ET-1 levels may be related to the mechanisms of obesity-related hypertension (57). Certain people have a predisposition for obesity and this places these people at increased risk for the development of CVD (45).

Not much is known about the relationship between central fat distribution and the release of ET-1 (57). In central obese subjects, there might possibly be an early cardiac involvement associated with endothelial dysfunction and higher ET-1 levels, which can promote hypertension (77). Parrinello *et al.* (57) found that plasma ET-1 levels are significantly higher in normotensive and hypertensive obese subjects than in lean controls and ET-1 levels are significantly higher in the hypertensive than in the normotensive central obese subjects. It should also be considered that variations of the genes encoding for vasoconstrictor proteins might affect susceptibility to hypertension in obese individuals (45). Different genes encode for the endothelin receptors and they, therefore, have separate tissue distributions and biologic properties as described earlier. Many polymorphisms of these receptor genes have been found, but future studies are needed to show the exact involvement of these in the predisposition for the development of certain CVD (119). There is a possibility that a polymorphism of the preproendothelin-1 gene could be linked to obesity-associated hypertension (45).

In certain rat models of hypertension, ET-1 plays an important role in BP elevation as it is a powerful vasoconstrictor peptide and regulator of blood flow. In these models ET-1 is over-expressed in the vessel walls, therefore in experimental models of hypertension, ET-1 may participate in the vascular damage that occurs in CVD and

BP elevation (121). In several experimental models with salt-sensitive hypertension, ET-1 is found to be over-expressed in the CVS. It has further been found that ET-1 levels are increased in hypertensive Africans compared with Caucasians (especially in response to acute stress), therefore, it is possible that ET-1 could be involved in the development of hypertension among Africans via SNS reactivity (122).

Insulin resistance and diabetes: ET-1 levels have also been found to be elevated in subjects with diabetes and in subjects with the MS, suggesting a role in the pathogenesis of these disorders (104,118). Endothelial dysfunction is a key feature of diabetes and may also be a major cause of the vascular complications associated with diabetes (21). Diabetes and hypertension can cause microvascular damage that could lead to elevated ET-1 levels (123). The endothelium shows impaired synthesis of vasodilators and an increased release of procoagulants and vasoconstrictors like ET-1 (21). Diabetes is characterised by impaired endothelium-dependent vasodilatation and vascular disease (124). In diabetics, chronic exposure to hyperinsulinemia and hypertriglyceridemia may be responsible for elevated ET-1 levels seen in these patients (118). Increased insulin levels have been linked to increased ET-1 receptor expression and it is, therefore, possible that hyperinsulinemia upregulates ET-1 receptors, which will contribute to the vasoconstrictor response of ET-1 (125). ET-1 levels are found to be higher in diabetic subjects with a family history of diabetes than in diabetics without a family history of the disease, suggesting a possible genetic or environmental influence (123). The above-mentioned defects can help to explain the increased incidence of atherosclerosis and hypertension among diabetics (21) as ET-1 is possibly involved in the development of atherosclerotic lesions in diabetic patients (118).

3.4.4 Blood pressure and renal haemodynamics

Renal haemodynamics take place at an early stage in obesity-related hypertension (126). Excess weight is a major contributor to the development of hypertension (127). Pressure natriuresis is impaired in all forms of chronic hypertension and although the precise mechanisms have remained elusive, it is possible that being overweight may play a major role (128). It has been postulated that the increase in SNS and RAS activity, together with IR and hyperinsulinemia that occur in obesity can cause renal sodium retention, which may contribute to rises in BP (36). When defining the pathogenic role of the kidney in hypertension, inherited as well as

acquired renal tubular defects need to be considered to explain alterations in BP (129).

Obesity is associated with marked sodium retention and volume expansion that exceed the requirements of additional adipose tissue (48). Obesity-related hypertension is possibly linked to increases in sodium reabsorption as a result of kidney dysfunction responsible for sodium and fluid retention, leading to a pressure natriuresis shift to higher BP values (47,48,127). Numerous studies strongly support an association between altered renal sodium handling and high BP (129). The pressure natriuresis shift is not likely to be the result of hyperinsulinemia and IR, but rather due to activation of the RAS, the SNS and altered intrarenal physical forces (48). Genetic, nutritional, metabolic and neurohormonal factors (alone or in combination) can impair renal sodium handling and influence BP homeostasis (129). Volume-loading hypertension in obesity was discussed in a previous section of this chapter. Hypertension among Africans is often associated with suppressed plasma renin activity and angiotensin II levels, which is consistent with sodium retention and adjusted volume expansion and BP in Africans is generally more salt-sensitive, although the mechanisms are not completely understood (53). The ET system could also play an important role in salt-sensitive elevations in BP as seen in Africans (122) as mentioned earlier.

3.4.4.1 Insulin resistance, sodium retention and blood pressure

Hypertension often co-exists with IR (92) and IR and hyperinsulinemia can result in chronic sodium retention (47). Sodium retention can in turn induce BP elevation (92). Insulin can increase renal sodium retention directly through its effects on renal tubules or indirectly through stimulation of the SNS and through augmenting Ang II-mediated aldosterone secretion (47). The long-term effects of insulin on the kidneys and SNS could lead to renal dysfunction and increased BP (48). Increased oxidative stress appears to be crucially involved in both Ang II and salt-induced IR (92). Insulin causes only mild sodium retention and increased SNS activity, but it exerts other effects on the CVS that will tend to reduce BP, mainly via peripheral vasodilatation due to its metabolic effects and stimulation of NO production (48). The molecular mechanism that underlies IR related to salt-sensitive hypertension is possibly unique (92). A possible mechanism that could link IR to salt-sensitivity in obesity could involve alteration in insulin receptor structure or function (47).

3.4.4.2 The renin-angiotensin system, sodium retention and blood pressure

Enhanced RAS activity has been reported in obese humans (47). Some aspects regarding the RAS were discussed earlier in this chapter. Here a more detailed discussion of the role of the RAS in disease is presented.

The renin-angiotensin system: The RAS is considered a master regulator of human physiology (130). It has been considered that the RAS has evolved as an adaptive mechanism to protect circulatory homeostasis (131). The RAS controls BP, fluid and electrolyte balance through co-ordinated effects on the heart, blood vessels and the kidneys (130). Although the RAS plays an important role in the regulation of normal BP, it is also distinctly involved in several cardiovascular pathologies (132). Activation of the RAS could be a key factor leading to abnormal cardiovascular functioning as it has been found that inhibition of the RAS effectively delays the progression of CVD (45). Elevated levels of RAS components are possibly involved in the pathogenesis of hypertension and may also play a role in other diseases like diabetes (131,132). Increased production of Ang II and/or enhanced Ang II activity is often associated with several cardiovascular risk factors (45,133). Some evidence also suggests a role of the adipose tissue RAS in obesity-associated MS (73).

The classical renin-angiotensin pathway: Renin is secreted from the juxtaglomerular apparatus of the kidney and acts on circulating angiotensinogen to produce angiotensin I. Angiotensin I has little effect on BP, but is converted by ACE to Ang II which acts on the heart and kidneys by binding to G-protein coupled AT₁-receptors and AT₂-receptors. The AT₁-receptor mediates vasoconstriction and deleterious effects like cardiac and vessel hypertrophy, while the AT₂-receptor mostly regulates the opposing effects. (130)

ACE is also involved in the inactivation of other vasodilator peptides like bradykinin (130). Bradykinin stimulates endothelial cells to release vasodilators (114). Inhibition of ACE can, therefore, lower BP via the following two mechanisms: prevention of formation of Ang II and potentiation of the hypotensive effects of bradykinin (114,130). Despite endothelial dysfunction, the regulatory function of ACE on Ang II and bradykinin is maintained except in severe cases (114). ACE inhibition has been the cornerstone of antihypertensive therapies for years (130).

Functions and actions of the renin-angiotensin system: Ang II has a wide variety of biological properties and the effects of the RAS are partly dependent on the compartment (plasma or interstitium) in which Ang II, the major effector peptide, is generated (131).

- ♦ **Blood pressure control:** Ang II was initially discovered as a vasoconstrictor peptide because it is involved in the regulation of vascular tone (45). The systemic RAS is a complex system (130) that regulates BP immediately by vasoconstriction and chronically through the release of aldosterone (131). Ang II is, therefore, a potent vasopressor that stimulates the release of aldosterone which causes water and sodium retention (130) that ultimately results in the expansion of intravascular volume (131).
- ♦ **Preservation of blood supply:** The RAS is involved in a complex mechanism that serves to preserve the blood supply to organs so that they can maintain cellular function. Ang II exerts this effect independently of the BP generated. It does this via two time-related events: a fast opening of collateral circulation and a slower response of new vessel formation termed angiogenesis. It is likely that these effects are involved in conditions like inflammation and diabetic retinopathy among others, where angiogenesis is prominent (134).
- ♦ **Remodelling, fibrosis and inflammation:** Elevated Ang II levels can lead to many hypertension-associated pathologies through non-haemodynamic effects (independent of its effect on BP), like mediating adverse morphologic and functional changes in the CVS via interaction with the AT₁-receptor (58). Ang II is released by the vascular endothelium after injury (130) and Ang II is now recognised as a growth factor that participates in tissue repair, remodelling, regulation of cell growth, matrix synthesis and fibrosis (131). Fibrosis is a major component of remodelling that occurs in hypertension. Substantial evidence also suggests that the cytokine transforming growth factor beta-1 (TGF-β₁) mediates Ang II-induced fibrosis in hypertension (58).

Factors such as mechanical strain, oxidized LDL-C and aldosterone can lead to upregulation of the AT₁-receptors. Increased arterial pressure in hypertensive states places increased strain on the vessel wall, which could amplify the effects of Ang II without substantial increases in Ang II levels and the RAS need not be activated for the effects of Ang II to be amplified (58). Activation of the RAS can

also potentially contribute to hypertension via pro-inflammatory activities of Ang II (45). Ang II may be a key mediator of events involved in the inflammatory process.

- Ang II increases vascular permeability by stimulating the release of prostaglandins and vascular endothelial cell growth factor (VEGF) that contributes to initiation of the inflammatory response (131).
- Ang II plays a role in the regulation of adhesion molecules and chemokines. It is also involved in the direct activation of chemotaxis, differentiation and proliferation. Activation of the RAS could also be involved in immunologically-induced inflammation (131).

Generally the inflammatory-reparative process serves a useful purpose, but often it results in scarring and dysfunction, suggesting that the RAS may be a double edged sword in inflammation (131).

- **Role in obesity-related hypertension:** As adipocytes are a source of substances with metabolic and cardiovascular action, such as angiotensinogen (86) Ang II can potentially stimulate the release of (via stimulation of the AT₁-receptor) prostacyclin, leptin, PAI-1 and NO from adipose tissue (45,73). Ang II binds to the receptors on the adipocyte membranes and to presynaptic nerve endings and blood vessels, therefore, it can influence adipose tissue metabolism directly or via the regulation of tissue perfusion and local SNS activity (73). Ang II (the active component of the RAS) could, therefore, in particular affect adipocyte metabolism (85), but the overall effects of Ang II on white adipose tissue seems to be rather weak, because neither Ang II nor RAS-blockade seem to affect whole body lipolysis (73). It seems that the adipose tissue RAS generally serves to regulate regional blood flow to the adipose tissue and it is involved in the regulation of the size and number of fat cells rather than participating directly in the regulation of energy substrate (75).

The current view of the role of the RAS in obesity-related hypertension is that activation of the local adipose tissue RAS can lead to increased Ang II levels and increased susceptibility of adipocytes to AT₁-receptor mediated effects. In obese hypertensive subjects there is also an increased local adipose tissue angiotensinogen formation, which is of interest because of the close relationship between Ang II and IR. Total increase in adipose tissue mass may be more

important in determining plasma angiotensinogen levels than increased angiotensinogen secretion from single adipocytes. (73)

Activation of the RAS could be a potential cause of hypertension in obesity via increased tubular sodium reabsorption and altered pressure natriuresis (48,127). In hypertension, increased sodium retention occurs in response to Ang II, unrelated to changes in glomerular filtration rate and aldosterone concentration (135). Increased renal microvascular reactivity and resistance could contribute to the blunted pressure natriuretic response during the development and progression of Ang II hypertension (136). Ang II regulates sodium homeostasis by modulating aldosterone secretion, renal vascular response and tubular sodium reabsorption (135). Obesity is associated with elevated aldosterone levels and an altered relationship between Ang II and aldosterone (47). In a study by Bokil and Porter (137) on Zucker obese rats, the possibility was raised that increased responsiveness of the central nervous system to Ang II may play a role in the predisposition of the obese rats to hypertension, therefore in hypertension, an increase in sodium retention could partly be the result of a hyper-responsiveness to Ang II (135). Ang II could, therefore, play an important role in obesity-induced hypertension (48).

The RAS has been suggested as a possible underlying mechanism that could explain the racial difference in the risk for hypertension. Africans have lower plasma renin activity than Caucasians and the relationship between ACE and BP differs between the two ethnic groups and this could reflect an underlying difference in the regulation of BP by the RAS (50).

- **Role in insulin resistance:** It has been reported that Ang II is involved in both salt-sensitive hypertension and IR (92). Harano *et al.* (89) observed a correlation between IR and Ang II in patients with heart failure and after treatment for heart failure IR improved or was reversed. Ang II inhibiting drugs (ACE inhibitors and AT₁-receptor antagonists) reduce BP but also restore insulin sensitivity (92).

In a rat study by Ogihara *et al.* (92), it was shown the RAS was suppressed in high-salt loaded rat models, while Ang II was increased in chronically Ang II-infused rats, therefore, it is not the Ang II level itself but rather the sodium retention and/or elevated BP that is associated with IR (92).

- **Interactions between endothelin-1, angiotensin II, insulin and nitric oxide:**
To maintain CVD processes and progression, activation of G-protein coupled receptors in response to vasoconstrictor peptides like Ang II or ET-1 and the resulting intracellular processes is essential (45). An upset in the normal balance of Ang II and NO in endothelial cells is associated with the manifestation of hypertension and related risk factors (115). Altered synthesis or enhanced inactivation of NO and an increase in ET-1 production lead to an imbalance that can induce arterial hypertension (124).

Factors such as Ang II and insulin stimulate the release of the vasoconstrictor ET-1 (57). Ang II and ET-1 potentiate one another's effects and Ang II also induces ET-1 expression (45,120). Insulin not only stimulates the release of the vasoconstrictor ET-1, but also the release of the vasodilator NO and an imbalance between these two substances may be involved in the pathophysiology of atherosclerosis and hypertension in insulin-resistant states associated with endothelial dysfunction (21). Ang II may in part be responsible for endothelial dysfunction because it induces resistance to the vasodilator action of NO (114). It has been demonstrated that oxidative stress promotes insulin resistance in high-salt and Ang II infused rat models (92).

3.4.4.3 The sympathetic nervous system, sodium retention and blood pressure

The exact mechanism of neurally-induced hypertension remains unclear (108), but in obesity there may be an increased dependence of BP on sympathetic control (48). Evidence suggests that a strong link exists between renal sympathetic activation and long-term arterial BP control (108).

Increased SNS activity has been seen in obesity (52). It has been suggested that the SNS is chronically activated in obese individuals as an attempt to prevent further weight gain and obesity-related hypertension is a consequence of the overactive SNS (47). Increased energy intake generally stimulates the SNS (48). Because the SNS is probably involved in resting metabolic rate and thermogenic responses to diet, it is possible that low SNS activity may lead to a decrease in energy expenditure that could lead to the development of obesity (23). It has been found that resting plasma norepinephrine levels and norepinephrine response to stimuli are elevated in obese subjects (48). It is known that epinephrine raises BP, but reports on epinephrine levels by ethnicity and gender are inconsistent and a recent study found

that plasma epinephrine was significantly higher among men and African women than Caucasian women (49). Obesity promotes the activation of adipose tissue vasoactive systems (the RAS and the ET-1 system), which could contribute to SNS activation and vasoconstriction that could lead to hypertension (45).

The increase in HR associated with obesity-related hypertension is partly the result of inhibition of parasympathetic activity (48). Homeostatic regulation of arterial pressure is maintained by arterial baroreceptors and activation of these receptors causes inhibition of SNS activity to the heart, but in hypertension, the activity of Ang II is enhanced in the brain where it exerts a powerful effect to modulate the baroreceptor reflex, which results in the reduced efficacy thereof (138). In obesity-related hypertension, increased sympathetic activity and decreased parasympathetic activity is seen (48).

Chronic increased renal adrenergic activation alters renal excretory function to produce sustained elevations in arterial pressure (108). Increased renal sympathetic activity could also in part contribute to sodium retention and abnormal pressure natriuresis in obesity (48,127). In contrast to the chronic renal sympathetic inhibition by the baroreceptor reflex, Ang II has sustained renal excitatory effects which lead to long-term opposing effects on renal sympathetic activity, which supports the involvement of sympathetic activation in hypertension via baroreflex dysfunction and activation of the RAS (108).

3.4.4.4 Intra-renal physical forces, sodium retention and blood pressure

Obesity can lead to changes in intra-renal physical forces that contribute to sodium retention due to increased tubular reabsorption. Histological changes have been observed in the renal medulla of obese humans and these changes lead to tubular compression, which consequently increases tubular reabsorption (48,127). This leads to activation of a macula densa feedback mechanism to cause renal vasodilatation and stimulation of renin secretion and activation of the RAS (36,48). Chronic obesity can cause serious structural changes in the kidney that could eventually lead to function loss, which will then further increase arterial pressure and in some cases this can result in severe renal injury (47,128).

3.5 Microalbuminuria and proteinuria

As a result of tubular injury, microalbuminuria and at a later stage proteinuria, often accompany obesity even before histologic changes can be seen in the kidney, which ultimately can contribute to the progression of renal damage, especially when it occurs in conjunction with hypertension (36). As shown in Table I, microalbuminuria is one of the WHO criteria for diagnosis of the MS (10).

4. Treating the metabolic syndrome and its components

Two general options can be employed to treat the MS, namely lifestyle intervention and pharmacological treatment of MS components like hypertension and dyslipidemia. The best treatment benefits are mostly obtained from lifestyle modification such as weight loss, because this strategy targets one of the root causes of the MS namely, obesity (18).

Obesity generally arises as the result of an inappropriate lifestyle, therefore, the best weight-management programmes involve lifestyle modification (24). Prevention of obesity is important because at present the various types of treatments seem not to be very successful (23,68). Given the impact of obesity on health, obesity is a public health issue that needs to be addressed seriously (22). Interventions are needed to improve physical activity and diet in communities nationwide (60). To manage the obesity epidemic one will firstly have to focus on treatments for people who are currently obese (lifestyle changes, pharmacologic and surgical interventions) and secondly, the environment will need serious attention through bold public initiatives to prevent the development of obesity (63). Obesity programmes should target low-income women, particularly African women and women with less education (70) and interventions should ultimately be culture-specific (40) in order to be successful.

For women, obesity treatment should depend on the severity of obesity, the presence of complications and the absence of exclusions like pregnancy (139). When embarking on a weight loss programme it is generally important that the principles of healthy nutrition are respected and regular exercise can provide health benefits and help to avoid weight gain (23). For weight loss to occur, a negative energy balance is needed (24). A rat study done by Roberts *et al.* (12) demonstrated that a low-fat, high-fibre diet could be an effective strategy for prevention and reversal of many of

the abnormalities of the MS. Drug treatment is another option to improve weight loss although none of the drugs that are being used at present produce weight loss indefinitely (23). Follow-up is very important when treating obesity because, as with other chronic diseases, when the treatment stops the disease comes back (139). There is a substantial need for more effective treatment of obesity (24), because the success of interventions for obesity is very poor. A possible reason could be because doctors and patients seem to disagree about the nature and causes of obesity (140).

Benefits of weight loss include:

Quality of life: Quality of life in the severely obese is improved by substantial weight loss (23). Evidence suggests that loss of 5–10% of body weight, when sustained, can lead to a significant reduction in cardiovascular and diabetic risk factors and even mortality in obese people (24).

Diabetes: Identifying subjects at risk for diabetes has become important because of the positive results found with lifestyle modification such as weight loss and medication in preventing or delaying the onset of diabetes (9).

Insulin resistance: Numerous studies in several populations have shown that body weight and physical fitness are powerful modulators of IR (90). IR also improves with weight loss (14). Not all overweight or obese persons are insulin resistant and the metabolic benefits of weight loss are greatest in subjects who are classified as having IR before weight reduction (90).

Glucose tolerance: It has been shown that weight loss improves glycemic control in insulin resistant diabetic patients (90).

Dyslipidemia: Intervention studies have shown that weight loss and reduced abdominal fat results in an improvement of an atherogenic lipid profile (14).

Blood pressure: Weight loss improves BP status in hypertensive patients and studies have shown that there is a relationship between improvements in IR and BP reductions in hypertensive subjects (90).

Weight loss through lifestyle modification, therefore, seems to be the best available intervention to improve not only the obesity component of the MS, but also many other abnormalities of the MS (12,18).

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Interrelationships between Metabolic Syndrome components associated with cardiovascular parameters among African women

Interrelationships between Metabolic Syndrome components associated with cardiovascular parameters among African women

J. Kotze, A.E. Schutte, J.M. van Rooyen

Abstract

Problem: The metabolic syndrome (MS) is common worldwide. The aim of this study was to determine the incidence of the MS components among African women, using the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) definition. Further objectives were to determine interrelationships between the obesity or insulin resistance (IR) component and other MS components and with related variables angiotensin II and endothelin-1. **Method:** 101 African women (age: 20-50 yrs) participated in the study. Blood pressure (BP) was taken with a Finometer device and arterial compliance (C) and other cardiovascular variables were also obtained. Anthropometric measurements were taken. Fasting glucose, insulin, lipids, angiotensin II and endothelin-1 were obtained from blood samples. IR was calculated using the homeostasis model assessment formula ($HOMA-IR = \text{fasting insulin} \times \text{fasting glucose} / 22.5$). **Results:** None of the MS components were identified in 20 subjects, 46 presented one component, 35 had two or more components and 16 of these subjects were identified with the MS according to the ATP III definition. The group with two or more MS components showed significantly higher ($p \leq 0.05$) body mass index (BMI), waist circumference (WC), BP, glucose and triglyceride values and lower HDL cholesterol (HDL-C) than the group with no MS components and the group with only one component. During multiple regression analyses, diastolic BP (DBP) and C were associated with WC in all groups. DPB was also associated with BMI in all groups, but C showed an association with BMI in all groups except for the group with no MS components. In the group with one MS criterion, angiotensin II and endothelin-1 were associated with IR and HDL-C was associated with WC and BMI. HDL-C was also significantly ($p \leq 0.05$) lower in this group than in the group with no MS components, the only significant difference between these groups. **Conclusion:** This suggests that abdominal obesity (WC) may play an important role in the MS as it showed significant associations with vascular complications (DBP and C). Angiotensin II, endothelin-1 and HDL-C may play a role during the development of the MS among younger African women, but further studies are required.

Key words: Metabolic syndrome, Africans, women, obesity, insulin resistance

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Instructions for authors

A summary of the instructions for authors for the *Journal of Diabetes and its Complications* is given below.

- Manuscripts should be typed in a standard sized font, with margins of at least one inch.
- Statistical methods should be identified.
- An abstract of 100–250 words, covering the main factual points, including statements regarding the problem, methods, results and conclusion should be typed on a separate page accompanied by three to five keywords.
- Appropriate headings and subheadings should be provided in the methods, results and discussion sections. The text should be kept clear and concise.
- Standard abbreviations may be used and where nonstandard abbreviations are used they should be defined where they first appear in the text.
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- Tables should be typed on separate pages with Roman numbers and title. Symbols for units should be confined to headings. Abbreviations should be kept to a minimum and all the abbreviations used should be explained.

Introduction

The metabolic syndrome (MS) describes a clustering of multiple risk factors for cardiovascular disease (CVD), including central obesity, hypertension, impaired fasting glucose, increased triglyceride levels and decreased high-density lipoprotein cholesterol (HDL-C) levels (1). These abnormalities are often referred to as 'diseases of civilisation' because they are rare in traditional societies (2). The 20th century marked many changes in society (3). Known as an epidemiological shift, it was characterised by a decline in infection-related mortality and an increase in mortality due to lifestyle diseases (4). In South Africa (SA), infections were the major cause of death in the past and up until the seventies, Africans had a longer life expectancy than Caucasians, because of lower rates of lifestyle diseases (5). This is no longer the case because of a rise in communicable diseases (HIV/AIDS) and non-communicable diseases (like obesity, hypertension and diabetes) (5,6).

The MS has become increasingly common in the United States (1,7) and it is estimated that it affects between 25% and 35% of the American population (8). In developing countries like Mexico, the prevalence of the MS has also been found to be high, with a rate of 13.6% when using the *World Health Organisation* (WHO) definition and a rate of 26.6% when using the definition of the *National Cholesterol Education Program's Third Adult Treatment Panel* (NCEP ATP III) (9). In SA, information regarding the prevalence of the MS among African women is scarce, but information concerning the components of the MS is presented in the paragraphs that follow, together with data from African populations elsewhere.

Women are particularly affected by obesity, with approximately 38% of African American women having a BMI > 30 kg/m² compared to 23% of Caucasian women (3). Distinct physiological, nutritional, cultural and environmental issues promote weight gain and prevent weight loss among African women (10). In SA, the prevalence of obesity among African women is also very high (11). Central obesity is a predisposing factor for the development of CVD (12) and abdominal obesity as indicated by a waist circumference > 80 cm is very common among African women (11). The inclusion of waist circumference in the ATP III definition of the MS reflects the high priority conferred upon waist circumference by the ATP III (13). Because waist circumference is a good predictor of non-communicable disease risk factor prevalence in African populations, it is the recommended measure when determining

abdominal obesity in South African women (11). During this study not all of the variables required by the WHO definition for the MS were collected, such as microalbuminuria. For these reasons the ATP III definition of the MS will be used in this study.

Hypertension is considered a global problem that contributes significantly to mortality on a worldwide scale (14). This is also the case in SA, where a high percentage of Africans suffer from hypertension (15,16). It has been suggested that physiological differences in sodium handling could be involved in racial differences in hypertension between Africans and Caucasians (3). Diabetes has also reached epidemic proportions worldwide and in most ethnic groups, diabetes is more prevalent among women than men (17). The relationship of insulin resistance (IR) with blood pressure (BP) is well documented in European and Hispanic American populations, but the relationship is weak or absent in the African American population (18). Other studies show a strong association between IR and BP among urban Africans (19). Ethnic disparities could be the result of genetic or racial differences in the pathogenesis of hypertension and IR (18).

The renin-angiotensin system (RAS) has also been implicated in racial differences in CVD risk (20). Elevated RAS components could be involved in the pathogenesis of hypertension and may play a role in diseases like diabetes and obesity (21-23). It is, therefore, possible that hypertension and obesity could be linked via several hormonal mechanisms such as angiotensin II (Ang II) and endothelin-1 (ET-1). The RAS is associated with CVD (21,24) on the one hand and obesity (25-27) on the other, because of the discovery of RAS components in adipose tissue (25,26,28). Hypertension (15) and obesity (11) are common in African populations, especially women. Ang II is also involved in both salt-sensitive hypertension and IR (29), which are common disorders among Africans and which form an integral part of the MS. For this reason it is important to explore the possible role of hormonal systems such as the RAS and ET-1 in the MS among African women.

The aim of this study was, therefore, to determine the incidence of the ATP III MS components among the African women that participated in the POWIRS (*Profile of Obese Women with Insulin Resistance Syndrome*) study. A further objective was to determine interrelationships between the obesity or the IR component and other MS components and also with related cardiovascular variables such as Ang II and ET-1.

Methods

Study design

A case-case-control study design was used for the POWIRS project, during which a subject group of 101 apparently healthy African women volunteers (20–50 years of age) were selected based on their BMI (lean [control], overweight [case] and obese [case]) (30). The study was approved by the Ethics Committee of the North-West University and all subjects gave informed consent.

Procedures

Subjects stayed overnight at a metabolic unit, where they underwent evaluation the following morning. During the evening, the subjects completed health and demographic questionnaires with the help of translators and field workers. Anthropometric measurements followed. At 20:00 all subjects received a light meal (no caffeine or alcohol) and they went to bed before 23:00 and fasted overnight. At 6:00 in the morning the first subject was woken up and BP measurements followed. Afterwards, fasting blood samples were obtained. This protocol was kept as constant as possible during the study to ensure resting BP values.

Blood pressure and cardiovascular measurements

The participants were introduced to the Finometer device (31-34) the previous evening to minimise anticipation stress. All BP measurements were taken with the subject in the Fowler's position, using the left arm (to avoid possible BP differences between the two arms). A continuous Finometer recording was taken for at least 7 minutes. After 2 minutes an individual and subject specific calibration was performed to adjust the finger pressure to the upper arm pressure. After this calibration, highly accurate readings were obtained. The average values for all cardiovascular variables were calculated from the recordings during the last 2 minutes of the reading. The data was stored on a hard disk. With the Beatscope 1.1 software programme systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR) and arterial compliance were obtained.

Body composition measurements

An anthropometrist measured weight, height and waist circumference with calibrated instruments (Precision Health scale and Holtain unstretchable metal tape) and standard methods and BMI was calculated using the following equation: BMI = weight (kg)/height (m²) (35).

Blood samples and biochemical analyses

A fasting blood sample was taken with a sterile butterfly set and syringes from the *vena cephalica*. Biochemical analyses for glucose, insulin, triglyceride and HDL-C, Ang II and ET-1 were performed later in the laboratory. Plasma glucose was analysed with the hexokinase method (inter assay CV-1.5%). Analysis of insulin was performed by enzyme immunoassay (BioSource EUROPE S.A. Belgium; inter assay-7.5%). Lipid concentrations were analysed on a Vitros DT60 II Chemistry System with Vitros DT slides. Analysis of Ang II levels were performed with a Euro-Diagnostica radioimmunoassay method. ET-1 levels were also analysed with a radioimmunoassay method (Biotrak Assay System, Amersham Biosciences).

Statistical analyses

The subject group was divided according to the number of ATP III MS criteria present (Table II). When three or more of the ATP III criteria (Table I) are identified in an individual, the MS can be diagnosed (1).

Table I. ATP III criteria for diagnosis of the metabolic syndrome

1. High blood pressure	SBP \geq 130 mmHg and/or; DBP \geq 85 mmHg or; Hypertension treatment.
2. Abdominal obesity	Waist circumference > 88 cm
3. & 4. Dyslipidemia	Triglyceride concentration \geq 1.69 mmol/L; and HDL-C concentration < 1.29 mmol/L
5. Hyperglycemia	IFG \geq 6.1 mmol/L

ATP III, adult treatment panel; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; IFG, impaired fasting glucose.

The software package Statistica v.6 (36) was used for the calculation of descriptive statistics, significant differences and multiple regression analyses. Least squares means with 95% confidence intervals were calculated for the ATP III MS criteria and other related variables (age, CO, SV, TPR, arterial compliance, Ang II and ET-1). Due to skewed distributions fasting plasma glucose, HDL-C, triglyceride, HOMA-IR, Ang II and ET-1 concentrations were logarithmically transformed. Analyses of covariance (ANCOVA) were used to test for significant differences ($p \leq 0.05$) between the groups, while adjusting for age with the Bonferroni correction method. Multiple stepwise regression analyses were performed to determine how each of the above variables contributes to the obesity component (waist circumference and BMI) or the IR component as the major contributor during the progression of the MS among African women.

Results

The overall sample consisted of 101 African women. Only 16 (15.8%) of these subjects presented with the MS as they had three or more of the ATP III MS criteria (1). The sample was classified into three groups depending on the number of ATP III criteria identified (Table I). No MS criteria were identified in 20 subjects, whereas 46 subjects presented only one criterion and 35 presented two or more criteria (Table II).

From Table II it is evident that the mean age of the group with two or more MS criteria was significantly higher ($p \leq 0.05$) than the group with no MS criteria, therefore, all subsequent variable analyses between groups were adjusted for age. The group with two or more MS criteria showed significantly higher ($p \leq 0.05$) values for BMI, waist circumference, SBP, and DBP than the group with no MS criteria and the group with one MS criterion. CO was the only other cardiovascular variable found to be significantly higher ($p \leq 0.05$) in those with two or more MS criteria than those with no MS criteria.

The group with two or more MS criteria also presented significantly higher values ($p \leq 0.05$) than the group with no MS criteria for HOMA-IR, fasting glucose, HDL-C and triglyceride concentration. HOMA-IR, fasting glucose and triglyceride concentration of the group with two or more MS criteria were found to be significantly higher ($p \leq 0.05$) than the group with only one MS criterion. The only significant difference between the group with no MS criteria and the group with one MS criterion was a

significantly lower ($p \leq 0.05$) HDL-C concentration for the latter group. No significant differences were found between any of the MS groups for SV, HR, TPR, arterial compliance, Ang II and ET-1.

The incidence of subjects that met the ATP III cut-points for the MS components in the whole subject group ($N = 101$) was found to be 42.6% for SBP, 24.8% for DBP, 31.7% for waist circumference, 59.4% for HDL-C, 6.9% for fasting plasma glucose and 3.0% for triglycerides. The percentage of subjects that met the ATP III cut-points in the group with only one MS criterion ($N = 46$) was found to be 28.3% for SBP, 8.7% for DBP, 13.04% for waist circumference, 65.2% for HDL-C and 2.2% for triglycerides. None of the subjects in this group had a fasting plasma glucose level that met the ATP III cut-point. The incidence of subjects that met the ATP III cut-points in the group with two or more MS criteria ($N = 35$) was found to be 82.9% for SBP, 60.0% for DBP, 74.3% for waist circumference, 85.7% for HDL-C, 20% for fasting plasma glucose and 5.7% for triglycerides.

Table II. Components of the metabolic syndrome and associated variables.

	All subjects	No MS criteria	One MS criterion	Two/more MS criteria
N	101	20	46	35
Age	31.3 (29.6-33.0)	27.0* (23.3-30.7)	30.5 (28.1-33.0)	34.6* (31.8-37.4)
BMI (kg/m²)	28.0 (26.7-29.2)	24.7 ^a (22.3-27.1)	26.1 ^b (24.6-27.7)	32.4 ^{ab} (30.5-34.2)
CO (L/min)	5.72 (5.49-5.95)	5.23 ^c (4.71-5.74)	5.57 (5.24-5.90)	6.21 ^c (5.82-6.60)
SV (mL)	84.7 (81.8-87.5)	79.9 (73.4-86.4)	83.8 (79.6-87.9)	88.4 (83.4-93.3)
HR (beats/minute)	68.3 (66.4-70.1)	65.7 (61.4-69.9)	67.2 (64.4-69.9)	71.4 (68.1-74.6)
TPR (mmHg.s/mL)	1.10 (1.04-1.15)	1.13 (1.01-1.25)	1.09 (1.01-1.17)	1.10 (1.00-1.19)
Arterial compliance (mL/mmHg)	1.85 (1.79-1.91)	1.84 (1.71-1.97)	1.85 (1.77-1.93)	1.84 (1.74-1.94)
Ang II (pmol/L)	23.4 (15.7-31.1)	31.2 (14.3-48.2)	22.0 (11.1-32.9)	16.8 (3.9-29.6)
ET-1 (fmol/mL)	15.7 (13.1-18.3)	16.0 (9.9-22.2)	14.0 (10.1-18.0)	17.7 (13.1-22.4)
HOMA-IR	3.09 (2.78-3.40)	2.34 ^d (1.71-2.96)	2.67 ^e (2.26-3.07)	4.10 ^{de} (3.62-4.6)
Incidence of ATP III criteria				
Waist circumference (cm)	84.0 (81.1-86.9)	74.5 ^f (69.5-79.4)	79.3 ^g (76.1-82.5)	95.5 ^{fg} (91.7-99.2)
SBP (mmHg)	129.8 (126.0-133.7)	122.0 ^h (115.8-130.2)	125.4 ⁱ (120.8-130.1)	140.0 ^{hi} (134.5-145.5)
DBP (mmHg)	77.7 (75.6-79.8)	72.9 ^j (69.0-76.9)	74.2 ^k (71.7-76.8)	85.3 ^{jk} (82.3-88.3)
Fasting plasma glucose (mmol/L)	5.19 (4.96-5.43)	4.91 ^l (4.39-5.42)	4.95 ^m (4.62-5.28)	5.68 ^{lm} (5.29-6.07)
HDL-C (mmol/L)	1.25 (1.19-1.32)	1.63 ^{no} (1.50-1.76)	1.23 ⁿ (1.15-1.31)	1.07 ^o (0.97-1.16)
Triglycerides (mmol/L)	0.71 (0.63-0.80)	0.71 ^p (0.54-0.88)	0.55 ^q (0.44-0.66)	0.93 ^{pq} (0.80-1.06)
	3 (3.0)	-	1 (2.2)	2 (5.7)

MS, metabolic syndrome; N, number of subjects; BMI, body mass index; CO, cardiac output; SV, stroke volume; HR, heart rate; TPR, total peripheral resistance; Ang II, angiotensin II; ET-1, endothelin-1; HOMA-IR, homeostasis model assessment insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure and HDL-C, high density lipoprotein cholesterol.

Values are means with 95% confidence intervals.

Means with the same superscript letter differ significantly ($p \leq 0.05$).

(*) = Indicates significant difference for age.

(^{a-o}) = Age adjusted significant differences.

For ATP III criteria values are incidence (N) and percentage (%).

(-) = None of the subjects presented with the relevant criterion.

In the stepwise multiple regression analyses the independent variables as shown in Table III-Table V were significantly associated ($p \leq 0.05$) with the dependent variables waist circumference (Table III), BMI (Table IV) and HOMA-IR (Table V).

It is clear from Table III that in the whole subject group and in the three separate subject groups age, DBP and arterial compliance explained the variance of waist circumference best. Ang II only showed a significant association in the group with no MS criteria.

Table III. Stepwise regression for waist circumference as the dependent variable versus independent variables. Regression coefficients (β) and level of significance, p are shown.

Independent variable	All subjects (N = 101) ($R^2 = 0.772$)	No MS criteria (N = 20) ($R^2 = 0.819$)	One MS criterion (N = 46) ($R^2 = 0.767$)	Two/more MS criteria (N = 35) ($R^2 = 0.705$)
Age	$\beta = 0.45$ $p < 0.001$	$\beta = 0.33$ $p = 0.042$	$\beta = 0.53$ $p < 0.001$	$\beta = 0.39$ $p = 0.005$
SBP	$\beta = -0.23$ $p = 0.057$	-	$\beta = -0.22$ $p = 0.122$	-
DBP	$\beta = 0.70$ $p < 0.001$	$\beta = 1.05$ $p < 0.001$	$\beta = 0.69$ $p < 0.001$	$\beta = 0.74$ $p < 0.001$
CO	$\beta = 0.94$ $p = 0.23$	-	-	$\beta = -0.40$ $p = 0.145$
SV	$\beta = 0.12$ $p = 0.2$	-	-	-
TPR	-	-	-	$\beta = -0.59$ $p = 0.081$
Arterial compliance	$\beta = 0.53$ $p < 0.001$	$\beta = 0.86$ $p < 0.001$	$\beta = 0.95$ $p < 0.001$	$\beta = 0.82$ $p < 0.001$
Fasting plasma glucose	$\beta = 0.16$ $p = 0.008$	-	-	$\beta = 0.17$ $p = 0.178$
HDL-C	-	$\beta = 0.78$ $p = 0.002$	$\beta = 0.41$ $p < 0.001$	-
Triglycerides	$\beta = 0.15$ $p = 0.011$	$\beta = -0.16$ $p = 0.162$	-	$\beta = 0.24$ $p = 0.092$
Ang II	$\beta = -0.06$ $p = 0.231$	$\beta = 0.36$ $p = 0.012$	$\beta = -0.10$ $p = 0.204$	$\beta = -0.179$ $p = 0.099$
ET-1	$\beta = 0.07$ $p = 0.147$	$\beta = 0.22$ $p = 0.071$	$\beta = 0.14$ $p = 0.074$	-

MS, metabolic syndrome; N, number of subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance; HDL-C, high density lipoprotein cholesterol; Ang II, angiotensin II; and ET-1, endothelin-1.

Significant ($p \leq 0.05$) values are shown in bold.

(-) indicates that no significant association was found.

β = standardised regression coefficient.

From Table IV it can be seen that in the whole subject group and in the groups with one and two or more MS criteria, age, DBP and arterial compliance again explained the variance in BMI best and in the group with no MS criteria, DBP also contributed to the variance in BMI.

Table IV. Stepwise regression for *body mass index* as the dependent variable versus independent variables. Regression coefficients (β) and level of significance, p are shown.

Independent variable	All subjects (N = 101) ($R^2 = 0.662$)	No MS criteria (N = 20) ($R^2 = 0.549$)	One MS criterion (N = 46) ($R^2 = 0.545$)	Two/more MS criteria (N = 35) ($R^2 = 0.724$)
Age	$\beta = 0.35$ $p < 0.001$	-	$\beta = 0.40$ $p = 0.002$	$\beta = 0.39$ $p = 0.004$
SBP	$\beta = -0.17$ $p = 0.257$	-	$\beta = -0.20$ $p = 0.322$	-
DBP	$\beta = 0.62$ $p < 0.001$	$\beta = 0.72$ $p = 0.011$	$\beta = 0.57$ $p < 0.001$	$\beta = 0.35$ $p = 0.020$
CO	$\beta = 0.07$ $p = 0.44$	$\beta = 0.27$ $p = 0.238$	-	$\beta = 0.15$ $p = 0.303$
SV	$\beta = 0.25$ $p = 0.024$	-	-	$\beta = 0.25$ $p = 0.084$
TPR	-	-	-	-
Arterial compliance	$\beta = 0.48$ $p < 0.001$	$\beta = 0.27$ $p = 0.252$	$\beta = 0.78$ $p < 0.001$	$\beta = 0.67$ $p < 0.001$
Fasting plasma glucose	$\beta = 0.13$ $p = 0.074$	-	-	-
HDL-C	-	$\beta = 0.86$ $p = 0.004$	$\beta = 0.29$; $p = 0.027$	-
Triglycerides	$\beta = 0.11$ $p = 0.102$	$\beta = -0.52$ $p = 0.009$	-	$\beta = 0.25$ $p = 0.032$
Ang II	-	-	$\beta = 0.16$ $p = 0.151$	$\beta = -0.14$ $p = 0.176$
ET-1	-	$\beta = -0.25$ $p = 0.175$	$\beta = 0.16$ $p = 0.127$	-

MS, metabolic syndrome; N, number of subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance; HDL-C, high density lipoprotein cholesterol; Ang II, angiotensin II; and ET-1, endothelin-1.

Significant ($p \leq 0.05$) values are shown in bold.

(-) indicates that no significant association was found.

β = standardised regression coefficient.

From Table V it is evident that fasting plasma glucose was the main contributor to the observed variance in HOMA-IR in the whole subject group and in the groups with one and two or more MS criteria. Ang II and ET-1 showed a significant association in the group with one MS criterion.

Table V. Stepwise regression for HOMA insulin resistance as the dependent variable versus independent variables. Regression coefficients (β) and level of significance, p are shown.

Independent variable	All subjects (N = 101) ($R^2 = 0.411$)	No MS criteria (N = 20) ($R^2 = 0.310$)	One MS criterion (N = 46) ($R^2 = 0.531$)	Two/more MS criteria (N = 35) ($R^2 = 0.485$)
Age	$\beta = 0.09$ $p = 0.212$	$\beta = -0.96$ $p = 0.004$	-	-
SBP	-	-	$\beta = 0.36$ $p = 0.006$	-
DBP	$\beta = 0.44$ $p = 0.013$	$\beta = 0.44$ $p = 0.11$	-	$\beta = 0.24$ $p = 0.317$
CO	$\beta = -0.17$ $p = 0.6$	-	$\beta = 0.49$ $p < 0.001$	$\beta = -0.63$ $p = 0.152$
SV	$\beta = -0.2$ $p = 0.152$	-	-	$\beta = -0.18$ $p = 0.354$
TPR	$\beta = -0.52$ $p = 0.125$	-	-	$\beta = -1.21$ $p = 0.007$
Arterial compliance	$\beta = 0.26$ $p = 0.064$	-	-	-
Fasting plasma glucose	$\beta = 0.39$ $p < 0.001$	-	$\beta = 0.58$ $p < 0.001$	$\beta = 0.34$ $p = 0.047$
HDL-C	-	$\beta = 0.64$ $p = 0.056$	$\beta = -0.15$ $p = 0.276$	-
Triglycerides	$\beta = 0.11$ $p = 0.25$	-	$\beta = 0.31$ $p = 0.019$	$\beta = 0.27$ $p = 0.085$
Ang II	-	$\beta = 0.30$ $p = 0.211$	$\beta = -0.27$ $p = 0.029$	-
ET-1	-	-	$\beta = -0.24$ $p = 0.031$	-

HOMA-IR, homeostasis model assessment insulin resistance; MS, metabolic syndrome; N, number of subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance; HDL-C, high density lipoprotein cholesterol; Ang II, angiotensin II; and ET-1, endothelin-1.

Significant ($p \leq 0.05$) values are shown in bold.

(-) indicates that no significant association was found.

β = standardised regression coefficient.

Discussion

With advancing age more of the MS criteria become apparent. Many studies have demonstrated that the prevalence of the MS rises with advancing age (13). Advancing age is considered a major and independent risk factor for CVD (1). It seems that age has minimal effect on IR, but weight tends to increase and physical activity decreases as people become older (37). This can also be seen from the multiple regression results of this study (Table III-Table V). Age was a significant marker for waist circumference in the whole subject group and the three subgroups. Age was also a significant marker for BMI in the whole subject group and the groups with one and two or more MS criteria. However, with IR as the dependent variable, age was significantly associated with IR only in the group with no MS criteria.

SBP, DBP, CO, SV and HR increased gradually from those with no MS criteria to those with two or more MS criteria (Table II). The ATP III criterion for high BP is classified as a BP \geq 130/85 mmHg (1). The group with two or more MS criteria had a mean SBP and DBP that exceeded the ATP III cut-points for classifying high BP (140.0/85.3 mmHg). This group also met the hypertension criteria of the WHO (BP \geq 140/90 mmHg) (38). The incidence of subjects that met the ATP III criteria for SBP (82.9%) and DBP (60.0%) was found to be high in the group with two or more MS criteria. High hypertension rates have previously been found among Africans and especially African women from SA (6,15) as well as other women of African origin elsewhere (3). It is of interest, however, that neither TPR nor arterial compliance differed at all between the three subgroups, but remained at almost exactly the same level. Volume loading type hypertension (23,39,40) could, therefore, clearly be seen in the group with two or more components of the MS. The relatively young age of this group [34.6 (31.8-37.4) years (yrs)] could possibly explain why the TPR has not shown any increases yet.

The ATP III considers abdominal obesity as indicated by a waist circumference $>$ 88 cm an important component of the MS (1) and in this study the group with two or more MS criteria had a mean waist circumference [95.5 (91.7-99.2) cm] that exceeded this cut-point and it was also significantly greater than that of the other groups. The incidence of subjects that exceeded the ATP III cut-point for waist circumference was found to be 31.7% of the whole group and as expected it was high in the group with two or more MS criteria (74.3%). This indicates the importance

of abdominal obesity as a factor during the development of the MS. The WHO considers a person to be overweight when his/her BMI ≥ 25 kg/m² and obese if his/her BMI ≥ 30 kg/m² (30). The mean BMI of the whole subject group and the groups with one and two or more MS components exceeded the WHO criteria for being overweight and the latter group also exceeded the WHO criterion for being obese. From the multiple regression analyses it is evident that the variables that explain the variance in body composition, as represented by waist circumference (Table III) and BMI (Table IV) best are DBP, arterial compliance and age. In some groups the expected involvement of lipids is also seen with regard to waist circumference (Table III) and BMI (Table IV).

Gradual decreases were seen in HDL-C levels (Table II) from those with no MS criteria to those with two or more MS criteria. Age-adjusted significant differences between the groups demonstrate that as more MS abnormalities cluster together, HDL-C levels decrease. The incidence of subjects that met the ATP III criterion for HDL-C was found to be high in the whole group (59.4%) as well as in the groups with one MS criterion (65.2%) and two or more MS criteria (85.7%). The mean HDL-C of the whole subject group and the groups with one and two or more MS criteria showed HDL-C levels lower than the ATP III cut-point of 1.29 mmol/L (Table I). Low HDL-C levels, therefore, seem to be an especially important factor of the MS among younger African women. A significant difference was found between the groups with no MS criteria and the group with one MS criterion only for HDL-C (Table II). In the multiple regression analyses HDL-C showed a significant association with waist circumference and BMI for the groups with no MS criteria and one MS criterion (Table III-Table IV). HDL-C also showed an association with HOMA-IR for both these groups, though not significantly (Table V). It is, therefore, possible that HDL-C plays an important role during the developmental stages of the MS in this subject group.

Although significant differences (Table II) were found between the groups for triglycerides and the triglyceride level of the group with two or more MS criteria [0.93 (0.80-1.06) mmol/L] was almost double that of the group with one MS criterion [0.55 (0.44-0.66) mmol/L], none of the groups showed a triglyceride level approaching hypertriglyceridemia (≥ 1.69 mmol/L). Higher triglyceride levels are usually accompanied by lower HDL-C levels (1). Raised triglycerides and low HDL-C levels are atherogenic abnormalities characteristic of the MS (17).

HOMA-IR and fasting plasma glucose showed gradual increases from the group with no MS criteria to the group with two or more MS criteria (Table II), but none of the groups presented hyperglycemia and even in the group with two or more MS components, the mean fasting plasma glucose [5.68 (5.29-6.07) mmol/L] was lower than the ATP III cut-point of 6.1 mmol/L (Table I). Only seven subjects met the ATP III criteria for fasting plasma glucose in the group with two or more MS criteria delivering an incidence of 20.0%. The relatively young age [34.6 (31.8-37.4) yrs] of this group could be the reason why their fasting plasma glucose is still low.

The multiple regression analysis for HOMA-IR (Table V) showed a different picture than that found for body composition (Table III-Table IV). The variables DBP, arterial compliance and age did not play such a noticeable role with HOMA-IR as was the case with body composition. Fasting plasma glucose showed a significant association with HOMA-IR in the whole subject group and the groups with one and two or more MS criteria and this is to be expected. Noteworthy from this analysis, however, is that Ang II and ET-1 demonstrated a significant association with HOMA-IR in the group with one MS criterion, which represents those who are probably still only in the developmental stages of the MS. This group is also the largest of the three groups (n = 46). Some associations were found for Ang II and ET-1 in the multiple regression analysis for body composition, though none of these were statistically significant.

Conclusions

Despite the fact that the highest risk MS group in this study was chosen to have only a minimum of two MS components (34.6% of the total subject group), this group showed relatively large differences when compared to the group with no MS criteria and the group with only one MS criterion. This is probably due to some subjects having more than two MS components. These components could be any two of the five ATP III criteria, namely BP, waist circumference, triglycerides, HDL-C or fasting glucose (1). In this group, the mean BP, HDL-C and waist circumference values met the ATP III criteria for classification of the MS.

It is known that triglyceride levels are low among Africans (41,42) and it is also observed here. Fasting plasma glucose levels were also found to be low and this could be due to the relatively young age of the group. The two MS components

identified in this group could, therefore, potentially be either BP, HDL-C or waist circumference. These factors could, therefore, be important components of the MS among younger African women, possibly playing a role during the initial developmental stages of the MS. HDL-C was the only significant difference found between the group with no MS criteria and the group with one MS criterion and in these groups, HDL-C also showed significant associations with waist circumference and BMI, emphasising the possible role of HDL-C and obesity in the developmental stages of the MS in this subject group.

Noteworthy associations were found for DBP, arterial compliance and age with levels of obesity (waist circumference and BMI) in the group with at least two MS components. These associations were also found between these variables and waist circumference for all the other groups. This shows the possible importance of the obesity component, particularly abdominal obesity (represented by waist circumference), during the development of the MS in African women as these associations were not evident with regard to HOMA-IR. It is concluded that abdominal obesity may play an important role in the development of the MS in young African women, since it is significantly associated with vascular complications (DBP and arterial compliance). Some significant associations were also found between glucose levels and HOMA-IR, as expected, but Ang II and ET-1 both showed significant associations with HOMA-IR in the group with one MS criterion, indicating that these hormones could be involved in the developmental stages of the MS. It is possible that the results for Ang II and ET-1 were obtained simply by chance, therefore it is suggested that more focussed studies are needed further in this regard.

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4

General findings and final comments

In this chapter a summary of the main findings of the study is given, the study limitations are discussed and recommendations are made.

General findings

The metabolic syndrome (MS) and its components have become a serious problem worldwide (1). The aim of this study was, therefore, to determine the incidence of the MS components among African women, using the NCEP ATP III (*National Cholesterol Education Program's Third Adult Treatment Panel*) definition. Further objectives were to determine interrelationships between the obesity or the insulin resistance (IR) component and other MS components, as well as with the other related cardiovascular variables such as angiotensin II (Ang II) and endothelin-1 (ET-1).

The POWIRS (*Profile of Obese Women with Insulin Resistance Syndrome*) study consisted of 101 African women between the ages of 20 and 50 years. This group was classified into three subgroups depending on the number of ATP III MS components (high blood pressure (BP), abdominal obesity, dyslipidemia and hyperglycemia) present (1). No MS components were identified in 20 of the subjects, whereas 46 subjects presented only one MS component and 35 of the subjects presented two or more of the MS criteria (Chapter 3: Table II).

From the above it can be seen that the aim of this study has two parts. The first of which is to determine the incidence of the ATP III MS components and associated variables in the different groups.

- The group with two or more MS components had a significantly higher BP, obesity [as represented by waist circumference and body mass index (BMI)],- glucose and triglyceride values and lower HDL cholesterol (HDL-C) values than the other groups. The mean BP, HDL-C and waist circumference values of this group met the ATP III criteria (1) for classification of the MS.
- The group with one MS criterion had a significantly lower HDL-C value than the group with no MS criteria. HDL-C was also found to be significantly associated with waist circumference and BMI in the group with one MS criterion.

These findings lead to the conclusion that BP, waist circumference and HDL-C could be involved in the development of the MS among younger African women.

- Age, diastolic blood pressure (DBP) and arterial compliance were significantly associated with waist circumference in all three groups and with BMI in most groups.
- Glucose, Ang II and ET-1 levels were significantly associated with IR in the group with one MS criterion.

To identify which variable(s) were the strongest contributors to either the obesity (waist circumference or BMI) or the IR component, the other aim of this study, multiple regression analyses were done.

Regarding possible interrelationships between the MS components, it is concluded that abdominal obesity (represented by waist circumference) may play an important role in the MS as it was significantly associated with vascular complications (represented by DBP and arterial compliance). It is further also possible that hormones such as Ang II and ET-1, together with IR, could play a role during the developmental stages of the MS.

Final comments and recommendations

- **Prevalence versus incidence:** The subject group consisted of 101 African women who participated in the study voluntarily and who were further included based on their BMI. Based on this study design it was not possible to estimate the prevalence of the MS among African women in general, though the incidence of the MS in the sample could be determined. This can only point toward certain trends among African women in general. The sample size was, however, sufficient for the aims of this study (as set out in Chapter 1), in which only the incidence of the components of the MS were determined. It is, therefore, recommended that future studies include a larger number of randomly selected subjects in order to estimate the prevalence of the MS in South African populations.

- **Group size:** The subject group can be subdivided into groups based on the number of ATP III criteria identified. The ATP III criteria states that 3 of the 5 MS criteria should be identified in an individual to classify the MS (1). When dividing the sample according to this it was found that 20 of the subjects did not have any of the MS components, 65 had one or two of the MS components and 16 had more than three of the MS components. Based on these results it was decided to divide the subjects as follows, 20 subjects with no MS components, 46 subjects with only one MS component and 35 subjects having two or more MS components. The latter group then being referred to as a high-risk MS group and the group with one MS component referred to as being in a developmental and lower risk stage of the MS. Dividing the group in this way delivered a more even distribution, but it is important to keep in mind that the group said to be in the developmental stage of the MS was also the largest group in the study.
- **Age:** From the results (Chapter 3: Table II) it can be clearly seen that age increases from one group to another as more MS components become apparent. Age particularly seems to affect body composition in this subject group (Chapter 3: Table III and Table IV). Although adjusting for age in the statistical analyses of this study, it is recommended that future studies use stricter age criteria when recruiting participants in order not to underestimate the affects of age particularly on body composition among African women. The subject group, however, could be considered still to be relatively young [31.3 (29.6-33.0) yrs] (Chapter 3: Table II). This could be the reason why the group with only one MS criterion is the largest group in the study. It is also, therefore, very possible that this group represents the developmental stages of the MS and that with increasing age, many of these subjects might develop more of the MS components.
- **Blood pressure:** It is possible that despite the help of translators and field workers, anticipation stress could have played a role during the BP measurements, known as the white-coat effect (2,3).

- **Waist circumference:** With the multiple regression analyses the selected group of independent variables (the ATP III MS components, cardiovascular variables and Ang II and ET-1) explained a higher percentage of the variability in waist circumference than in BMI for the whole subject group, $R^2 = 0.77$ and $R^2 = 0.66$ respectively. This was the case for most of the other groups as well. This confirms the importance of waist circumference as the preferred obesity measure with regard to the MS (1,4) and CVD among African women (5).
- **Dyslipidemia:** The lipid profile of the MS is usually represented by a higher triglyceride level accompanied by a lower HDL-C level (1). The HDL-C abnormality of the MS was evident from the results of this study (Chapter 3: Table II-Table IV). None of the groups in this study demonstrated a triglyceride level that even approached the ATP III cut-point. Therefore, for recommendations of a population specific definition of the MS for Africans, it seems that the triglyceride cut-point of the ATP III definition could be too high.
- **Confounding factors:** These are external factors during the selection process that could have influenced the results of the study. The participants in this study were recruited from a governmental institution in the North West Province of SA, where they were tested to be HIV negative 3 months prior to the actual study. At the time of the study it was not known what their HIV status was. It is, therefore, recommended that future studies regarding the MS should only include participants who are confirmed to be HIV negative at the time of the study. Other factors such as smoking habit and the use of medication, like antiretroviral therapy (ART) that could influence the results were ascertained by questionnaires. It has been shown that certain HIV ART drugs have side-effects resulting in MS associated factors, namely elevated triglycerides, waist-to-hip ratio and fasting insulin levels (6). Despite the help of translators and fieldworkers, it is possible that the subjects could have found it difficult to understand questionnaires regarding confounding factors and honesty when answering these questionnaires can only be assumed.

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