Cardiovascular dysfunction in black South Africans: an investigation from various perspectives

IM Palmer M.Sc.

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PROMOTER: Prof. AE Schutte
CO-PROMOTER: Prof. HW Huisman

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~Psalm 28:7~

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

AdipoR1	Adiponectin receptor-1
AdipoR2	Adiponectin receptor-2
AIDS	Acquired immunodeficiency syndrome
AMP	Adenosine monophosphate
AmP1 gene	Adiponectin gene
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARIC Study	Atherosclerosis Risk in Communities study
BMI	Body mass index
CARDIA Study	Coronary Artery Risk Development in Young Adults
COX-2	Cyclooxygenase–2
CVD	Cardiovascular disease
C_W	Arterial compliance/Windkessel compliance
DBP	Diastolic blood pressure
eCcr	Estimated creatinine clearance
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ET-1	Endothelin-1
GFR	Glomerular filtration rate
GLUT-4	Glucose transporter type 4
HDL	High density lipoproteins
HIV	Human Immunodeficiency Virus
HMW	High molecular weight
HOMA-IR	Homeostasis model assessment for insulin resistance
hsCRP	High sensitivity C-reactive protein
ICAM	Intercellular adhesion molecule
IL-1RA	Interleukin-1 receptor antagonist
IL 6	Interleukin-6
IL-10	Interleukin-10
ISH	International Society of Hypertension
LDL	Low density lipoproteins

LMW	Low molecular weight
MANOVA	Multiple analysis of variance
MAP	Mean arterial pressure
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemotactic (chemoattractant) protein-1
MetS	Metabolic syndrome
NO	Nitric oxide
PAI-1	Plasminogen activator inhibitor-1
PDGF	Platelet derived growth factor
PP	Pulse pressure
SAfrEIC	South African study regarding the influence of Sex, Age and Ethnicity on Insulin sensitivity and Cardiovascular function
SBP	Systolic blood pressure
SOD	Superoxide dismutase
TC	Total cholesterol
TNF-α	Tumour necrosis factor-α
TPR	Total peripheral resistance
UA	Uric acid
VCAM	Vascular cell adhesion molecules
VSMC	Vascular smooth muscle cells
WC	Waist circumference
WHO	World Health Organization
XDH	Xanthine dehydrogenase
XO	Xanthine oxidase

TITLE: CARDIOVASCULAR DYSFUNCTION IN BLACK SOUTH AFRICANS: AN INVESTIGATION FROM VARIOUS PERSPECTIVES

SUMMARY

Motivation: The prevalence of cardiovascular dysfunction, especially hypertension, in Africans has increased dramatically over the past few decades. Despite considerable in-depth studies, cardiovascular diseases remain the leading cause of morbidity and mortality. Further escalations are predicted, especially in developing countries such as South Africa, if measures are not taken to combat the trend. Numerous cardiovascular risk factors have been investigated within African-Americans as well as Caucasians. However, it is not known to what extent African-Americans and Africans from South Africa are comparable. Therefore, it is essential to investigate risk factors and their possible contributory role in the high susceptibility of cardiovascular dysfunction in the black South African population.

Aim: To investigate potential risk factors and their possible involvement and association with the high prevalence of cardiovascular dysfunction within the black South African population.

Methodology: Manuscripts presented in Chapters 2, 3 and 4 made use of the data obtained from the cross-sectional SAfrEIC (The South African study regarding the influence of Sex, Age and Ethnicity on Insulin sensitivity and Cardiovascular function) study. The study group included 756 asymptomatic, apparently healthy African men and women as well as Caucasian men and women, recruited from the North West Province, South Africa. Anthropometric and cardiovascular measurements were taken as well as their lipid profiles, fasting insulin levels, and uric acid and adiponectin levels. Independent t-tests, analyses of variance (ANOVA) and analyses of covariance (ANCOVA) were used for comparison of variables between groups to determine significant differences. Partial correlations coefficients were used to show association between variables while adjusting for confounders. Multiple analyses of covariance (MANCOVA) were performed to compare variables between the groups, whilst adjusting for relevant confounders. Stepwise multiple and single regression analyses were also used to determine and confirm the most significant associations between variables.

All subjects gave informed consent in writing and the Ethics Committee of the North-West University approved the study. The reader is referred to the "Materials and Methods" section of Chapters 2, 3 and 4 for a more elaborate description of the subjects, study design and analytical methods used in each paper.

Results and conclusions of the individual manuscripts

- Results from Chapter 2 revealed significantly lower uric acid levels for African men compared to Caucasian men. Despite these lower levels, the association between uric acid and blood pressure is more pronounced within the African men. The strong positive relationship between uric acid and blood pressure might be explained by uric acid's independent relationship with vascular resistance. Uric acid also revealed a positive association with triglycerides in both the African and Caucasian men. These results suggest that uric acid *per se* can act as a risk factor in the development of cardiovascular dysfunction in African men.

- Results from Chapter 3 showed opposing changes in insulin secretion for African men and Caucasian men with increasing age. Whereas insulin levels increased in Caucasian men with progressive age, insulin levels in African men tended to decrease with ageing. Additionally, the insulin-blood pressure relationship within African men revealed opposite results as to what was expected. While the Caucasian men revealed a more positive association between insulin and blood pressure within the younger individuals, older individuals revealed a negative association between insulin and blood pressure. This implies that the vasoconstrictory actions of insulin seem to dominate in young individuals while the vasodilatory actions of insulin take over in older individuals. The turnaround probably acts as a counter protective mechanism against age-related cardiovascular dysfunction. On the contrary, despite decreased insulin secretion in older African men, they exhibit a more positive association between insulin and blood pressure, whereas younger subjects showed a more negative association. These results might suggest dissociation between insulin and blood pressure. Insulin *per se* might, therefore, not act as a risk factor, but rather the lack of insulin-mediated vasodilatory effects as observed within younger Africans.

- Results from Chapter 4 contradicted the notion found in the literature that age-related increase in adiponectin levels are due to impaired renal function. Although the results from this chapter confirmed a significant association between renal function (estimated creatinine clearance) and adiponectin levels – a multiple regression model revealed insulin resistance (HOMA-IR) as the major contributor to adiponectin levels. Adiponectin levels increased with progressive ageing only in the Africans. No such change was observed for the Caucasians. This might be due to development of functional adiponectin resistance or perhaps due to a decline in pancreatic cell mass with ageing.

In conclusion, the cardiovascular profile of Africans seems to be more detrimentally affected compared to Caucasians. Results from this study have elucidated on the associations and potential involvement of possible risk factors including, uric acid, insulin, C-peptide, as well as adiponectin, with regards to the high prevalence of cardiovascular dysfunction within the black South African population.

Keywords: Africans, cardiovascular dysfunction, ageing, hypertension, uric acid, insulin, C-peptide, adiponectin.

ARIKAANSE TITEL: KARDIOVASKULÊRE DISFUNKSIE IN SWART SUID AFRIKANERS: 'N ONDERSOEK VANUIT VERSKEIE PERSPEKTIEWE

OPSOMMING

Motivering: Die voorkoms van kardiovaskulêre disfunksie, veral hipertensie in swart Afrikane het dramaties toegeneem oor die afgelope paar dekades. Ten spyte van aansienlike in-diepte navorsing, bly kardiovaskulêre siektes een van die belangrikste oorsake van morbiditeit en mortaliteit. Verdere toenames word verwag, veral in ontwikkelende lande soos Suid-Afrika, indien daar nie stappe geneem word om hierdie tendens te verhoed nie. Verskeie kardiovaskulêre risikofaktore is reeds ondersoek in swart Afro-Amerikaners sowel as in Kaukasiërs, maar, dit is nie bekend tot watter mate swart Afro-Amerikaners en swart Afrikane van Suid-Afrika met mekaar vergelyk kan word nie. Dit is dus noodsaaklik om risikofaktore en hul moontlike bydraende rolle vir die hoë vatbaarheid van kardiovaskulêre disfunkies in die swart Afrikane populasie te ondersoek.

Doelstelling: Om potensiële risikofaktore en hul moontlike betrokkenheid en verwantskappe met die hoë voorkoms van kardiovaskulêre disfunksie in swart Afrikane te ondersoek.

Metodologie: Die manuskripte wat in Hoofstukke 2, 3 en 4 vervat is, het gebruik gemaak van die dwarsdeursnee SAfrEIC (*The South African study regarding the influence of Sex, Age and Ethnicity on Insulin sensitivity and Cardiovascular function*) projek. Die studie groep het 756 asimptomatiese, ooglopend gesonde swart mans en vrouens sowel as Kaukasiër mans en vrouens vanuit die Noordwes Provinsie van Suid-Afrika ingesluit. Antropometriese en kardiovaskulêre metings is geneem, sowel as die lipiedprofiel, vastende insulienvlakke, asook uriensuur- en adiponektienvlakke. Onafhanklike t-toetse, analise van variansie (ANOVA) asook analise van kovariansie (ANKOVA) is gebruik om betekenisvolle verskille tussen groepe te bepaal. Meervoudige analise van kovariansie (MANKOVA) is gebruik om betekenisvolle versille tussen groepe te bepaal terwyl daar gekorrigeer is vir relevante veranderlikes. Parsiële korrelasie koëffisiënte is gebruik om assosiasies tussen veranderlikes te bepaal terwyl daar vir sekere veranderlikes gekorrigeer is. Stapsgewyse meervoudige regressie analises

asook normale regressie analises is verder uitgevoer om die mees betekenisvolle assosiasies tussen veranderlikes te bepaal en bevestig.

Alle proefpersone het skriftelike ingeligte toestemming gegee. Die studie is goedgekeur deur die Etiekkomitee van die Noordwes-Universiteit. Die leser word verder verwys na die "Materials and Methods" afdeling van Hoofstukke 2, 3 en 4 vir 'n meer uitgebreide beskrywing van die proefpersone, studie-ontwerp en analitiese metodes wat gebruik is.

Resultate en gevolgtrekkings van die individuele manuskripte

- Resultate van Hoofstuk 2 toon aan dat swart mans betekenisvolle laer uriensuurvlakke het in vergelyking met Kaukasiër mans. Ten spyte van hul laer vlakke, is die assosiasie tussen uriensuur en bloeddruk veel meer prominent in die swart mans. Die sterk positiewe verwantskap tussen uriensuur en bloeddruk kan moontlik verduidelik word aan die hand van die onafhanklike assosiasie van uriensuur met vaskulêre weerstand. Uriensuur toon ook 'n positiewe assosiasie met trigliseriedes in beide die swart en Kaukasiër mans. Hierdie resultate toon aan dat uriensuur *per se* kan optree as 'n risikofaktor in die ontwikkeling van kardiovaskulêre disfunksie in swart mans.

- Resultate van Hoofstuk 3 toon teenoorgestelde veranderinge aan in insuliensekresie in swart en Kaukasiër mans met toenemende ouderdom. Insulienvlakke neem toe in Kaukasiër mans met toenemende ouderdom, waar in die swart mans dit 'n afnemende tendens toon. Die verwantskap tussen insulien en bloeddruk in swart mans het ook 'n teenoorgestelde resultaat getoon as wat verwag was. Terwyl jong Kaukasiër mans 'n meer positiewe verhouding tussen insulien en bloeddruk getoon het, het die ouer Kaukasiër mans 'n meer negatiewe verwantskap aangedui tussen insulien en bloeddruk. Dit wil meebring asof die vasokonstriktoriese funksies van insulien meer dominant is in jonger individue terwyl die vasodilatoriese funksies oorneem in ouer individue. Hierdie ommekeer dien moontlik as beskerming teen ouderdom verwante kardiovaskulêre disfunksie. Inteendeel, ten spyte van 'n afname in insuliensekresie toon die ouer swart mans 'n meer positiewe assosiasie tussen bloeddruk en insulien, terwyl die jonger mans 'n meer negatiewe assosiasie aandui. Hierdie resultate dui op 'n moontlike dissosiasie tussen bloeddruk en insulien.

Insulien *per se* tree dus nie op as 'n risikofaktor nie, maar eerder die gebrek aan insulien-afhanklike vasodilatasie soos waargeneem in die jonger swart mans.

- Resultate van Hoofstuk 4 het die teenstelling bewys rakende die stelling wat gevind word in die literatuur dat ouderdom-verwante toename in adiponektienvlakke te wyte is aan verswakte nierfunksie. Alhoewel die resultate van hierdie hoofstuk 'n sterk verwantskap bevestig tussen adiponektien en nierfunksie (benaderde kreatinien opruiming), het 'n veelvuldige regressie model getoon dat insulien weerstandbiedendheid (HOMA-IR) 'n groter bydrae maak tot adiponektien vlakke. Adiponektienvlakke het toegeneem met ouderdom in die swart mans maar nie in die Kaukasiër mans nie. Dit mag die gevolg wees van die ontwikkeling van funksionele adiponektien weerstandbiedendheid of moontlike afname in pankreasselmassa met toenemende ouderdom.

Ten slotte, die kardiovaskulêre profiel van die swart populasie is meer nadelig geaffekteerd in vergelyking met die van Kaukasiërs. Resultate van hierdie studie het meer duidelikheid gewerp op die assosiasies en potensiële betrokkenheid van moontlike risikofaktore insluitende uriensuur, insulien, C-peptide, asook adiponektien met betrekking tot die hoë voorkoms van kardiovaskulêre disfunksie in die swart Suid-Afrikaanse populasie.

Sleuterwoorde: Swart Afrikane, kardiovaskulêre disfunksie, veroudering, hipertensie, uriensuur, insulien, C-peptied, adiponektien.

PREFACE AND OUTLINE OF THE STUDY

This thesis consists of three manuscripts submitted for publication, of which two were accepted and published. Following Chapter 1 (Introductory chapter), Chapter 2 determines differences in uric acid levels as well as differences in correlates between uric acid levels and cardio-metabolic parameters within African and Caucasian men. Chapter 3 investigates the possibility of an insulin-blood pressure relationship within the African and Caucasian population. Chapter 4 assesses the relationship between ageing and adiponectin levels from the perspective of renal function in African and Caucasian people. Chapter 5 contains a summary and discussion of all the results provided, conclusions are drawn and recommendations are made. The relevant references are provided at the end of each chapter according to the authors' instructions of the specific journal in which the articles were published or submitted for publication. In order to keep the references in this thesis uniform, the technical style for the references used in the manuscripts submitted for publication are according to the relevant Author Instructions. For Chapters 1 and 5 references are according to the Vancouver style.

A brief description of the content of the different chapters is given below:

Outline of the study

CHAPTER	CONTENT
Chapter 1	General introduction, literature review, motivation, aims, objectives, and hypotheses
Chapter 2	Serum uric acid and the cardiovascular profile of African and Caucasian men
Chapter 3	Ethnic and gender differences regarding the insulin-blood pressure relationship
Chapter 4	Ageing and adiponectin levels in an African population: an investigation from a renal perspective
Chapter 5	General findings and conclusions

❖	Manuscript 1 (Chapter 2):	Accepted and published in *Journal of Human Hypertension* (2009)
❖	Manuscript 2 (Chapter 3)	Accepted and published in *Diabetes Research and Clinical Practice* (2007)
❖	Manuscript 3 (Chapter 4)	Submitted to *Regulatory Peptides* (2010)

AUTHORS' CONTRIBUTIONS

The contribution of each of the researchers involved in this study is given in the following table:

Name	**Role in the study**
Miss. IM Palmer (M.Sc.) (Physiologist)	Responsible for literature searches, statistical analyses, collection of data, design and planning of manuscripts, interpretation of results and writing of all manuscripts
Prof. AE Schutte (Ph.D.) (Physiologist)	Promoter. Supervised the writing of the manuscripts, study design, collection of data, as well as initial planning and design of manuscripts
Prof. HW Huisman (Ph.D.) (Physiologist)	Co-promoter. Supervised the writing of the manuscripts, collection of data, as well as initial planning and design of manuscripts

The following is a statement from the co-authors confirming their individual role in each study and giving their permission that the three manuscripts may form part of this thesis.

I declare that I have approved the above-mentioned manuscripts, that my role in the study, as indicated above, is representative of my actual contribution and that I hereby give my consent that they may be published as part of the Ph.D. thesis of Lanthé Palmer.

Prof. AE Schutte

Prof. HW Huisman

CHAPTER 1

INTRODUCTION

1. GENERAL INTRODUCTION

1.1 Hypertension in Africa

The prevalence of hypertension within the African population has made a dramatic twist within the last 80 years. According to an article published by Donnison in 1929 (1), the prevalence of hypertension was unheard of. To the contrary, hypotension was much more common within a native Kenyan population. This observation was also confirmed by another study conducted by Williams in Uganda (2). A study performed by Kaminer and Lutz in 1960 (3) also revealed lower blood pressure levels in Bushmen from Sub-Saharan Africa.

Today, things look vastly different. The prevalence of cardiovascular disease (CVD) especially hypertension, evolved from a relative rarity to a major public health concern within the black population (4-7). The widely held perception that the burden of disease in Sub-Saharan Africa is composed mainly of communicable diseases is being set aside. This switch from communicable diseases to more chronic non-communicable diseases is known as "epidemiological transition" (8,9). Despite considerable in-depth studies regarding CVD, it still remains one of the leading causes of morbidity and mortality, and it is predicted to increase substantially in South Africa over the next few decades if measures are not taken to combat the trend (10).

Several epidemiological studies revealed that the African population has a much higher prevalence of hypertension and more severe target-organ damage compared to their Caucasian counterparts (4-7). Numerous contributing factors involved in CVD have been placed under extensive investigation over the past few years to establish possible associations and perhaps even cause-and-effect. However, most of these risk factors have been investigated within African-American or other African populations. Therefore, it is paramount to investigate risk factors linked to the high susceptibility of CVD within the black South African population. In Figure 1.1 a few possible risk factors are illustrated.

Figure 1.1: Modifiable, non-modifiable and other risk factors for cardiovascular disease. (Collected from various sources: (11,12))

It is not feasible to investigate all possible risk factors, thus, for the scope of this study only a few potential risk factors were selected to scrutinise and elucidate more on their possible involvement and contribution to the high prevalence of cardiovascular dysfunction within the black South African population.

2. MOTIVATION, AIMS, OBJECTIVES AND HYPOTHESES FOR EACH MANUSCRIPT

This thesis consists of three manuscripts submitted for publication. Since the relevant literature background for each manuscript is discussed in the papers and in the literature section, only a brief motivation for each chosen topic will be provided here.

2.1 Uric acid and the cardiovascular profile of African and Caucasian men (Chapter 2)

Motivation

The importance of uric acid as a risk factor for cardiovascular disease has been debated and investigated over the past few years (13-17). In a previous study we revealed that African women from South Africa have significantly lower uric acid levels compared to their Caucasian counterparts (18).

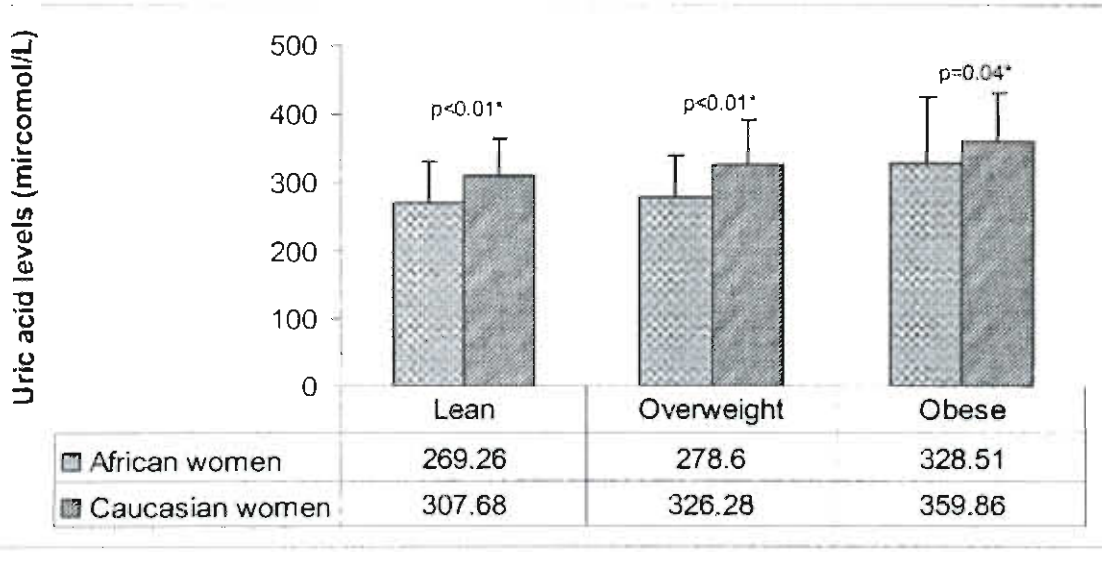

Figure 1.2: Uric acid levels of African and Caucasian women for the different obesity levels after adjusting for age and waist circumference (values are mean ± standard deviation) (adopted from ref (18)).

These results contradict the literature which identifies the black population as a high-risk group regarding elevated serum uric acid levels (19-21). Our previous study only

included women and, therefore, no conclusion regarding uric acid levels in African and Caucasian men could be drawn. In their study Fang and Alderman (21) reported higher uric acid levels in African men compared to African women. Due to uric acid's strong link with cardiovascular disease (13,15,21-23) and the fact that the African men are extremely vulnerable to the development of hypertension (5,6), it is of utmost importance to investigate uric acid as a possible risk factor related to the high prevalence of cardiovascular disease amongst this group.

Aim

To investigate uric acid levels in African and Caucasian men.

Objectives

1. To determine whether differences in uric acid levels exist between African and Caucasian men.
2. To establish possible ethnic differences in correlates between uric acid and cardio-metabolic variables.

Hypotheses

Based on our previous work and the literature, the following hypotheses were formulated:

1. African men have lower uric acid levels compared to Caucasian men.
2. African men show stronger correlations between uric acid and cardio-metabolic variables compared to their Caucasian counterparts.

2.2 Ethnic and gender differences regarding the insulin-blood pressure relationship (Chapter 3)

Motivation

Ageing is associated with several physiological changes in the body. Such changes include endocrinological alterations in the synthesis, secretion, circulating levels, metabolism, and biological activity of hormones (24). Age-related insulin secretory dysfunction is associated with increased insulin and C-peptide levels, which is frequently

characterised by insulin resistance and subsequently type 2 diabetes (25,26). Several epidemiological studies have shown that insulin secretory dysfunction associated with increasing age is linked to cardiovascular dysfunction (27-29), and might be the underlying cause of age-associated cardiovascular diseases such as hypertension. However, most of these studies only included African-Americans (30) and Caucasians (25), and data within a South African context are lacking. Furthermore, Schutte *et al.* (31) proposed a possible turnaround in the relationship between insulin and blood pressure, suggesting a more positive association within younger individuals, and a more negative association within elderly individuals.

It is, therefore, essential to have a better understanding of age-related changes in insulin secretion as well as changes in the insulin-blood pressure relationship, and how they relate to the high propensity of hypertension within the African population (5,6). Data gathered can also be applied to the development of preventive measures and therapeutic interventions within the African group.

Aim

To establish possible ethnic and gender differences regarding the insulin-blood pressure relationship within a South African context.

Objectives

1. To compare African and Caucasian groups with regards to the changes in the concentrations of fasting plasma insulin and C-peptide levels with increasing age.
2. To determine the relationship between fasting insulin/C-peptide with blood pressure of Africans and Caucasians using stratified age groups.

Hypotheses

Based on the available literature, the following hypotheses were formulated:

1. African and Caucasian people indicate an increase in insulin and C-peptide with increasing age.
2. African and Caucasian people show a positive association between insulin and blood pressure within younger individuals, whereas the older individuals tend to have a more negative association between insulin and blood pressure.

2.3 Ageing and adiponectin levels in an African population: an investigation from a renal perspective (Chapter 4)

Motivation

Adiponectin is known as a cardiovascular-protective adipokine (32,33) due to its anti-atherogenic (34,35), anti-diabetic (35) and anti-inflammatory (36) properties. Since cardiovascular disease is allied with morbidity and mortality in the elderly population (37-39), it is expected that this important adipokine will show an inverse relationship with ageing. Conversely, previous studies have indicated that with an increase in age, there is a concomitant rise in adiponectin levels (40-42). In their paper, Isobe *et al.* concluded that this age-related incline in adiponectin levels can be explained in terms of impaired renal function (41).

Yet this observation is challenged by an article published by Guebre-Egziabher *et al.* (43) where it was reported that elevated adiponectin was more related to metabolic disturbances, especially obesity, than to a decline in renal function *per se*.

Aim

To assess the relationship between ageing and adiponectin levels from the perspective of renal function in apparently healthy African and Caucasian people.

Objectives

1. To establish whether differences exist regarding adiponectin levels between Africans and Caucasians and how these levels change with an increase in age.
2. To determine renal function by means of estimated creatinine renal clearance within each of the ethnic groups, and how this correlates with adiponectin and obesity levels with ageing.

Hypothesis

Based on the available literature, the following hypotheses were formulated:

1. Africans have lower adiponectin levels compared to Caucasians, and both Africans and Caucasians will show a rise in adiponectin levels with increasing age.
2. Renal function (estimated renal clearance) has a strong positive correlation with adiponectin levels, but is dependent on metabolic disturbances.

3. LITERATURE REVIEW

3.1 Essential hypertension and its prevalence in South Africa

Essential hypertension is a common cardiovascular disorder and is multi-factorial in nature. The etiology differs immensely amongst different populations of the world, and by definition, essential hypertension refers to high blood pressure with no identifiable cause, and accounts for 95 to 99% of the cases reported (44). A few decades ago, Arthur Guyton proposed that every type of hypertension starts with volume overload due to the impaired ability of the kidney to excrete salt. However, researchers later on discovered that in essential hypertension, the kidney is the victim rather than the culprit, and it is now seen as a progressive cardiovascular disorder arising from complex and interrelated variables (45).

According to the World Health Organization (WHO)/International Society of Hypertension (ISH) blood pressure can be classified as follows (46):

Table 1.1: Classification of hypertension according to the World Health Organization (WHO)/International Society of Hypertension (ISH)

JNC 7 Blood pressure category	SBP (mmHg)	DBP (mmHg)
Optimal	<120	<80
Normal	120-129	80-84
High normal	130-139	85-89
Hypertension:		
Grade 1 (Mild)	140-149	90-99
Grade 2 (Moderate)	150-179	100-109
Grade 3 (Severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

The guidelines from the World Health Organization (WHO)/International Society of Hypertension (ISH) are similar to the guidelines stipulated by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC). However, Europe is a

more homogenous community and the ESH/ESC guidelines are more appropriate for Europeans, whereas the WHO/ISH guidelines were endorsed more globally.

Hypertension is becoming a public health emergency worldwide, and despite intensive research, the global prevalence of CVD for the year 2000 was 26.4%, with a projected prevalence increase of 60% for the year 2025 (47). The current situation in South Africa is not better, and reflects the global trend with concerning high figures. According to recent studies conducted (7,48), it was revealed that the prevalence of hypertension is distressingly high within the black population. Adding to the burden of high epidemiological prevalence is the fact that hypertension occurs at a much younger age in the black population, being more severe and leading to earlier subsequent organ damage (48-50).

Despite the increasing incidence of hypertension in black South Africans, the underlying mechanisms related to high blood pressure are ill-defined and more research should be done to address this issue.

3.2 Basic principles and hemodynamics of the cardiovascular system

3.2.1 *Arterial blood pressure*

Blood pressure consists of two basic components namely the steady component (mean arterial pressure [MAP]) as well as the pulsatile component (systolic [SBP], diastolic [DBP] and pulse pressure [PP]) (51). Mean arterial pressure gives an indication of the average pressure during the cardiac cycle, and is determined by two hemodynamic measurements: cardiac output and vascular resistance (52,53) and is usually estimated by the following equation:

$$MAP \approx DBP + 1/3\,[SBP - DBP] \qquad 1.1$$

However, this rule has recently been challenged (54), and a new calculation method has been proposed using a reliable numerical integral of the calibrated pressure wave. According to this study, the mean pressure is underestimated using the traditional formula, however, this can be corrected by adding 40% of the pulse pressure to the diastolic pressure i.e.:

$$MAP = DBP + 0.4 \times PP \quad (1.2)$$

The pulsatile component on the other hand is influenced by: ventricular ejection, large artery compliance and timing of wave reflection (52,53), and is estimated by pulse pressure (PP):

$$PP = SBP - DBP \quad (1.3)$$

In contrast to mean arterial pressure, the pulse pressure does not remain constant throughout the circulatory system (53) with the central pulse pressure being lower than the brachial pulse pressure (55). This is the consequence of a combination of two hemodynamic phenomena: 1) as the blood propagates through the vascular conduits toward the peripheral vasculature, there is a progressive reduction in blood vessel diameter and increase in vascular resistance (56) and 2) changes in timing and amplitude of wave reflections (56).

Ventricular ejection generates a pressure wave that propagates in a forward direction, away from the heart (57) at a speed known as pulse wave velocity (51,57). This wave is reflected back toward the heart from any point in the arterial tree where a discontinuity is found (51,57) for instance at an arterial branch. Thus, the pulse wave velocity provides an overall, accessible estimate of the elastic properties of the central and peripheral arteries (58,59).

In healthy individuals, the reflected wave reaches the heart during the diastolic phase (58) promoting coronary perfusion. However, in the event of arterial stiffness the reflected wave reaches the aorta during the systolic phase augmenting the central blood pressure (51,58). Since the heart only perceives central pressure and not brachial pressure (60), the left ventricular afterload increases (60), consequently promoting left ventricular hypertrophy (61), and concomitant congestive heart failure (62).

3.2.2 *Arterial stiffness and vascular resistance*

The arterial system has two essential functions in the cardiovascular system. The first is a buffering function against the pressure oscillations (63,64). The second is to act as a conduit system – delivering blood at high pressure to peripheral tissues (64).

During systole, approximately 40% of the stroke volume is moved forward into the peripheral vasculature; however, the remaining 60% of the blood remains within the larger elastic arteries (51). During diastole, the arteries recoil back to their original shape and the accumulated blood gradually moves forward towards the peripheral tissues (51), providing constant perfusion to the tissues, especially to the coronary arteries.

In order to counteract the sudden rise in pressure, the walls of large central arteries are rich in elastin, a resilient protein, which allows the vessels to distend (65). It also contains a collagen fibre network which is efficient at maximum pressures (65,66). This ability of larger arteries (central arteries) to capacitate increased volumes of blood during systole is known as the Windkessel compliance effect (67). Furthermore, to ensure a steady and constant blood flow in the arteriolar and capillary system, a certain degree of resistance must be applied to the blood flow. The necessary resistance is determined by the cross-sectional diameter of the peripheral vascular system, and is known as vascular resistance (53).

Arterial stiffness, vascular resistance and associated cardiovascular risks

Arterial stiffness has long been recognized as a risk factor for cardiovascular diseases (68-70). This decrease in elasticity (increased stiffness) holds great potential risk for cardiovascular diseases (71), including myocardial infarction, left ventricular hypertrophy and hypertension (72,73). There are a number of factors and pathophysiological states that will significantly decrease arterial distensibility and compliance of the larger/conduit arteries. Atherosclerosis is considered one of the most important risk factors for arterial stiffness and is a progressive disease instigated from the amalgamation of endothelial dysfunction and inflammation (74). Continuous augmented central blood pressure leads to increased wall stress, responsible for plaque formation via indirect stimulation of vascular cell adhesion molecules (VCAM) and intercellular adhesion molecule – 1 (ICAM-1) (74).

A previous study reported that African-Americans are considered to be at high risk regarding arterial stiffness and that it occurs earlier in life or that it is more accelerated compared to Caucasians (75), possibly due to earlier exposure to risk factors. Ethnic differences in arterial stiffness are, therefore, of great importance, especially in the black

South African population due to their high susceptibility to cardiovascular diseases (5,6,7).

Increased vascular resistance is a hallmark of essential hypertension (76), and results primarily from a reduced luminal diameter (77,78). These changes in resistance might contribute to the pathogenesis of hypertension (79). A reduction in the luminal diameter of the vessels will result in an increase in the resistance, and a concomitant elevation of blood pressure (80).

A key role has been assigned to the vascular endothelium in the participation of cardiovascular dysfunction. Previously viewed as an inert vascular lining, the endothelium is now considered proactive, releasing vasoactive substances to regulate vasomotor function, and affect hemostasis (81,82). A trademark of endothelial dysfunction is impaired nitric oxide release (83), a potent vasodilator opposing the effects of endothelium-derived constrictors such as endothelin-1 and angiotensin-II (83). When the endothelial wall is damaged or injured, it loses its protective characteristics and converts to one that is vasoconstrictive, procoagulant and antifibrinolytic (81,84). Thus, the interaction of increased arterial stiffness and vascular resistance as well as vascular dysfunction is a detrimental combination, and can exacerbate the development of high blood pressure.

3.3 Risk factors for hypertension investigated in this thesis

As illustrated by Figure 1.1, hypertension is a multi-factorial condition and the extent of its etiology stretches far beyond the scope of this study. However, an attempt was made to look at a few possible contributing culprits. These include age, insulin and C-peptide, adiponectin as well as uric acid – all of which will be discussed in more detail below.

3.3.1 Age

"Senectus ipsast morbu – senescence is a disease in itself" (85)

Human ageing is a complex process and is one of the most harmful, non-modifiable risk factors for cardiovascular disease. It plays a pivotal role in the underlying cause of hypertension and atherosclerotic disease (66,86), and with the world population of

people over 70 yrs estimated at approximately 610 million (87), it is becoming a rising public concern.

Ageing manifests as structural and functional changes within the cardiovascular system and might predispose the ageing heart to develop pathological changes (88). These changes are often the platform and hallmark of cardiovascular dysfunction observed in the elderly population (89,90).

Ageing and the heart

Cardiac structural alterations associated with ageing include cardiomyocyte cell loss, with subsequent hypertrophy of the remaining myocytes (88), and left ventricular hypertrophy (91). Hypertrophy of the left ventricle leads to decreased ventricle chamber diameter, collagen deposition (92) as well as a diminished responsiveness to β-adrenergic stimulation (85).

At a functional level, a decline in cardiac function may result from a diminution of the intrinsic contractile properties of the cardiac muscle. Prolonged contraction duration (93) results in a diminished heart rate, with each heartbeat exhibiting an increased end-diastolic end-filling (85).

Ageing and the vasculature

The vascular system is markedly altered by the ageing process, and is the main factor responsible for structural and functional changes in the arterial wall (94). Progressive ageing is accompanied by elastic fibres that are more disorganised, thinner and more fragmented compared to those of younger individuals (94). This might at least be partially explained by the up-regulation of elastase activity (95), a proteolytic enzyme responsible for fragmentation of elastin fibres found in the large elastic vessels as well as the skin (96). Elastin fibres play an essential role in the arteries, and any alterations of elastin will result in concomitant changes in arterial distensibility (86). Arterial stiffness is another sequel of arterial ageing due to the deposition of extracellular matrix (collagen), fibronectin as well as smooth muscle cells within the arterial compartments (97,98).

It is clear that vascular remodelling contributes in part to the high prevalence of cardiovascular dysfunction observed in the elderly population. The most fundamental of

these are impaired arterial distensibility. As a consequence of arterial stiffness, the pulse wave reflection returns during the late systolic phase, causing an increase in central systolic blood pressure (99) and ventricular afterload, and consequently left ventricular hypertrophy. Increased vascular stiffness also induces a raised pulse pressure (69) resulting in thickening of the intima media layer (100), strongly associated with cardiovascular diseases (101,102).

3.3.2 Insulin, C-peptide and associated vascular function

Insulin is a small peptide hormone, synthesised in significant quantities in the β-cells of the pancreas (103,104). It comprises of two polypeptide chains: A with 21 amino acid residues and B with 30 amino acid residues, connected to each other via disulphide bridges (103). Insulin is synthesized as pre-proinsulin which is the precursor for pro-insulin (103).

Pro-insulin consists of the two chains (A and B chains) with a connecting peptide, the so-called C-peptide connecting the two chains (103). The conversion of pro-insulin into mature insulin results from the cleavage of the C-peptide from the A and B chains (104). This is accomplished via the action of pro-hormone convertase 2 and 3 as well as carboxy peptidase H (103). The two peptides are then stored in secretory granules (105) from where they are later co-released in equimolar amounts into the circulation (106).

For many years, a general belief existed amongst researchers that C-peptide possesses little if any physiological function (107,108), that it was a mere by-product of insulin synthesis (109) and at most, facilitates the folding of the pro-insulin molecule and the generation of the disulfide bridges between the A-chain and B-chain (110).

Scientists argued that for peptides to be biologically active and exert their functions, they need a so-called "active site" which plays an important role in the binding of the ligand to the receptor (111). The lack of a known active site has long hampered the recognition of C-peptide as a biologically active hormone (111).

Another observation kept researchers believing that C-peptide was biologically inactive, and that was that C-peptide varies significantly between different species with regards to its amino acid sequence and peptide length (105,109).

However, over the last few years, new evidence emerged to contradict this view. Observations from several studies provide a basis for the hypothesis that C-peptide is biological active with several physiological effects. These possible effects of C-peptide will be discussed in the following paragraphs.

Cardiovascular and metabolic function

Insulin is well known for its metabolic importance at cellular level, which encompasses carbohydrate metabolism, lipid metabolism and protein synthesis (112). Insulin is in many ways involved in carbohydrate metabolism. Its effects extend from facilitated diffusion of glucose into cells (113), increasing glycogen synthesis (114), stimulating glycolysis (115) and inhibiting gluconeogenesis (116). Lipid metabolism effects include fatty acid synthesis in adipocytes and the liver, as well as formation and storage of triglycerides (112).

In the cardiovascular system, insulin stimulates the production and release of several endothelial mediators, responsible for the dynamic control of vascular function (117). These include nitric oxide, endothelin-1 and reactive oxygen species (117,118). Through an array of signaling pathways, insulin mediated production of endothelial nitric oxide, starts with the phosphorylation of the insulin receptor substrate 1 (IRS-1) (118), leading up to increased endothelial nitric oxide synthase activity and nitric oxide production. In addition to its vasodilatory actions, insulin also exerts opposing vasoconstrictive effects resulting from sympathetic outflow (28). In healthy humans hyperinsulinemia increases sympathetic nerve activity (28,119), however, in the presence of insulin resistance, insulin-mediated vasodilation is blunted (120) and the vasoconstrictive pressor effects of insulin become dominant. This mechanism might elevate vascular resistance, contributing to elevated blood pressure (28).

During the condition of insulin resistance the tissues have a diminished ability to respond to the action of insulin – and usually the precursor for type 2 diabetes (121,122). To compensate for the resistance, the pancreas secretes even more insulin (hyperinsulinemia), and over time, the excess insulin secretion leads to a decline in insulin production as a result of exhaustion of the β-cells (121). Insulin resistance is a prominent component of cardiovascular diseases, including hypertension, coronary artery disease, and atherosclerosis (28,118), which are all characterised by endothelial

dysfunction (118). Several mechanisms linking endothelial dysfunction and diabetes or insulin resistance have been proposed. One possible mechanism linking insulin resistance and endothelial dysfunction includes stimulation of plasminogen activator inhibitor-1 (PAI-1) (124), a major inhibitor of fibrinolysis (125).

Additionally it is hypothesised that the elevated C-peptide levels might deposit in the vessel walls in early atherogenesis, due to the increased endothelial permeability (126). Through chemotactic effects C-peptide induces the migration of monocytes and $CD4^+$ lymphocytes into the sub-endothelial space and the intima (Figure 1.3). The proposed mechanism might be a possible explanation why patients suffering from Type 2 diabetes and insulin resistance are so vastly susceptible to the development of atherosclerotic lesions.

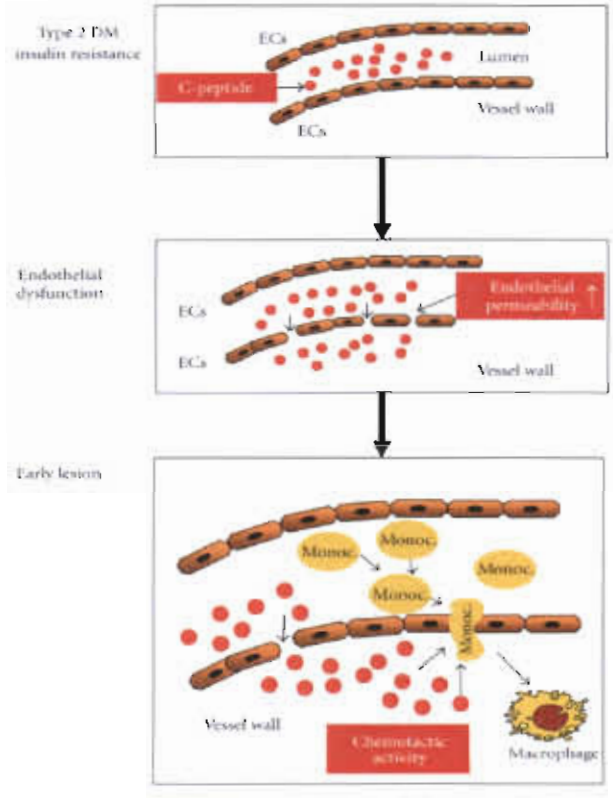

Figure 1.3. Potential role of C-peptide in early pathogenesis with insulin resistance and early Type 2 diabetes mellitus. (Type 2 DM: Type 2 diabetes mellitus; ECs: endothelial cells; Monoc: monocytes) (Reprinted from (126))

Another mechanism proposed for the development of plaque formation in diabetic patients, is that insulin (28,127) and C-peptide (128) promote smooth muscle cell proliferation, a hallmark of the atherosclerotic process (126). However, contradictory results were found by Kobayashi *et al.* (128) who demonstrated an inhibition of rat smooth muscle cells proliferation after treatment with human C-peptide.

According to Nakamoto *et al.* (129), coronary blood flow is increased during the early stages of diabetes mellitus. In their research they found that the administration of C-peptide to diabetic rats revealed no change in coronary blood flow, and an increase in nitric oxide production. However, a concomitant administration with insulin decreased both the coronary flow and nitric oxide production. It could be that in the presence of hyperinsulinemia the vasodilatory effects of elevated C-peptide are blunted. The hallmark of endothelial dysfunction is impaired nitric oxide release (130).

Nitric oxide is a potent vasodilator, opposing the effects of endothelium-derived constrictors such as angiotensin II (Ang II) and endothelin-1 (131,132). A reduction in the bioavailability of nitric oxide is an important step in the development of endothelial dysfunction and atherosclerosis, yet there are several studies performed that clearly showed that C-peptide has a nitric oxide-mediated vasodilatory effect (133).

Previous studies revealed that African women have a higher prevalence of Type 2 diabetes compared to Caucasian women (7% vs. 3.6%) (134-136). Overall, Africans tend to be more insulin resistant compared to Caucasians (137,138). Now more than a decade later, data concerning the prevalence of insulin resistance/Type 2 diabetes in the black South African population are still limited, and with urbanisation and obesity levels on the rise (139), it is so much more important to investigate this matter.

Renal function

Renal microvascular responses to insulin include renal vasodilation (140) mediated predominantly by the endothelial release of nitric oxide (141,142). Insulin also exerts a vasoconstrictor influence on renal vasculature via activation of the renin-angiotensin-system (143), however, in insulin-sensitive individuals the vasodilator effect is much greater than the vasoconstrictor effects (143). A possible mechanism proposed for the vasoconstrictor effect of insulin is that insulin stimulates proximal sodium reabsorption

(144,145) resulting in a decreased delivery of sodium to the macula densa, which in return will stimulate renin secretion (146). A study conducted by DeFronzo *et al.* (147) revealed that insulin also enhances phosphate reabsorption within the proximal tubular as well as sites distal to the proximal tube. Insulin resistance is also often accompanied by hyperuricemia (148). It is proposed that hyperinsulinemia enhances uric acid reabsorption via the proximal tubules leading to elevated levels of uric acid (149), which are also associated with cardiovascular disorders.

Patients suffering from Type 1 diabetes usually show glomerular hyperfiltration during the first years after the onset of the disease (150,151). In contrast, patients that suffer from Type 2 diabetes, who have normal levels of insulin and C-peptide (152) usually do not show any signs of the development of glomerular hyperfiltration or hypertrophy. Several experimental studies on rats delivered conclusive results that short-term infusion of C-peptide in Type 1 diabetic rats showed a marked decrease in glomerular filtration rate (105,151,153) – therefore relieving the condition of glomerular hyperfiltration. It can be speculated that C-peptide has a possible reno-protective function.

Insulin, C-peptide and obesity

Obesity, especially central obesity, represents one of the primary factors for the development of insulin resistance/hyperinsulinemia (154,155). A possible mechanism for the strong association between obesity and insulin resistance is that adipose tissue seems to alter the action of insulin through the release of several metabolically active adipokines (154). Increased adipose mass in obesity could lead to alterations in adipocytes hormones (adipokines) that regulate insulin sensitivity.

One such an adipokine is adiponectin, which in addition to its anti-inflammatory (36) and anti-atherogenic (34) properties, also exhibits insulin-sensitising characteristics (154). The primary mechanism by which adiponectin enhances insulin sensitivity seems to be mediated through the oxidation of fatty acids and the inhibition of hepatic gluconeogenesis by inhibiting key enzyme activities (155,156). Whereas obesity is usually associated with increased secretion of adipokines, adiponectin shows an inverse relation with increased adipose mass (154), in part associated with the development of insulin resistance.

Leptin is another adipocyte-derived hormone that plays a pivotal role in the regulation of food intake and energy expenditure (157). It is also responsible for lipid and glucose metabolism (158) as well as inhibiting insulin action by acting directly on pancreatic β-cells (159). Leptin resistance often accompanies obesity (160), resulting in defective leptin action on the β-cells, with consequential hyperinsulinemia.

Inflammatory markers produced by adipocytes include tumour necrosis factor-α (161,162) as well as interleukin-6 (163,164), both known to alter insulin sensitivity at different pathway levels (162,165,166).

The effect of age on insulin and C-peptide

Insulin resistance and impaired glucose tolerance are inevitable of the ageing process and known to incline progressively with increasing age (167). This can partially be explained by insulin secretory defects and action (25,168). Although the exact mechanisms responsible are not fully elucidated, a few possible mechanisms are hypothesized.

GLUT-4 protein is the primary transporter in skeletal muscle responsible for insulin-stimulated glucose uptake (169). Levels of muscle GLUT-4 decline with increasing age, and depletion of this transporter results in insulin resistance and diabetes (170). Another possible explanation is a diminished sensitivity of the β-cell to incretin hormones due to impairments in secretion and action of glucagon-like-peptide 1 and glucose-dependent insulinotropic peptide (168,171).

Studies in both animals (172,173) as well as humans (174) revealed significant age-related decline in insulin secretion with increasing age. This might possibly be contributed to progressive loss of β-cell function (175) with increasing age.

3.3.3 Adiponectin

Adiponectin (also referred to as AdipoQ, Acrp30 or apM1) is an expression of the apM1 gene (176), consists of 244-amino-acids and accounts for ~ 0.01 % of the total plasma proteins (43). It is composed of an N-terminal collagen-like sequence and a C-terminal globular domain (177), and in circulation can either exist as a full-length or a smaller proteolytic cleavage fragment (176), however, in plasma it exists mainly as a full-length

formation (177). In serum it is found as multiple oligomeric forms namely lower molecular weight (LMW) or as high molecular weight (HMW) (176).

Adiponectin is an adipocyte-derived hormone (178) with circulating concentration levels of about 5 - 30µg/ml (34). It is secreted in response to metabolic stimuli in order to sensitise the liver and muscles to the actions of insulin (179). The plasma half life of adiponectin is about 2.5 hours (180) compared to most other polypeptide hormones with a half-life time between 15 and 30 min.

Cardiovascular and metabolic function

Adiponectin received growing attention as a therapeutic treatment for cardiovascular disease due to its broad range of cardiovascular protective properties. Several studies indicated a link between low levels of adiponectin and the prevalence of cardiovascular risk events (181-185). Adiponectin has been shown to play an essential role in the suppression of inflammation (36,186) often associated with metabolic disorders that may result in Type 2 diabetes. According to researchers, it was found that adiponectin induced the expression of anti-inflammatory cytokines such as interleukin-10 (IL-10) (188,188) and interleukin-1 receptor antagonist (IL-1RA) in a variety of cells including monocytes and monocyte-derived macrophages (187). Interleukin-10 can inhibit the production of other pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) as well as induce further production of IL-1RA, another anti-inflammatory product (187).

Adding to the abovementioned protective action is another beneficial feature of adiponectin, namely its anti-atherogenic properties (35). Adiponectin reduces monocyte attachment to aortic endothelial cells. This action is mediated by inhibiting the expression of vascular cell adhesion molecules (VCAM), intercellular adhesion molecule (ICAM), and E-selectin (189). Furthermore, adiponectin also suppresses smooth muscle cell proliferation and migration, induced by platelet-derived growth factor (PDGF) (190). Other vascular functions exerted by adiponectin include direct production of endothelial nitric oxide via the phosphatidylinositol 3-kinase pathways involving phosphorylation of endothelial nitric oxide synthase by means of activation of AMP protein kinase (34). The ability of adiponectin to stimulate nitric oxide production directly might lead to vasodilation and increased blood flow, enhancing glucose uptake (191), suggesting the notion that adiponectin possesses insulin-mimetic and insulin-sensitising actions (192).

The possibility that adiponectin directly stimulates GLUT-4 receptors cannot be ruled out (193,194). Other metabolic actions include regulating energy balance by stimulating free fatty acid oxidation (195).

Disparities exist concerning ethnic differences in adiponeclin levels. While some studies found that Africans have a lower adiponectin level compared to Caucasians (196,197), others have found no differences (198). Due to its beneficial properties within the cardiovascular system, it is important to investigate adiponectin and its associations with cardio-metabolic variables for possible treatment of cardiovascular dysfunction, especially within the black population.

Renal function

Decreased glomerular filtration rate (GFR) as observed in kidney disease, is often accompanied by elevated adiponectin levels (41) (Discussed in more detail under topic "*Ageing and adiponectin*"). It has been suggested that adiponectin is elevated compensatorily as a counter protective mechanism to improve endothelial dysfunction present in kidney disease (199).

Adiponectin and obesity

Adiponectin is an adipocyte-derived hormone (200), but unlike most other adipokines such as leptin (201), TNF-α (202) and resistin (203), circulating concentration levels of adiponectin tend to decrease with increasing adipocyte tissue mass (40). Hypoadiponectinemia is associated in particular with increased visceral fat (204), which might act as the causal link between obesity and associated cardiovascular diseases.

Ageing and adiponectin

Adiponectin levels have been reported to be elevated within the elderly population (42,206), but the exact underlying mechanism has not been clarified. However, a few possible mechanisms have been postulated.

The potential role of the kidney has been investigated as a possible culprit in the age-related hyperadiponectinemia (41,206). Ageing is associated with a number of physiological and pathophysiological changes, including renal impairment (207). Zocalli

et al. found significantly elevated levels of adiponectin in individuals with end-stage renal disease (208) entailing a central role of the kidneys in adiponectin clearance.

Another possible role can be attributed to sarcopenia, and is defined as the age-related loss of lean muscle mass (209,210). Adiponectin receptors, especially AdipoR1 are located within muscle cells (211), and with a loss in lean muscle, there might be a concomitant decline in these receptors, with compensatory hyperadiponectinemia and subsequently adiponectin resistance.

3.3.4 Uric acid

Uric acid is the final oxidation product of purine nucleotides catabolism (212) catalysed by the enzyme xanthine dehydrogenase/xanthine oxidase (XDH/XO) (213). It is mainly produced in the liver and the gut (214) and then secreted into the blood stream. However, according to a study by Matsuura (215), it was found that uric acid is also associated with visceral obesity (discussed in-depth later).

In most mammals uric acid is degraded by the hepatic enzyme, urate oxidase (uricase), to allantoin and clearance is reliant largely upon renal excretion (215). Approximately two thirds of the daily turnover of uric acid is cleared by means of renal excretion, whereas the remaining one third is excreted via the gut as faeces (216).

Cardiovascular function

There is an ongoing debate about the role of uric acid and its relation to cardiovascular disease. While there is no controversy about serum uric acid being a risk marker (13,22,23), the topic of uric acid as a risk factor is still disputed amongst researchers (17,217-220). Despite the disparities regarding elevated uric acid levels (hyperuricemia) as a cardiovascular risk marker or a risk factor, it is still important to understand the mechanism by which uric acid relates to cardiovascular function.

Hyperuricemia levels are commonly associated with hypertension (23,221), and present in approximately 25% of hypertensive subjects and 75% of people suffering from malignant hypertension (215). Although exact mechanisms are not fully understood, it is speculated that hypertension can develop due to uric acid-mediated renal vasoconstriction resulting from impaired endothelial nitric oxide availability (215,222,223)

especially at the macula densa (224), with a key role of the renin-angiotensin system (223,224).

Additional vascular effects include vascular smooth muscle cell proliferation (225,226). There is also evidence that uric acid possesses the ability to exacerbate inflammation (215). Uric acid induces monocyte chemoattractant protein-1 (MCP-1) synthesis by activating mitogen activated protein kinase (p38 MAP) (226). Uric acid also stimulates human mononuclear cells to produce interleukin-1, interleukin-6 and TNF-α (227,228). Another study reported that uric acid increases the expression of endothelin-1 (ET-1) (229).

Uric acid and its detrimental effects on the vascular system have been discussed in the previous paragraphs but there is, however, one beneficial feature. Uric acid possesses powerful antioxidant properties (230) and constitutes as much as two thirds of the antioxidant capacity in the human plasma (231-233). It is particular effective in scavenging hydroxyl, superoxide, and peroxinitrate radicals (233). By binding with peroxynitrate, it forms a stable nitric oxide donor, thereby reducing the risk for potential peroxynitrate-induced oxidative damage, protecting the vascular system against oxidative stress (234). Superoxide dismutase (SOD3) is a critical enzyme in maintaining endothelial vascular function, and Hink *et al.* reported that uric acid can prevent the extracellular degradation of this important enzyme (235).

Perhaps somewhat paradoxical is the fact that uric acid can be converted to a pro-oxidant under certain circumstances producing reactive oxygen species instead of scavenging (236). In the early stages of atherosclerosis uric acid can act as an antioxidant, however, in the later, more developed stages of atherosclerosis, the antioxidant characteristics shift to take on those of a pro-oxidant.

According to several studies conducted, the black population is at higher risk for the development of hyperuricemia compared to Caucasian groups (19-21), conversely Alderman reports no ethnic difference (237) between African-Americans and Caucasians from the United States of America. Our own data have also shown lower uric acid levels in African women (18).

Renal function

Hyperuricemia is often a feature of insulin resistance (21), and this might be explained by the fact that hyperinsulinemia increase tubular reabsorption of sodium, resulting in a blunted ability of the kidney to excrete uric acid (238). Since uric acid clearance is mediated by the kidney, a reduction in glomerular filtration might lead to hyperuricemia (239).

Other effects include interstitial inflammation, microvascular rarefaction, afferent arteriolopathy and interstitial fibrosis (19).

Effect of obesity on uric acid

For many years, the general notion existed that adipose tissue acts only as a storage depot, however, this view is no longer valid, and adipose tissue is now considered a complex and highly active endocrine organ (240). As previously mentioned, adipose tissue secretes an extensive variety of adipokines including, leptin (201), TNF-α (202), resistin (203), and adiponectin (240) to mention but a few.

To add to the complexity of obesity, one must take into account an even more relevant part of obesity: namely fat distribution. Two types of fat deposition have been categorised – one is subcutaneous adipose tissue and is located mainly underneath the skin (241), and the second and perhaps the most important one, is visceral adipose tissue, and is characterized mostly by depots of adipose tissue around the abdominal area and the gastrointestinal organs (242). The difference between these two is of great importance since metabolic and cardiovascular complications are directly related to visceral tissue depots rather than subcutaneous depots (242-244). This also holds true for hyperuricemia. Studies revealed that high uric acid levels are to a greater extent associated with visceral obesity, than subcutaneous obesity (214,245). Even thought the exact mechanism is not clear, Matsuura *et al* suggest that free fatty acids (FFAs) which are often associated with visceral adipose tissue, might stimulate triglyceride synthesis in the liver (215). They further found a significant positive association between uric acid and triglycerides, suggesting that an overproduction of uric acid might be linked to increased triglyceride synthesis.

Ageing and uric acid

There is an age-related increase in serum uric acid levels noticeable especially in women (246). This might possibly be explained by commencement of menopause. Estrogen seems to have an enhancing effect on renal clearance of uric acid (247), however, with the onset of menopause, estrogen levels decline and the uricosuric effect is blunted (248), resulting in elevated uric acid levels.

To summarise, there is a broad extent of aspects identified as cardiovascular risk markers and factors. Those especially highlighted will be investigated further in the subsequent chapters.

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