A Prospective Study of Cardiovascular Disease and Its Risk Factors in Populations with Rheumatoid Arthritis that are at Different Stages of the Epidemiological Transition

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Declaration

This is to certify that this thesis is my work and has not been submitted before for any degree or examination at this or any other University. I have worked intensively together with particularly my supervisor Professor Patrick Dessein in the process. I performed the carotid ultrasound measurements in the patients enrolled at the Rheumatology Department of the Charlotte Maxeke Academic Hospital, Johannesburg which comprised approximately 50% of included patients in the current investigations. I also made all clinical assessments in these patients at the Charlotte Maxeke Academic Hospital and contributed to the conception of each of the studies, interpretation of the results and writing of the manuscripts.

This thesis is dedicated to all rheumatoid arthritis patients, locally and abroad.

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Publications arising from this work

1. Solomon A, Christian BF, Norton GR, Woodiwiss, Dessein PH. Risk factor in black and other Africans with established rheumatoid arthritis. J Rheumatol 2010;37:953-60.
2. Dessein PH, Woodiwiss AJ, Norton GR, Solomon A. Rheumatoid arthritis is associated with reduced adiposity but not with unfavourable major cardiovascular risk factor profiles and enhanced carotid atherosclerosis in black Africans from a developing population: a cross-sectional study. Arthritis Res Ther 2013;15:R96.
3. Solomon A, Woodiwiss AJ, Abdool-Carrim AT, Stevens BA, Norton GR, Dessein PH. The carotid artery atherosclerosis burden and its relation to cardiovascular risk factors in black and white Africans with established rheumatoid arthritis: a cross-sectional study. J Rheumatol 2012;39:1798-806.
4. Solomon A, Norton GR, Woodiwiss AJ, Dessein PH. Obesity and carotid atherosclerosis in African black and Caucasian women with established rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2012;14:R67.
5. Dessein PH, Norton GR, Joffe BI, Abdool-Carrim AT, Woodiwiss AJ, Solomon A. Metabolic cardiovascular risk burden and atherosclerosis in African black and Caucasian women with rheumatoid arthritis: a cross-sectional study. ClinExpRheumatol 2013;31:53-61.
6. Dessein PH, H-C Hsu, Tsang L, Millen AME, Woodiwiss AJ, Norton GR, Solomon A, Gonzalez-Gay MA. Kidney function, endothelial activation and atherosclerosis in black and white Africans with rheumatoid arthritis. PLoS One 2015;10(3):e0121693.doi:10.1371/journal.pone.0121693.

Impact factor of the journals in which the manuscripts were published

Arthritis Research and Therapy	3.979
Clinical and Experimental Rheumatology	2.724
Journal of Rheumatology	3.236
PLoS One	3.234

Abstract

Rheumatoid arthritis (RA) increases the risk of particularly atherosclerotic cardiovascular disease in developed populations. The sub-Saharan black African population is currently at an earlier epidemiological health transition stage. Consequently, black Africans experience a markedly reduced risk of atherosclerotic cardiovascular disease.

The main objectives of this thesis were to determine whether (1) the atherosclerotic cardiovascular risk burden is reduced in black compared to other African patients with RA; (2) RA impacts on cardiovascular risk factor profiles and ultrasound determined carotid intima-media thickness among black Africans and (3) the atherosclerosis burden and its association with traditional and non-traditional risk factors differ in black compared to white Africans with RA.

Black compared to other Africans with RA had more prevalent hypertension and obesity but smoked and consumed alcohol less frequently. However, the overall traditional and non-traditional atherosclerotic cardiovascular risk burden was as large in black as in other Africans with RA.

RA was not independently associated with unfavourable traditional and non-traditional atherosclerotic risk factors including systemic inflammation among black Africans. Carotid intima-media thickness was similar in black RA and non-RA Africans.

The carotid intima-media thickness and plaque prevalence were as large in black compared to white African patients with RA. Blood pressure, dyslipidemia, Framingham score, systemic inflammation and extraarticular manifestations were associated with atherosclerosis in white but not black African RA patients. The Arthritis Impact

Measurement Scales tension score was consistently related to atherosclerosis in black but not white African patients with RA.

Black African RA women experienced a markedly larger adiposity burden than their white counterparts. However, body mass index was associated with carotid intima-media thickness and waist-to-hip ratio with plaque in white but not black women with RA.

The US National Cholesterol Education Program Adult Treatment Panel III metabolic syndrome was identified in 30.8% of black compared to 9.7% of white African women with RA ($p = 0.009$). In white African RA women, the metabolic syndrome definition was associated with carotid intima-media thickness and the triglyceride criterion and number of metabolic syndrome criteria were associated with plaque. In black African RA women, only the blood pressure criterion was associated with carotid intima-media thickness, which represents mostly age and blood pressure induced hypertrophy of medial cells rather than atherosclerosis.

Reduced estimated glomerular filtration rate was found in 49.1% of black compared 30.6% of white African patients with RA ($p=0.004$). In Receiver Operating Characteristic curve analysis, eight of nine evaluated estimated glomerular filtration rate equations were associated with carotid artery plaque to a clinically useful extent for cardiovascular risk stratification in black but not white African patients with RA. By contrast, estimated glomerular filtration rate was related to the endothelial activation markers of monocyte chemoattractant protein-1 and angiopoietin 2 in white but not black African patients with RA.

In conclusion, the overall cardiovascular risk factor and atherosclerosis burden are currently as large in black compared to white African patients with RA. Modifiable traditional risk factors and disease characteristics were consistently unrelated to atherosclerosis in black

African patients with RA. Impaired kidney function comprised the only routinely available cardiovascular risk factor that was useful in identifying black African RA patients with high risk atherosclerosis.Systematic vascular imaging and possibly the use of novel cardiovascular risk biomarkers may be required for adequate cardiovascular risk stratification among black African patients with RA.

Abbreviations:

CVD	cardiovascular disease
RA	rheumatoid arthritis
SCORE	systematic coronary risk evaluation

Acknowledgements:

I would like to thank my supervisor and mentor, Professor Patrick Dessein and his wife Linda for their support, patience and dedication and without whom this dissertation would not have been possible. In addition, I would like to thank my wife Safiyya, my Mom Farieda and my children Rafeea, Aaqilah and Faaliha for their understanding and patience. Lastly a special note of thanks to my dad, Cassim Ahmed Solomon who tragically passed at the time the thesis was been prepared

Introduction

Rheumatoid arthritis (RA) is a prototypic chronic high-grade inflammatory and destructive joint disease. RA increases the risk of mostly atherosclerotic cardiovascular events to an extent that is as large as in patients with diabetes [1]. A recent meta-analysis of 14 studies among 41 490 patients with RA revealed a pooled relative risk for incident cardiovascular disease of 1.48 (95% CI 1.36 to 1.62) with a significantly increased risk of myocardial infarction and cerebrovascular accidents of 68% and 41%, respectively [2]. In a meta-analysis of 24 mortality studies among 111 758 RA patients, the weighted standardized mortality rate for cardiovascular disease death was 1.59 (95% CI 1.46 to 1.73) with a significantly increased risk of death from ischemic heart disease and cerebrovascular accidents of 59% and 52%, respectively [3]. Further, in a meta-analysis [4]of 13 studies that compared to the general population, the relative risk of a cardiovascular disease event is 2.59 (95% CI 1.77 to 3.79) and 1.27 (95% CI 1.16 to 1.38) in RA patients <50 years compared to those aged ≥50 years. The increased risk of cardiovascular events is therefore particularly high in young RA patients.

The presenting cardiovascular disease manifestationsalso differ in patients with RA compared to people without RA. In this regard, the frequencies of silent myocardial infarction, sudden death, death after an acute coronary

syndrome and heart failure with preserved ejection fraction are each increased in RA [5,6].

How RA enhances atherogenesis remains poorly understood. Traditional and non-traditional cardiovascular risk factors as well as genetic factors are associated with atherosclerosis as well as incident cardiovascular events in RA [7-11]. Amongst non-traditional cardiovascular risk factors, high-grade inflammation is particularly implicated in increased atherogenesis among patients with RA. Indeed, high grade inflammation induces cytokine driven metabolic abnormalities including impaired glucose metabolism and low HDL cholesterol concentrations, the latter through increased catabolism [12,13]. A meta-analysis of 15 studies produced a significant 74% increased risk of diabetes and reduction in mean HDL cholesterol concentrations of 18 mg/dl (0.45 mmol/l) amongst patients with RA [14]. Equally important, high-grade inflammation in RA has direct adverse effects on the endothelium [15].

Another important metabolic abnormality induced by increased cytokine production as well as corticosteroid use and physical disability related inactivity consist of rheumatoid cachexia [13]. This affects up to 60% of RA patients and is characterized by loss of lean body and muscle mass, which is replaced by fat and, consequently, an overall unchanged body mass index. The

rheumatoid cachexia component of excess body fat content further enhances cardiovascular disease risk [13].

The prevention of cardiovascular events in patients with RA remains inadequate [1]. In this regard, current algorithms based on traditional risk factors that include the Framingham score as well as the Systematic Coronary Risk Evaluation (SCORE) were shown to underestimate cardiovascular risk in RA [16]. Congruently, evidence was recently reported that a Framingham score of ~≥10% risk for any cardiovascular event and SCORE of ~≥1%risk for a fatal cardiovascular event represent very high cardiovascular risk as evidenced by carotid plaque presence and thereby call for intervention with cardiovascular drugs in RA [17]. The respective recommended cut-off values for the Framingham score and SCORE are 20% and 5%, respectively, in non-RA subjects. Additionally, the recent European League Against Rheumatism recommendations include the application of a 1.5 multiplier upon employing risk calculators for cardiovascular disease risk stratification in the presence of RA [18]. Whether either of these 2 approaches can improve cardiovascular risk management and thereby cardiovascular disease outcomes in patients with RA awaits further investigation.

There is another major concern in the context of current cardiovascular risk stratification strategies that are recommended for use in patients with RA.

Indeed, whereas the bulk of information on cardiovascular disease and its stratification derives from investigations performed in developed countries, 80% of cardiovascular events now occur in developing populations [19,20]. Importantly in the present context, consequent to previous colonialism and the subsequent apartheid system that ended in 1994, African black persons currently represent a developing population. African black people are undergoing rapid urbanization, which comprises a process that was documented to impact substantially on cardiovascular risk factor profiles and the frequency as well as nature of associated cardiovascular events. This phenomenon is described as the epidemiological health transition that consists of 4 stages as is illustrated in Figure 1 [20]. Whereas developed populations are in stage 4 of the respective transition, most sub-Saharan black African persons are reportedly in stages 1 and 2. This results in more frequent hypertension and heart failure together with less prevalent atherosclerotic cardiovascular disease in black Africans. It is therefore conceivable that reported data on cardiovascular risk and its stratification in RA patients originating in developed populations cannot be merely extrapolated to those belonging to developed populations.Meanwhile, the prevalence of RA is similar in urbanized black Africans to that in persons from developing populations.

What is the current cardiovascular disease risk burden in the black African population at large?

Reliable large scale epidemiological data on cardiovascular disease frequencies in African black people are scarce. Nevertheless, a 2010 South African Medical Research Council report listed cerebrovascular disease as fifth and coronary artery disease as the eighth most common causes of death [21]. Also, peripheral arterial disease was found in 29% of outpatients in a South African rural community [22].

It was amply documented that the black African population is indeed at an earlier health transition stage compared to that observed in developed populations. Thus, heart failure that is mostly due to hypertension, and idiopathic dilated cardiomyopathy are currently the most commonly diagnosed conditions in black African patients presenting with heart disease [23]. Coronary artery disease is often reported as being distinctively uncommon in this population. Alarmingly however, a recent investigation performed in Johannesburg, South Africa, identified coronary artery disease in 10% of black African patients presenting with heart disease [23]. Stroke incidence remains also lower in the black African population compared to developed population but it occurs at a younger age and is possibly associated with increased mortality rates in this population [24-26]. Further, the ratio of ischemic to

hemorrhagic stroke was recently reported to be similar in black compared to white African patients [24]. Overall, the prevalence of atherosclerotic cardiovascular disease appears to be still markedly lower in the black African population than that seen in developed or high-income countries. Recently reported data indicate however that atherosclerotic cardiovascular disease frequencies are increasing in this developing population. This has crucial implications in the planning and application of optimized cardiovascular disease prevention strategies in the black African population. What do cardiovascular disease risk factor profiles in black African persons currently look like?

The low coronary artery disease incidence has been mostly attributed to low total and high HDL cholesterol concentrations in the black African population [27]. However, more recent studies identified particularly low HDL cholesterol concentrations in this population [28]. This finding could further account for the low total cholesterol levels in black African people [28].The low atherosclerotic cardiovascular disease burden may therefore originate in a relatively short lifetime exposure rather than favourable lipid profiles in black Africans [29]. This is typical for a population that is undergoing rapid urbanization. Also, hypertension is reportedly highly prevalent in the black African population [30]. In fact, apart from low tobacco consumption, the

prevalence of all major traditional cardiovascular disease risk factors is large and rising in recent studies [31-33]. In addition, large obesity rates were documented particularly in black African women [34]. With regard to psychosocial stress, the recent World Health Organization Mental Health Survey revealed that anxiety and other mood disorders were more prevalent and severe in South Africa than in other participating countries [35]. As also illustrated in Figure 1, this is again in line with an early epidemiological health transition stage.

Chronic kidney disease is a further potential cardiovascular risk factor that may be particularly relevant in the present context. Chronic kidney disease increases the risk of cardiac death up to 20-fold irrespective of age, sex, race and diabetes status [36]. The risk of cardiovascular events and mortality is enhanced in persons with a glomerular filtration rate below 60 ml/min/1.73m^2 and rises incrementally as kidney function declines [36].The frequency of CKD is not clearly established in Sub-Saharan Africa but may be much larger than in developed countries [37]. To summarize then, atherosclerotic cardiovascular disease risk factors may not be as favourable as was perceived until recently in black Africans. Do cardiovascular risk factors impact on cardiovascular disease to the same extent in black African persons as in people originating in developed countries?

The associations of modifiable cardiovascular risk factors with acute myocardial infarction were similar in the INTERHEART Africa study compared to the overall INTERHEART study. Smoking, diabetes, hypertension, abdominal obesity and dyslipidemia provided a population attributable risk of 89.2% for acute myocardial infarction [38]. However, a history of hypertension represented a higher myocardial infarction risk in the African black group. Hypertension was the most frequently implicated cause of stroke in relatively large studies amongst black African patients[24,39]. Noticeably, the potential influence of excess adiposity on stroke risk was not reported and the cause remained unidentified in 43% of cases [24]. Excess adiposity associates with hypertension as well as left ventricular diastolic function and systemic inflammation in this population [40,41]. Both systolic and diastolic blood pressure are further important determinants of diastolic function in this population [42]. With regard to smoking, the risk of tobacco related CVD in urban African black persons does not differ from that observed in developed populations [43]. Even mild current smoking was strongly associated with blood pressure in an African black population study [44]. Psychosocial stress but not hypertension is associated with angiopoietin-2 and vascular endothelial growth factor-A concentrations in black Africans [45]. The

latterare markers of angiogenesis, which associate with vascular dysfunction in African black subjects [45].

Taken together, RA has adverse effects on atherosclerotic cardiovascular risk factor profiles and enhances cardiovascular event and mortality rates by ~50% in patients from developed countries. Persons belonging to developing populations have different cardiovascular risk factor profiles and cardiovascular disease event presentations consequent to being at an earlier epidemiological health transition stage. It is therefore conceivable that black African patients with RA experience disparate atherogenic mechanisms. This has implications in optimal cardiovascular disease risk stratification and prevention in black Africans with RA.

This thesis comprises 6 manuscripts that explore cardiovascular risk factor profiles and their associations with ultrasound determined carotid artery intima-media thickness and plaquein African black patients with RA. The data were recorded prospectively in consecutive patients. Each paper was published in a highimpact journal and multivariable analysis was applied consistently.

The hypothesis that was tested in paper 1 was that atherosclerotic cardiovascular disease risk factor profiles are more favourable in black compared to other (white, Asian or mixed ancestry) African patients with RA,

as reported in non-RA subjects. The evaluated risk factors included (1) major traditional: hypertension, dyslipidemia, smoking and diabetes, (2) other traditional: underweight, obesity, metabolic syndrome, chronic kidney disease, alcohol consumption, tension, depression and body height, (3) non-traditional: rheumatoid factor status and markers of inflammation and (4) arterial stiffness: brachial pulse pressure.

In paper 2, the tested hypothesis was that RA impacts adversely on cardiovascular risk factor profiles and carotid intima-media thickness amongst black Africans, as reported in developed populations. We compared traditional cardiovascular risk factors, C-reactive protein and interleukin-6 concentrations and carotid ultrasound findings between non-RA and RA subjects. Also, the potential determinants of systemic inflammation, the impact of systemic inflammation on traditional cardiovascular risk factors and the associations of cardiovascular risk factors with atherosclerosis were explored.

In paper 3, we hypothesized that the atherosclerosis burden is smaller and that its association with cardiovascular risk factors differs in black compared to white African patients with RA, again in line with reported data in non-RA subjects [43]. For this purpose, cardiovascular risk factor profiles and carotid

intima-media thickness and plaque were recorded amongst black and white Africans with RA.

Published data on the influence of adiposity on atherosclerotic cardiovascular disease in patients with RA from developed populations are contradictory [13,46-49]. As obesity rates are particularly large in black African women, this risk factor could be suspected to contribute more to atherogenesis in black compared to white African women. This hypothesis was tested in paper 4. We compared anthropometric measures in black and white African women with RA and assessed their associations with carotid artery intima-media thickness and plaque. We also explored the impact of clinical adiposity measures on different metabolic risk factors. Finally, we determined whether the anthropometric measure-atherosclerosis relationships were explained non-metabolic or/and metabolic cardiovascular risk factors.

Current metabolic syndrome definitions describe excess adiposity together with its complications. In paper 5, we hypothesized that the burden of metabolic abnormalities is larger and has a greater impact on atherosclerosis in black compared to white women with RA. The relationships ofthe US National Cholesterol Education Program Adult Treatment Panel III definition and criteria as well as the number of the respective criteria with carotid artery

intima-media thickness and plaque were systematically compared between black and white African women with RA.

The hypotheses that were tested in paper 6 included: (1) kidney function is more impaired in black compared to white African patients with RA, and (2) impaired kidney function has a larger adverse impact on endothelial activation and atherosclerosis in black compared to white Africans with RA. We calculated 9 estimated glomerular filtration rate equations and determined their relations with carotid artery intima-media thickness and plaque as well as markers of endothelial activation, which represents the earliest stage of atherogenesis upon exposure to cardiovascular risk factors. Patients with RA experience particularly interleukin-6 mediated marked endothelial activation that regresses upon treatment with disease modifying agents and tumor necrosis factor-α inhibition [15,50,51]. The endothelial activation markers that were evaluated in paper 6 included E-selectin, vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and angiopoietin 2. Receiver operating characteristic curve analysis was employed to assess the performance of estimated glomerular filtration rate equations and their optimal cut-off values in identifying plaque presence.

The major outcomes in papers 2 – 6 of this thesis were carotid ultrasound determined intima-media thickness and plaque as surrogate markers of

atherosclerosis [52-53]. The intima-media thickness was measured in the distal common carotid artery and plaque presence was identified throughout the extra-cranial carotid artery tree. Plaque develops most commonly in the carotid bulb due to low shear stresses and high oscillations in shear stresses [52]. Both carotid intima-media thickness and plaque were validated as surrogate markers of true biological vessel wall thickness against histological specimens [52]. Nevertheless, intima-media thickening occurs mostly in response to blood pressure induced enlargement of the arterial media. By contrast, plaque represents intima thickening engendered by atherogenic cardiovascular risk factor exposure. Indeed, compared to carotid intima-media thickness, carotid plaque is a more powerful predictor of incident cardiovascular events [52,53]. Congruently, in contrast to carotid plaque, intima-media thickness improves the prediction of cardiovascular risk only minimally beyond traditional risk factors [52,53]. The use of carotid intima-media thickness in the identification of patients that require prevention with cardiovascular drugs has therefore recently become a matter of controversy [52-54].A major purpose of the present work was to quantify atherosclerosis extent by determining carotid intima-media thickness and plaque presence.

In summary, this thesis evaluates the (1) atherosclerotic cardiovascular risk factor profile, (2) impact of RA on atherosclerotic cardiovascular risk factors

and carotid intima-media thickness, (3) atherosclerosis burden and (4) relationships of traditional and non-traditional atherosclerotic cardiovascular risk factors with atherosclerosis in black African patients with RA. The main objective was to elucidate atherogenesis and cardiovascular disease risk stratification in black Africans with RA.

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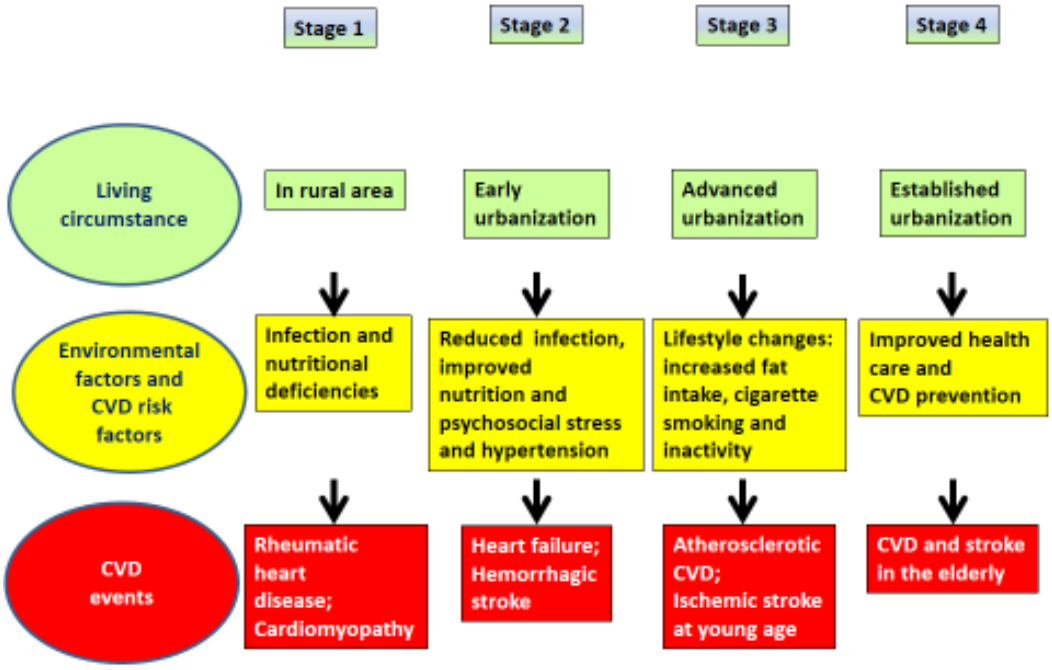

FIGURE 1. The epidemiological health transition stages and its characteristics.

CVD: cardiovascular disease.

Paper 1

In this initial study, atherosclerotic cardiovascular risk factors were compared between black and other (white, Asian and mixed ancestry) Africans with RA. In keeping with being at an earlier epidemiological health transition stage, black Africans experienced an increased prevalence of hypertension and obesity, and smoked and employed alcohol less frequently. Concurrent low total and HDL cholesterol concentrations resulted in unaltered atherogenic indices. Interestingly, despite increased overall adiposity as represented by the body mass index, triglyceride concentrations were lower in black compared to other Africans with RA. In this regard, the frequency of abdominal obesity as reflected by the metabolic syndrome waist circumference criterion was similar in black and other African RA patients. Most importantly in the present context, the overall traditional atherosclerotic cardiovascular risk burden as estimated by high cardiovascular disease risk according to the Framingham score and Systematic Coronary Risk Evaluation, having one or more major traditional atherosclerotic cardiovascular risk factor, or meeting the criteria for the metabolic syndrome definition as well as the number of metabolic syndrome features, was consistently similar in black compared to other Africans with RA. Also, pulse pressure as a measure of arterial stiffness did not differ by population grouping. Additionally, non-traditional cardiovascular risk

factors or the RA characteristics of rheumatoid factor positivity and markers of disease activity and severity were similar in black compared other Africans with RA. Finally, tension and depressive symptoms did not differ between black and other Africans with RA.

Taken together, this study documents that black African RA patients experience an atherosclerotic cardiovascular disease risk factor burden that is as large as in their non-black counterparts. This contrasts to the overall findings reported in the non-RA black population. Our finding therefore calls for cardiovascular disease risk evaluation and management irrespective of ethnic origin and epidemiological transition stage in Africans with RA.

Does RA impact on cardiovascular risk in black Africans to the same extent as it does in persons belonging to developed populations?

Risk Factor Profiles for Atherosclerotic Cardiovascular Disease in Black and Other Africans with Established Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Black Africans reportedly experience a distinctly low risk for atherosclerotic cardiovascular disease (CVD). We investigated whether this protection was present among Africans with established rheumatoid arthritis (RA).

Methods. We determined disparities in CVD risk factor profiles (major conventional: hypertension, dyslipidemia, smoking, and diabetes; other conventional: underweight, obesity, metabolic syndrome, chronic kidney disease, alcohol consumption, tension, depression, and body height; nonconventional: rheumatoid factor status and markers of inflammation) and arterial stiffness (brachial pulse pressure) between 291 black and 335 other (229 white, 64 Asian, and 42 mixed ancestry) consecutive Africans with RA in multivariable regression models.

Results. After adjusting for demographic characteristics and healthcare sector attendance, black Africans had more prevalent hypertension (OR 1.76, p = 0.01) and diabetes (OR 1.90, p = 0.07), smoked less frequently (OR 0.12, p < 0.0001), and had concurrent lower total and high-density lipoprotein cholesterol concentrations that resulted in unaltered atherogenic indices (p = 0.2) than the other participants in the study. These findings translated into global scores for major conventional risk factor-mediated future CVD event rates that were not reduced in black patients. Proportions of individual metabolic syndrome components differed between black and other patients but their total numbers of metabolic risk factors (p = 0.4) and metabolic syndrome frequencies (OR 1.44, p = 0.1) were similar. Black ethnicity did not independently associate with rheumatoid factor status, markers of inflammation, and brachial pulse pressures.

Conclusion. The overall conventional and nonconventional atherosclerotic CVD risk burdens and arterial stiffness were not reduced in black patients with RA. CVD risk should be assessed and managed independent of ethnic origin and epidemiological transition stage in RA. (First Release March 15 2010; J Rheumatol 2010;37:953–60; doi:10.3899/jrheum.091032)

Key Indexing Terms:
ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK ETHNIC ORIGIN
EPIDEMIOLOGICAL TRANSITION RHEUMATOID ARTHRITIS

The enhanced risk for cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is well established[1-13]. Atherogenesis in RA is mediated by conventional cardiovascular risk factors and disease characteristics, particularly high-grade inflammation[1-13]. Additionally, interactions between RA characteristics and conventional cardiovascular risk factors can accelerate atherogenesis[3,5,7].

In subjects without RA, the major conventional cardiovascular risk factors of hypertension, dyslipidemia, smoking, and diabetes predict the bulk of future cardiovascular events[14,15]. Most information on CVD originates in developed countries that are largely inhabited by white populations[16]. However, 80% of the CVD burden now arises in middle-income and low-income countries[16]. The current increase in incident CVD in poorer populations is attributable to the epidemiological transition induced by socioeconomic development that consists of the emergence of atherosclerotic cardiovascular risk, engendered by nascent hypertension followed by obesity, dyslipidemia, diabetes, and cigarette smoking[17].

Until 30 years ago, CVD was reportedly less prevalent in blacks without RA compared to white Americans, but black Americans currently experience more adverse risk factor

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profiles for atherosclerosis and higher cardiovascular event rates than their white counterparts[18-21]. Black Africans are presently considered to be at an earlier stage of the epidemiological transition with particularly more favorable lipid profiles and thereby at lower risk for atherosclerosis compared to other Africans[19,22]. Nevertheless, a recent emergence of risk factors for atherosclerotic CVD has been well documented in this population[22-24] and coronary artery disease is now diagnosed in 10% of black South Africans who present to hospital with heart disease[25]. South Africa is socioeconomically more developed than other sub-Saharan African countries but is further characterized by persistent, vast income and health inequities[26].

The INTERHEART investigators recently documented that conventional cardiovascular risk factors associate with acute myocardial infarction (MI) to a similar extent in different ethnic groups and geographical locations worldwide including in Africa[16,19]. RA is as prevalent in black as in white urbanized Africans[27,28]. To our knowledge, whether ethnic origin and epidemiological transition stage affects cardiovascular risk in individuals who have developed RA has not been investigated. As part of a recently initiated study on atherogenesis in African populations with RA[29], we studied conventional and nonconventional risk factor profiles for atherosclerosis and arterial stiffness. Our aim was to determine whether among Africans with RA, black patients experience a reduced risk burden for atherosclerotic cardiovascular disease.

MATERIALS AND METHODS

We enrolled consecutive patients who met the American College of Rheumatology criteria for RA[30] at a public healthcare center (Charlotte Maxeke Johannesburg Academic Hospital) and a private one (Milpark Hospital; Table 1). All invited patients had previously been treated with disease-modifying agents and agreed to participate. The study was approved by the Ethics Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand. Written informed consent was obtained from each patient.

Assessments. The recorded cardiovascular risk factor profiles are presented in Table 2 and Figure 1. All patients fasted for at least 8 hours prior to blood sampling. Hypertension was diagnosed in patients with a blood pressure > 140 mm Hg systolic and/or > 90 mm Hg diastolic, and when antihypertensives were prescribed. Dyslipidemia was diagnosed when the atherogenic index [total cholesterol/high-density lipoprotein cholesterol (HDL) ratio] was > 4[15,31]. We assessed current smoking status. Patients with a fasting plasma glucose ≥ 7 mmol/l, or in whom glucose-lowering agents were prescribed, were diagnosed with diabetes. Patients with a body mass index (BMI) < 20 kg/m^2 were considered to be underweight[32]. We used the recently reported RA-specific BMI threshold (> 28 kg/m^2)[33] in identifying cases with generalized obesity. Patients were classified as having the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII)-defined metabolic syndrome (MetS) using the ethnicity-specific criteria as recently updated by the American Heart Association and the National Heart, Lung and Blood Institute[34]. The glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease equation and chronic kidney disease (CKD) was diagnosed when the GFR was < 60 ml/min[35]. We assessed alcohol consumption (a protective cardiovascular risk factor in subjects without RA)[16], and depression and tension were evaluated using the Arthritis Impact Measurement Scales (AIMS)[36]. Body height was recorded as a cardiovascular risk factor that originates in environmental and genetic factors acting early in life[37].

The evaluated RA characteristics considered as potential cardiovascular risk factors included rheumatoid factor status, C-reactive protein (CRP) concentrations, the 28-joint Disease Activity Score (DAS28), the Health Assessment Questionnaire disability index (HAQ-DI), and the number of deformed joints.

Brachial pulse pressure, a marker of arterial stiffness, was defined as the difference between systolic and diastolic blood pressure[38-40].

Data management and analysis. We grouped the cardiovascular risk factors into 3 categories. The 1st was the major conventional cardiovascular risk factors, comprising the modifiable risk factors of hypertension, dyslipidemia, smoking, and diabetes, which form part of both the Framingham score[14] and the Systematic COronary Risk Evaluation (SCORE)[15]. These risk factors are the most established ones in atherogenesis in the population without RA. As estimates of the overall major conventional cardiovascular risk burden, we evaluated the mean (SD) number of major risk factors and the proportions of patients who had at least 1 major risk factor as well as those who were at high risk (10-year risk ≥ 20%)[14,15] for coronary heart disease (established CVD and/or diabetes and/or a Framingham score of ≥ 20)[14] or fatal cardiovascular disease (established CVD and/or diabetes and/or a SCORE of ≥ 20)[15]. The 2nd risk category was other conventional cardiovascular risk factors, including underweight, generalized obesity, the MetS, alcohol use, CKD, depression, tension, and body height. The 3rd risk category was nonconventional cardiovascular risk factors, consisting of rheumatoid factor status and markers of current (DAS28, CRP, HAQ-DI) and cumulative inflammation (HAQ-DI and number of deformed joints). Except for alcohol use, tension, obesity, and body height, each of the assessed risk factors in this investigation was previously shown to enhance the risk for CVD in not only the general population but also in patients with RA[1-13,41-43].

Dichotomous variables are expressed as proportions or percentages and continuous variables as mean (SD). Abnormally distributed characteristics were logarithmically transformed prior to statistical analysis and for these variables, geometric means (SD) are given.

Relationships between black ethnicity and CVD risk were investigated in multivariable logistic and linear regression models as appropriate and with consistent adjustment for age, gender, and healthcare center attendance. Prescribed antihypertensive therapy and statin use were further adjusted upon assessing associations with brachial pulse pressure and lipid values, respectively. Finally, the metabolic cardiovascular risk was further compared between black and other Africans by using the NCEP ATPIII MetS criteria definitions[34].

Statistical computations were made using the GB Stat™ program (Dynamic Microsystems Inc., Silver Spring, MD, USA). Since many multivariable analyses were conducted, significance was set at $p < 0.01$.

Table 1. Overall African patients with RA by gender and healthcare center.

Characteristic	Patients			
	Black, n (%)	White, n (%)	Asian, n (%)	Mixed, n (%)
All participants	291 (46.5)	229 (36.6)	63 (10.0)	43 (6.9)
Gender				
Women	259 (49.0)	186 (35.1)	49 (9.3)	35 (6.6)
Men	32 (33.0)	43 (44.3)	14 (14.4)	8 (8.3)
Healthcare center				
Public	282 (66.5)	61 (14.4)	47 (11.1)	34 (8.0)
Private	9 (4.5)	168 (83.1)	16 (7.9)	9 (4.5)

RESULTS

A total of 626 patients were investigated, 424 in our public and 202 in our private healthcare center. Eighty-three per-

Table 2. Cardiovascular risk factor profiles in black compared to white, Asian, or mixed African patients with RA. Significant ($p < 0.05$) associations of black ethnicity with cardiovascular risk factors in logistic regression models are shown in bold type.

Characteristics	Black Africans (n = 291)	White, Asian, or Mixed Africans (n = 335)	OR* (95% CI)
Women	89.0	80.6	—
Major conventional CV risk factors			
Hypertension	66.0	54.5	**1.76 (1.14–2.74)**
T chol/HDL chol > 4	18.3	19.8	0.83 (0.51–1.36)
Smoking	3.4	18.2	**0.12 (0.06–0.26)**
Diabetes	13.1	6.9	1.90 (0.96–3.78)
≥ 1 major risk factor	71.1	67.5	1.08 (0.69–1.70)
10-year risk for CHD ≥ 20%	14.8	13.1	1.17 (0.67–2.07)
10-year risk for fatal CVD ≥ 20%	14.5	12.5	1.09 (0.62–1.92)
Other conventional CV risk factors			
BMI < 20 kg/m^2	8.6	11.1	0.59 (0.31–1.13)
BMI ≥ 28 kg/m^2	52.5	28.7	**2.03 (1.35–3.05)**
Metabolic syndrome	31.3	20.3	1.44 (0.92–2.25)
MDRD GFR < 60 ml/min	4.6	9.1	0.46 (0.21–1.04)
Alcohol use	0.7	26.9	**0.12 (0.03–0.56)**
Nonconventional CV risk factors			
Rheumatoid factor-positive	75.6	77.5	0.94 (0.61–1.46)
Continuous variables	**Black Africans, Mean (SD)**	**White, Asian, or Mixed Africans, mean (SD)**	**p***
Age, yrs	54.3 (10.8)	57.2 (12.1)	—
Major conventional CV risk factors			
T chol, mmol/l	4.57 (0.98)	4.93 (1.05)	0.0002
HDL chol†, mmol/l	1.45 (1.48)	1.54 (1.36)	0.2
T chol/HDL chol†	3.08 (1.47)	3.12 (1.37)	0.2
LDL chol, mmol/l	2.54 (0.86)	2.81 (0.93)	0.003
No. of major risk factors	1.0 (0.8)	1.0 (0.8)	0.7
Other conventional CV risk factors			
Triglycerides†, mmol/l	1.01 (1.72)	1.11 (1.66)	< 0.0001
AIMS tension	3.9 (1.9)	3.7 (2.0)	0.7
AIMS depression	3.6 (1.9)	2.8 (2.0)	0.7
Height, cm	160 (10)	163 (11)	0.2
Nonconventional CV risk factors			
DAS28	3.2 (1.5)	2.7 (1.4)	0.6
CRP†, mg/l	7.6 (3.5)	5.2 (3.6)	0.8
HAQ score	0.78 (0.66)	0.65 (0.64)	0.1
Deformed joints	9 (8)	8 (10)	0.2
Arterial stiffness			
Pulse pressure, mm Hg	50 (14)	47 (12)	0.2

T chol: total cholesterol; CV: cardiovascular; CHD: coronary heart disease; CVD: cardiovascular disease; BMI: body mass index; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; HDL: high-density lipoprotein; MDRD GFR: Modification of Diet in Renal Disease glomerular filtration rate; LDL: low-density lipoprotein; AIMS: Arthritis Impact Measurement Scales. * OR and p value for comparisons between black and white or Asian Africans or those of mixed ancestry after adjustment for age, gender, and healthcare center as well as lipid-lowering and antihypertensive in models that include lipid variables and pulse pressure, respectively. † Logarithmically transformed.

cent of the patients were either black (46.5%) or white (36.5%; Table 1). Nine black and 168 white patients were seen in private healthcare ($p < 0.0001$ for each group compared to public healthcare attendance). Asian patients and those of mixed ancestry attended both centers with similar frequencies ($p = 0.1$ and $p = 0.3$, respectively). Black patients were more often women and on average 2.9 years younger (Table 2). In all patients, the mean (SD) disease duration was 9.1 (2.4) years, and disease-modifying agents, nonsteroidal antiinflammatory agents, prednisone [mean (SD) dose 4.7 (1.8) mg/day], and statins were currently prescribed in 97.8%, 18.4%, 4.8%, and 6.1% of cases, respec-

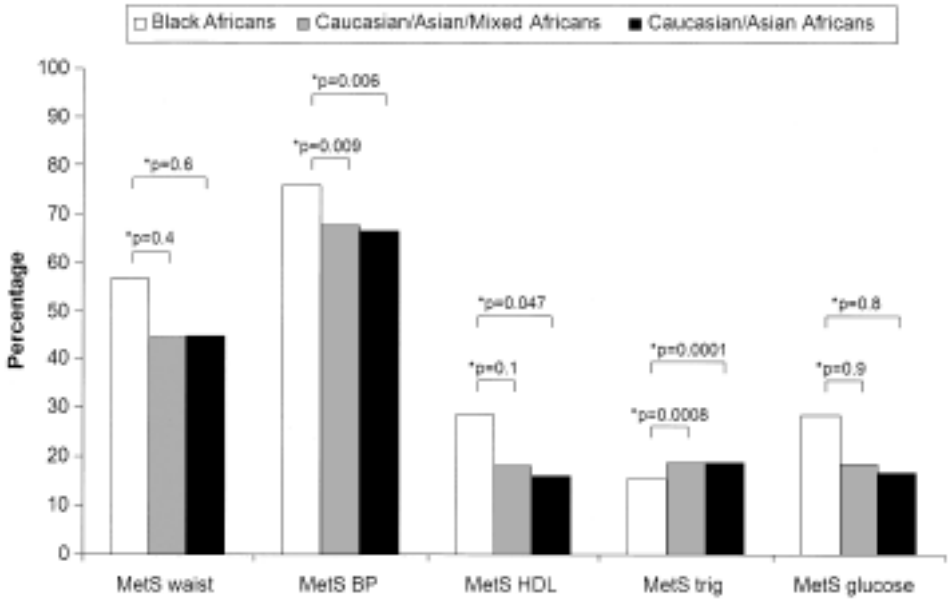

Figure 1. Proportions of the National Cholesterol Education Program Adult Treatment Panel III-defined metabolic cardiovascular risk factors in black and other Africans (before and after exclusion of subjects of mixed ancestry) with RA. MetS: metabolic syndrome; BP: blood pressure; HDL: high-density lipoprotein cholesterol; trig: triglycerides. *Analysis adjusted for age, gender, and healthcare sector.

tively. None of these characteristics differed in black compared to other patients. However, tumor necrosis factor-α blockers were used only in non-black patients who were seen in private healthcare (n = 6), cyclooxygenase inhibitors were less frequently used in black cases (n = 2 vs 17 in non-blacks), and antihypertensives were more often taken by black patients (53.3 vs 38.5%; OR 1.82, 95% CI 1.32–2.50).

Conventional and nonconventional cardiovascular risk factor profiles and arterial stiffness in black and other African patients with RA. Table 2 shows that hypertension and dyslipidemia were the most prevalent conventional risk factors. The 11% of subjects who used tobacco smoked 11 (SD 2) cigarettes daily and in the 15% who consumed alcohol, the daily intake was 0.9 (SD 0.3) units.

Adjusted for age, gender, and healthcare center attendance, and lipid-lowering agents and antihypertensives when appropriate (Table 2), black patients sustained more prevalent hypertension, less smoking, a trend toward higher diabetes prevalence (OR 1.90, p = 0.07), and lower total and low-density lipoprotein (LDL) cholesterol concentrations but similar cholesterol/HDL cholesterol ratios compared to other Africans. Estimates of the overall major conventional cardiovascular risk burden were consistently similar in black and other Africans with RA. Among the other conventional risk factors, triglyceride concentrations were lower and generalized obesity more prevalent, while the overall prevalence of the MetS did not differ in black compared to other Africans with RA. Alcohol use was less frequent in black patients. Nonconventional cardiovascular risk factor profiles were similar in black and other Africans. Finally, arterial stiffness did not differ in black compared to other Africans.

Mixed-ancestry Africans without RA reportedly still experience a somewhat lower risk for coronary heart disease than white and Asian Africans[19]. When we repeated these analyses after exclusion of Africans of mixed ancestry, our findings were unaltered (Table 3).

When all the analyses in Tables 2 and 3 were repeated with further adjustment for disease duration, the results were unaltered (data not shown).

NCEP ATPIII-defined metabolic cardiovascular risk in black compared to other Africans with RA. The previous analyses revealed that although black patients with RA experienced an overall similar prevalence of the MetS, the individual MetS risk factors of hypertension frequency and triglyceride concentrations differed in black compared to other Africans with RA. We further analyzed the data in order to clarify whether these relationships persisted once the NCEP ATPIII individual MetS criteria definitions[34] were applied. These results are shown in Figure 1. After adjustments for age, gender, and healthcare center attendance, black African patients experienced more prevalent NCEP ATPIII-defined hypertension (OR 1.84 to 2.00), less often elevated triglyceride concentrations (OR 0.37 to 0.43), similar frequencies of abdominal obesity (OR 1.12 to 1.19), reduced HDL cholesterol concentrations (OR 1.46 to 1.71), and elevated plasma glucose concentrations (OR 1.02 to 1.07). The number of MetS criteria in black patients was 2.0 (1.1) compared to 1.7 (1.2) and 1.6 (1.2) in other patients before and after exclusion of people of mixed ancestry,

Table 3. Cardiovascular risk factor profiles in black compared to white or Asian African patients with RA. Significant ($p < 0.05$) associations of black ethnicity with cardiovascular risk factors in logistic regression models are shown in bold type.

Characteristics	Black Africans (n = 291)	White or Asian Africans (n = 293)	OR* (95% CI)
Women	89.0	80.5	—
Major conventional CV risk factors			
Hypertension	66.0	53.4	**1.76 (1.09–2.84)**
T chol/HDL chol > 4	18.3	18.9	0.80 (0.47–1.36)
Smoking	3.4	17.8	**0.13 (0.06–0.28)**
Diabetes	13.1	6.6	1.76 (0.84–3.71)
≥ 1 major risk factor	71.1	65.8	1.14 (0.70–1.85)
10-year risk for CHD ≥ 20%	14.8	12.3	1.14 (0.61–2.11)
10-year risk for fatal CVD ≥ 20%	14.5	12.0	1.05 (0.57–1.95)
Other conventional CV risk factors			
BMI < 20 kg/m^2	8.6	10.7	0.70 (0.34–1.42)
BMI ≥ 28 kg/m^2	52.5	27.5	**2.21 (1.41–3.47)**
Metabolic syndrome	31.3	19.5	1.42 (0.87–2.32)
MDRD GFR < 60 ml/min	4.6	8.7	0.44 (0.19–1.04)
Alcohol use	0.7	30.1	**0.12 (0.02–0.54)**
Nonconventional CV risk factors			
Rheumatoid factor-positive	75.6	77.6	0.93 (0.57–1.50)
Continuous variables	**Black Africans Mean (SD)**	**White or Asian Africans, mean (SD)**	**p***
Age, yrs	54.3 (10.8)	56.9 (12.1)	—
Major conventional CV risk factors			
T chol, mmol/l	4.57 (0.98)	4.96 (1.05)	< 0.0001
HDL chol†, mmol/l	1.45 (1.48)	1.56 (1.35)	0.2
T chol/HDL chol†	3.08 (1.47)	3.11 (1.36)	0.2
LDL chol, mmol/l	2.54 (0.86)	2.83 (0.90)	0.0004
No. of major risk factors	1.0 (0.8)	0.9 (0.8)	0.7
Other conventional CV risk factors			
Triglycerides†, mmol/l	1.01 (1.72)	1.10 (1.68)	< 0.0001
AIMS tension	3.9 (1.9)	3.7 (2.0)	0.6
AIMS depression	3.6 (1.9)	2.7 (2.1)	0.8
Height, cm	160 (10)	164 (11)	0.4
Nonconventional CV risk factors			
DAS28	3.2 (1.5)	2.6 (1.5)	0.4
CRP†, mg/l	7.6 (3.5)	4.8 (3.7)	0.5
HAQ score	0.78 (0.66)	0.60 (0.61)	0.5
Deformed joints	9 (8)	7 (9)	0.3
Arterial stiffness			
Pulse pressure, mm Hg	50 (14)	47 (12)	0.09

T chol: total cholesterol; CV: cardiovascular; CHD: coronary heart disease; CVD: cardiovascular disease; BMI: body mass index; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; HDL: high-density lipoprotein; MDRD GFR: Modification of Diet in Renal Disease glomerular filtration rate; LDL: low-density lipoprotein; AIMS: Arthritis Impact Measurement Scales. * OR and p value for comparisons between black and white or Asian Africans after adjustment for age, gender, and healthcare center as well as lipid-lowering and antihypertensive in models that include lipid variables and pulse pressure, respectively. † Logarithmically transformed.

respectively ($p = 0.4$ after adjustment for age, gender, and healthcare center).

DISCUSSION

Our study revealed disparities in several individual conventional risk factor profiles among black and other Africans with RA. Such findings reportedly reflect different epidemiological transition stages in subjects without RA[17,19]. Differences in conventional CVD risk factors included a higher prevalence of hypertension and lower smoking frequency in black patients that resulted in an unaltered overall major conventional CVD risk burden relative to other

African patients. Similarly, black ethnicity was associated with a lower prevalence of MetS triglyceride concentrations and a higher frequency of MetS hypertension that together translated into a similar overall metabolic risk burden compared to other Africans with RA. Additionally, we found no disparities in nonconventional risk factor profiles between black and other African patients. Finally, and in keeping with an unaltered overall CVD risk burden, arterial stiffness was not reduced in blacks compared to other patients with RA.

Although data on atherosclerotic CVD in sub-Saharan Africa are few[19], the increased prevalence of hypertension in our black patients with RA is reminiscent of what was published on black Africans without RA as well as on Americans[19,44]. Nevertheless, because of factors including a reduced intake of saturated fat, black subjects without RA in Africa reportedly have more favorable lipid profiles than other individuals on that continent[19,22,45]. It is the low total cholesterol and high HDL cholesterol concentrations in black Africans that are believed to account for the current low prevalence of ischemic heart disease in this population[22]. In our investigation, black patients had lower total and LDL cholesterol concentrations than other patients with RA. In the general population, the cholesterol/HDL cholesterol ratio exceeds total, HDL, and LDL cholesterol concentrations in predicting incident CVD[31]. We found that black patients with RA experienced not only lower total cholesterol but also concurrent lower HDL cholesterol concentrations and thereby atherogenic indices or total cholesterol/HDL cholesterol ratios that did not differ from those found in other Africans with RA. Additionally, although the prevalence of diabetes is increasing in black Africans, it is still reportedly lower than in whites living in Africa[46]. Among Africans with RA in our study, black patients experienced a trend (OR 1.76 to 1.90, $p = 0.07$) toward a higher prevalence of diabetes in age, gender, and healthcare sector adjusted analysis. Our results on individual major conventional CVD risk factors translated into an overall risk burden for atherosclerosis that was similar in black and other patients with RA, as estimated by the number or presence of one or more of the respective risk factors or being at high risk for incident coronary heart disease or fatal CVD. Importantly in the present context, hypertension is more strongly associated with acute MI in black Africans than in other populations[19]. Our findings suggest that an earlier epidemiological transition stage, as manifested by the presence of lower total and LDL cholesterol concentrations and less frequent smoking in black Africans with RA, fails to render immunity to the risk of atherosclerosis as it reportedly does in the general black African population[19,22].

Other conventional risk factors for atherosclerotic CVD in not only the population at large but also in patients with RA include the MetS and its components[6,9], being underweight[32], CKD[42], and depression[41]. In our multivariable analyses, black and other patients with RA exhibited similar prevalences of underweight and CKD, and AIMS depression. Except for NCEP ATPIII-defined raised glucose and reduced HDL cholesterol concentrations and abdominal obesity, the frequencies of MetS features differed in black compared to other Africans. This comprised a higher prevalence of elevated blood pressure and less frequently increased triglyceride concentrations. Notably, using the National Health and Nutrition Examination Survey, Sumner and Cowie recently reported that, compared to non-Hispanic whites and Mexican Americans, non-Hispanic blacks were more likely to be insulin-resistant despite experiencing lower triglyceride concentrations[47]. Reduced insulin sensitivity was also found in black Africans without RA[48]. Despite different individual metabolic risk factor profiles in black compared to other Africans with RA, black patients did not sustain an altered number of MetS criteria and prevalence of the MetS. Our findings indicate that the overall metabolic CVD risk is likely to be similar in black and other Africans with RA and certainly not lower in black patients.

The RA characteristics of current and cumulative inflammation markers constitute documented important nonconventional CVD risk factors in RA[4,5,13,42]. After adjusting for potential confounders including public healthcare attendance, a surrogate for socioeconomic disadvantage in our context[26,49,50], the inflammatory burden did not differ in black compared to other Africans with RA. Interestingly, and in agreement with our findings, Iren and colleagues recently reported no differences in HAQ-DI and DAS28 in black compared to white Americans with RA, when adjusted for confounders including socioeconomic status[51].

Increased brachial pulse pressure strongly associates with the prevalence and incidence of CVD, and its risk factors are generally similar to those for atherosclerosis[38-40]. We found that the mean brachial pulse pressure did not differ between black and other patients in multivariable analysis. These findings substantiate the notion that the overall risk for atherosclerotic CVD is unlikely to be reduced in black Africans with RA.

We prospectively evaluated detailed CVD risk factor profiles in 626 consecutive patients with RA. We did not perform a power analysis prior to the initiation of our study. However, based on our results, a minimum of 15, 34, 46, and 158 patients needed to be included in the 2 groups of African and other patients with RA in order to document a significant ($p < 0.01$) difference of 1, 1, 1, and 5 mm Hg in the number of major conventional CVD risk factors, the number of MetS components, DAS28, and pulse pressure, respectively, at 80% power. The cross-sectional design of our study precludes drawing inferences on the direction of causality. Also, although an increased brachial pulse pressure reflects arterial stiffness[38-40], our current finding of a higher than expected risk for atherosclerosis in black

patients with RA calls for the assessment by more direct measures of subclinical cardiovascular disease in future investigations that address the effect of ethnic origin on CVD risk in RA. We are currently addressing these issues.

Although black Africans with RA smoke less frequently and have lower MetS triglyceride concentrations than other Africans with this disease, they experience more frequent hypertension that therefore should be particularly targeted in CVD risk management. Despite potentially different epidemiological transition stages and/or biological factors among African populations, the overall conventional and nonconventional risk burdens for atherosclerotic CVD and arterial stiffness were not reduced in black compared to other patients with RA in our study. CVD risk should be comprehensively assessed and managed irrespective of ethnic origin in individuals who have contracted RA, including those in developing populations.

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Paper 2

This study assessed whether RA influences atherosclerotic cardiovascular risk factors and atherosclerosis in the black African population as it reportedly does in developed populations. The analysis revealed a series of novel and unanticipated findings:

1. Body mass index was reduced in RA by 4.5 kg/m^2 compared to non-RA subjects. On the other hand, waist-hip ratio was unaltered in RA.
2. Dyslipidemia was less prevalent in RA but this was no longer the case after adjustment for adiposity and chloroquine use.
3. Hypertension, diabetes and smoking prevalence, and the number of major cardiovascular risk factors did not differ by RA status.
4. Concentrations of C-reactive protein were similar and those of interleukin-6 were reduced in RA. This was probably due to the reduced adiposity burden in RA. Indeed, adiposity was most strongly associated with systemic inflammation irrespective of RA status.
5. RA activity and severity were consistently unrelated to systemic inflammation.
6. The carotid intima-media thickness was not different in RA compared to non-RA subjects.

7. Low density lipoprotein cholesterol concentrations were associated with carotid intima-media thickness. However, this cardiovascular risk factor explained a mere 2.3% of the variance in carotid intima-media thickness.

In summary, each of these findings contrasts to findings reported on the impact of RA on atherosclerotic cardiovascular disease risk in developed populations. Our results indicate that an absent release of interleukin-6 into the circulation may account for the unaltered cardiovascular disease risk in black Africans with compared to those without RA. Interestingly, extraarticular manifestations are also distinctly uncommon in black Africans with RA. This indicates that the inflammatory process in RA may indeed be restricted to the joints in this population.

Is the atherosclerosis burden reduced in black compared to white Africans with RA? Also, is the potential impact of atherosclerotic cardiovascular disease risk factors on atherosclerosis similar in black compared to white Africans with RA?

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RESEARCH ARTICLE Open Access

Rheumatoid arthritis is associated with reduced adiposity but not with unfavorable major cardiovascular risk factor profiles and enhanced carotid atherosclerosis in black Africans from a developing population: a cross-sectional study

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Abstract

Introduction: Rheumatoid arthritis (RA) is characterized by inflamed joint-derived cytokine-mediated high-grade systemic inflammation that enhances cardiovascular metabolic risk and disease in developed populations. We investigated the potential impact of RA on cardiovascular risk factors including systemic inflammation and atherosclerosis, and their relationships in black Africans from a developing population.

Methods: We evaluated demographic features, adiposity indices, major traditional cardiovascular risk factors, circulating C-reactive protein and interleukin-6 concentrations and ultrasound determined carotid intima-media thickness (cIMT) in 274 black Africans; 115 had established RA. Data were analyzed in confounder-adjusted mixed regression models.

Results: The body mass index and waist-height ratio were lower in RA compared to non-RA subjects (29.2 (6.6) versus 33.7 (8.0), $P < 0.0001$ and 0.58 (0.09) versus 0.62 (0.1), $P = 0.0003$, respectively). Dyslipidemia was less prevalent in patients with RA (odds ratio (OR) (95% confidence interval (CI) = 0.54 (0.30 to1.00)); this disparity was no longer significant after further adjustment for reduced adiposity and chloroquine use. RA was also not associated with hypertension, current smoking and diabetes. The number of major traditional risk factors did not differ by RA status (1.1 (0.8) versus 1.2 (0.9), $P = 0.7$). Circulating C-reactive protein concentrations were similar and serum interleukin-6 concentrations reduced in RA (7.2 (3.1) versus 6.7 (3.1) mg/l, $P = 0.7$ and 3.9 (1.9) versus 6.3 (1.9) pg/ml, $P < 0.0001$, respectively). The cIMT was 0.700 (0.085) and 0.701 (0.111) mm in RA and non-RA subjects, respectively ($P = 0.7$). RA disease activity and severity parameters were consistently unrelated to systemic inflammation, despite the presence of clinically active disease in 82.6% of patients. In all participants, adiposity indices, smoking and converting angiotensin inhibitor non-use were associated with increased systemic inflammation, which related to more atherogenic lipid profiles, and circulating low density lipoprotein concentrations were associated with cIMT (partial R = 0.153, $P = 0.032$); RA did not impact on these relationships (interaction $P \geq 0.1$).

Conclusions: Among black Africans, patients with established RA experience reduced overall and abdominal adiposity but no enhanced major traditional risk factor and atherosclerosis burden. This study further suggests that an absent interleukin-6 release by inflamed RA joints into the circulation may account for this unaltered cardiovascular disease risk.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory and potentially destructive joint disorder that is complicated by enhanced atherosclerosis and incident cardiovascular event rates similar to diabetes [1-6], as well as cardiovascular mortality [4,7].

In the general population, the bulk of cardiovascular disease (CVD) is attributable to the traditional risk factors of hypertension, dyslipidemia, smoking and diabetes [8,9]. In addition, cytokine-mediated systemic inflammation as generally estimated by circulating C-reactive protein concentrations (CRP), contributes to atherogenesis [10-19]. Systemic inflammation originates mostly in excess adiposity and smoking, and mediates CVD through adverse effects on metabolic cardiovascular risk factors as well as more direct effects at the endothelial level [10-19].

RA is characterized by circulating CRP concentrations that are typically increased several fold even when the disease appears clinically controlled [20,21]. Although, in RA, adiposity and smoking associate independently with serum CRP concentrations [22], the inflammation extent is mostly accounted for by circulating joint derived cytokines, particularly interleukin-6 [20-22].

Several genetic polymorphisms were recently found to be associated with CVD in RA [23-27]. Amongst the modifiable cardiovascular risk factors, it is the chronic high-grade systemic inflammatory state that is currently considered to best explain the excess CVD in RA [20,21,28-31]. Congruent with this paradigm, systemic inflammation is associated with metabolic risk factors, including insulin resistance and decreased high density lipoprotein (HDL) cholesterol concentrations in RA [20,21,32,33]. A recent meta-analysis of traditional cardiovascular risk factors in RA indeed confirmed the presence of lower HDL cholesterol concentrations and an enhanced diabetes frequency [34]. Importantly in the present context also, high-grade inflammation in RA is complicated by a reduced lean mass and particularly muscle mass together with increased body fat accumulation, a condition most often termed rheumatoid cachexia [35,36]. Adiposity associates with metabolic risk factors in RA [36-38]. With regard to more recently identified cardiovascular risk factor pathways, circulating interleukin-6 concentrations are independently associated with endothelial activation [21] that decreases upon suppression of interleukin-6 production in RA [39].

Besides systemic inflammation in RA, antirheumatic agents can modify cardiovascular risk factors. Although short term glucocorticoid therapy in patients with markedly active RA can enhance insulin sensitivity [20], chronic use of this intervention associates with insulin resistance [40], atherosclerosis [41] and cardiovascular event rates [42]. Chloroquine therapy induces favorable lipid profiles [43,44] and lowered diabetes risk [45] and leflunomide use hypertension [46] and dyslipidemia [47].

As applies to the general population, available data on atherogenesis in RA were generally obtained in subjects that belong to developed populations, whereas 80% of CVD now occurs in low income or developing countries [38,48-52]. In this regard, we recently documented consistent disparities in individual cardiovascular risk factor profiles including more marked overall adiposity, an increased prevalence of hypertension and less frequent alcohol consumption in patients with RA from developing groups of black African descent compared to their white counterparts from a developed population, as well as risk factor-atherosclerosis relationships amongst both groups [38,51,52]. Non-RA black African subjects experience not only a very large prevalence of obesity [53] and hypertension [54,55], but also a strikingly large systemic inflammation burden [56-58], whereas serum C-reactive protein concentrations are not increased in black Africans compared to white patients with RA [52]. Further, cumulative inflammation as estimated by the number of deformed joints, is independently associated with decreased overall and abdominal obesity in African black but not white women with RA [38]. In the present study, we examined the potential impact of RA on cardiovascular risk factors, including systemic inflammation, carotid atherosclerosis and their relationships amongst 274 African blacks.

Materials and methods

Study participants

The present investigation was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of Witwatersrand approved the protocols applied in non-RA and RA subjects (approval numbers: M02-04-72 and renewed as M07-04-69 in non-RA subjects and M06-07-33 in RA subjects). Participants gave informed, written consent. The present study design has previously been described [38,50-52,56,59-61]. Briefly, 115 African black patients who met the 1988 American College of Rheumatology criteria for RA [62] were enrolled at the Charlotte Maxeke Johannesburg Academic Hospital. All invited patients agreed to participate. Only two RA subjects used prednisone and, hence, to avoid confounding of the data analysis by this intervention, the respective participants were excluded. All patients used disease modifying agents for rheumatic disease (DMARDs) at the time of the study. Age- and sex-matched non-RA subjects were participants in a population study on cardiovascular risk and disease that is also conducted in Johannesburg [56,59-61]. This investigation comprises randomly recruited nuclear families of black African descent with siblings older than

16 years. Of the 159 non-RA participants, 124 had CRP measurements and 92 carotid ultrasound evaluations; the other recorded variables did not differ in non-RA subjects with and without CRP and carotid ultrasound assessments. Data were missing in fewer than 5% of any of the other recorded cardiovascular risk factors in the study participants.

Baseline characteristics

We recorded demographic features, life style factors comprising alcohol use (at least one unit per month) and exercise (at least once per month) that included time spent in walking, for example, to reach public transportation, and cardiovascular and non-steroidal anti-inflammatory drug (NSAID) use. Height, weight and waist and hip circumference were measured using standard approaches. Body mass index (BMI) cut-off points of <20, 20 to 24.9, 25 to 29.9 and >29.9 kg/m^2 were employed to identify underweight, normal weight, overweight and obese status, respectively. Abdominal obesity indices included waist circumference and waist-height ratio whereas fat distribution was estimated by the waist-hip ratio [38]. In patients with RA, we additionally recorded disease duration, the Clinical Disease Activity Index (CDAI) [63], the number of deformed joints (cumulative inflammation or disease severity), rheumatoid factor status and the use of traditional or synthetic DMARDs. Patients with RA had no access to biological DMARD therapy at the time of the study [38,50-52].

Conventional cardiovascular risk factors

Hypertension was defined as an average systolic blood pressure ≥140 or/and diastolic blood pressure ≥90 mmHg or/and current use of antihypertensive medications. Uncontrolled and untreated hypertension were diagnosed in patients with a systolic blood pressure ≥140 or/and diastolic blood pressure ≥90 mmHg who used and did not use antihypertensive agents, respectively. Standard laboratory blood tests of renal and liver function, hematological parameters, lipids and glucose were performed. Dyslipidemia was diagnosed when the atherogenic index, that is, the cholesterol-HDL cholesterol ratio was more than four and proatherogenic non-HDL cholesterol concentrations were calculated by subtracting HDL cholesterol from total cholesterol concentrations [38,44,50-52]. We documented smoking habits. Diabetes was identified as the use of glucose lowering agents or a fasting plasma glucose ≥7 mmol/l. The overall major conventional cardiovascular risk factor burden was estimated by the number and proportion of patients with one or more of such risk factors that comprised hypertension, dyslipidemia, current smoking status and diabetes, as well as the Framingham 10-year risk prediction scores for coronary heart disease (myocardial infarction or coronary death) [8] and general CVD (myocardial infarction, coronary death, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral vascular disease or heart failure) [9].

Systemic inflammation

Serum CRP and interleukin-6 comprised the evaluated laboratory inflammatory markers in the present investigation. CRP concentrations were determined using immunoturbidimetric methods. In non-RA subjects, this was done on the AU analyzer (Olympus, Essex, UK), the lower detection limit was 0.05 mg/l and the inter- and intra-assay coefficients of variation were 1.3 and 0.4%, respectively; in RA patients it was performed on the DxC/LX analyzer (Beckman Coulter, Inc., Brea, CA, USA), the lower detection limit was 1 mg/l and the inter- and intra-assay were 2.5 and 5.0%, respectively. In the general population, a CRP concentration >1 mg/l reportedly predicts increased incident CVD [16,19]. Seventy-four blood samples from subjects who did not participate in the present study were tested on both the AU and DxL/LX systems and the Spearman correlation coefficient between the obtained CRP values was 0.994. Interleukin-6 concentrations were measured using a solid-phase sandwich enzyme-linked immunosorbant assay (ELISA) (Quantikine®HS, R&D Systems, Inc., Minneapolis, MN, USA). The lower detection limit ranged from 0.016 to 0.110 pg/ml and inter- and intra-assay coefficients of variation were 7.8 and 7.4%, respectively.

Carotid artery atherosclerosis

Carotid artery intima-media thickness (cIMT) measurements were made using a linear array 7.5 MHz probe attached to a high resolution B-mode ultrasound machine (SonoCalc IMT, Sonosite, Inc., Bothell, WA, USA) in both RA and non-RA subjects, as recently described [38,51,52]. This equipment involves the application of a unique semi-automated border detection program that was previously documented to provide highly reproducible intra- and inter-rater results in other as well as our settings [38,51,52,61,64]. Carotid artery plaque is currently identified in our RA patients [38,51,52] but not in non-RA subjects and, hence, results on plaque are not shown in the present report.

Data analysis

Dichotomous variables are expressed as proportions or percentages and continuous variables as mean (SD). Non-normally distributed characteristics were logarithmically transformed prior to statistical analysis and for these variables geometric means (SD) are given. The

selection of confounders in multivariable regression models was both data driven and based on biological plausibility.

Disparities in demographic features between RA and non-RA subjects were compared using the Student's *t*-test and univariate logistic regression analysis as appropriate. Relationships of RA with baseline recorded characteristics, major cardiovascular risk factors, systemic inflammation and atherosclerosis were first investigated in multivariable logistic and continuous regression models as appropriate with consistent adjustment for demographic characteristics since age differed numerically by RA status. The associations between RA and cardiovascular risk factors, systemic inflammation and atherosclerosis status were then re-assessed in models that included additional potential confounders or/and mediators.

In all participants, the relation of circulating CRP and interleukin-6 concentrations with potential determinants of systemic inflammation and metabolic cardiovascular risk factors were investigated in demographic characteristic as well as in multiple confounder adjusted models. The impact of RA on these relationships was determined by employing interaction terms [38,51,52]. Finally, in patients with RA, the associations of clinical disease activity and severity variables with systemic inflammation were investigated in demographic and multiple confounder adjusted models.

Statistical computations were made using the GB Stat™ program (Dynamic Microsystems, Inc., Silverspring, MD, USA).

Results

Baseline characteristics in African black subjects with and without RA

Table 1 gives the baseline characteristics in the study participants. The proportion of women was numerically larger by 3.4% amongst those with compared to those without RA. Alcohol was consumed only by non-RA subjects (17.6%), who also exercised more than their RA counterparts. The BMI was substantially lower in RA compared to non-RA subjects (difference in mean = 4.5 kg/m^2). In age and sex adjusted analysis, black Africans with RA had more frequently a normal BMI (odds ratio (OR) (95% confidence interval (CI)) = 3.42 (1.69 to 6.95)) and were less often obese (OR (95% CI) = 0.35 (0.21 to 0.59)) than those without RA. Abdominal obesity measures (waist and waist-height ratio) were larger in non-RA subjects whereas RA was not associated with an altered fat distribution (waist-hip ratio). Hypertension was treated in 72.1% and 61.5% (OR (95% CI) = 1.76 (0.93 to 3.33)) of RA and non-RA cases, respectively. Antihypertensive agents were more frequently employed (OR (95% CI) = 1.87 (1.12 to 3.11)) and the mean number of antihypertensives prescribed was twice as large in subjects with compared to those without RA; this was mostly due to a more regular use of angiotensin converting enzyme inhibitors (OR (95% CI) = 10.00 (4.80 to 20.85)) and calcium channel blockers (OR (95% CI) = 4.01 (1.66 to 9.69)). Amongst treated hypertensive participants, 58.5% of non-RA subjects compared to 67.7% of RA patients had uncontrolled hypertension (systolic blood pressure ≥140 or/and diastolic blood pressure ≥90 mm Hg) (OR (95% CI) = 1.49 (0.71 to 3.14)).

In patients with RA, the mean disease duration was 12.5 years, 76.5% tested rheumatoid factor positive, 17.4% experienced clinical remission and 53% moderate or high disease activity. Methotrexate and chloroquine comprised the most frequently prescribed DMARDs and the mean number of DMARDs used was 2.4.

Conventional cardiovascular risk factor profiles in African black subjects with and without RA

Table 2 shows the conventional cardiovascular risk factor profiles in black Africans with and without RA. In age- and sex-adjusted analysis (Model 1 in Table 2), RA was associated with less frequent dyslipidemia (OR (95% CI) = 0.54 (0.30 to 1.00)) and consistently more favorable individual lipid parameters. Subjects with RA had a similar frequency of ever smoking but had discontinued smoking more often than their non-RA counterparts. Amongst smokers, the mean number (SD) of cigarettes smoked per day was low at 4.1 (2.3). The overall major conventional cardiovascular risk factor burden as estimated by the number of major risk factors, the presence of at least one major risk factor and the 10-year risks for coronary heart disease and cardiovascular disease were similar in subjects with and without RA.

Besides disparities in adiposity measures between RA and non-RA subjects (Table 1), other factors that could have confounded or mediated our findings in Model 1 (Table 2) included chloroquine [43-45] and leflunomide use [46,47]. Thus, amongst patients with RA and in age, sex, cardiovascular drug, obesity measure and lifestyle factor adjusted analysis, potentially relevant relationships ($P < 0.2$) were found between chloroquine and leflunomide use and the cholesterol-HDL cholesterol ratio (partial R = -0.153, $P = 0.13$ and partial R = 0.158, $P = 0.12$, respectively). Leflunomide use also potentially impacted on systolic blood pressure but this constituted an inverse relationship (partial R = -0.177, $P = 0.08$) thereby arguing against an adverse effect of leflunomide on blood pressure amongst black Africans with RA. None of the other RA characteristics (Table 1) were found to be potential confounders or mediators in the associations between RA and cardiovascular risk factors ($P > 0.2$).

The mediating or confounding effects of disparities of adiposity indices between RA and non-RA subjects,

Table 1 Baseline characteristics in African black subjects with and without rheumatoid arthritis

	Rheumatoid arthritis		
Characteristic	**Present (*n* = 115)**	**Absent (*n* = 159)**	***P*-value[a]**
Demographics			
Age, years	55.7 (10.3)	56.5 (10.9)	0.5
Female (%)	89.6	86.2	0.45
Lifestyle factors			
Alcohol use (%)	0	17.6	-
Units per week, number[b]	0	0.27 (1.08)	-
Exercise (%)	41.7	42.8	1.0
Hours per week, number[b]	**0.1 (1.0)**	**1.7 (2.4)**	**0.0004**
Anthropometric measures			
Body mass index	**29.2 (6.6)**	**33.7 (8.0)**	**<0.0001**
<20 kg/m^2 (%)	5.4	2.5	0.2
20 to 24.9 kg/m^2 (%)	**25.2**	**8.8**	**0.0004**
25 to 29.9 kg/m^2 (%)	25.2	23.3	0.8
>29.9 kg/m^2 (%)	**44.1**	**64.8**	**0.0001**
Waist circumference, cm	**93.1 (13.3)**	**97.5 (15.0)**	**0.01**
Waist/height	**0.58 (0.09)**	**0.62 (0.1)**	**0.0003**
Hip circumference, cm	**110 (18)**	**116 (15)**	**0.002**
Waist/hip[b]	0.85 (1.14)	0.84 (1.13)	0.4
Cardiovascular drugs			
Antihypertensive agents			
Use (%)	**53.9**	**40.2**	**0.02**
Number	**1.0 (1.1)**	**0.5 (0.7)**	**<0.0001**
>1 agent (%)	**36.5**	**8.8**	**<0.0001**
Diuretic (%)	38.3	39.0	1.0
Angiotensin converting enzyme inhibitor (%)	**40.8**	**6.9**	**<0.0001**
Calcium channel blocker (%)	**16.5**	**5.0**	**0.002**
Beta blocker (%)	3.5	0	-
Angiotensin receptor blocker (%)	0.9	0	-
Glucose lowering agents			
Oral glucose lowering agent (%)	13.9	10.1	0.3
Insulin (%)	0.9	2.5	0.3
Statin (%)	19.1	0	-
Nonsteroidal antiinflammatory agent (%)	6.1	4.4	0.6
Rheumatoid arthritis characteristics			
Disease duration, years	12.5 (8.8)		
Clinical Disease Activity Index[b] [58]	8.3 (2.6)		
<2.8 or remission (%)	17.4		
2.7 to 10 or mild disease activity (%)	29.6		
11 to 22 or moderate disease activity (%)	40.0		
>22 or high disease activity (%)	13.0		
Deformed joints, number[b]	6.2 (2.7)		
Rheumatoid factor positive (%)	76.5		
Disease modifying agents			
Methotrexate (%)	92.2		
Chloroquine (%)	80.9		
Sulphasalazine (%)	25.2		
Leflunomide (%)	20.0		
Azathioprine (%)	14.8		
Tetracyclin (%)	10.4		
Cyclophosphamide (%)	6.1		
Penicillamine (%)	2.6		

Results are expressed as mean (SD) or proportions/percentages. [a]Except for associations between rheumatoid arthritis status and demographic characteristics, adjusted for age and gender; [b]non-normally distributed variables for which geometric mean (SD) is given.

Table 2 Conventional cardiovascular risk factors, systemic inflammation and atherosclerosis in African black subjects by RA status

Characteristic	Rheumatoid arthritis		Adjusted models							
	Present (n = 115)	Absent (n = 159)	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]		Model 5[e]	
Categorical variables			**OR (95% CI)**		**OR (95% CI)**		**OR (95% CI)**		**OR (95% CI)**		**OR (95% CI)**	
Hypertension (%)	74.8	65.4	1.65 (0.95 to 2.96)		1.66 (0.94 to 2.96)		**2.03 (1.07 to 3.85)**		-		1.88 (0.97 to 3.67)	
T chol/HDL chol >4	21.6	33.5	**0.54 (0.30 to 1.00)**		0.73 (0.40 to 1.33)		0.64 (0.31 to 1.30)		0.87 (0.31 to 3.07)		0.88 (0.28 to 2.79)	
Smoking												
Ever (%)	16.5	14.5	1.37 (0.66 to 2.85)		-		-		-		-	
Former (%)	13.0	6.9	**2.48 (1.03 to 5.99)**		-		-		-		-	
Current (%)	3.5	7.6	0.46 (0.14 to 1.51)		-		-		-		-	
Diabetes (%)	15.7	12.0	1.41 (0.69 to 2.85)		1.87 (0.86 to 4.06)		-		1.48 (0.37 to 5.99)		1.53 (0.38 to 6.28)	
≥1 major RF (%)	75.7	78.1	0.87 (0.49 to 1.53)		0.86 (0.48 to 1.53)		0.66 (0.24 to 1.81)		1.23 (0.34 to 4.12)		0.88 (0.28 to 3.79)	
Continuous variables			**Partial R**	***P***	**Partial R**	***P***	**Partial R**	***P***	**Partial R**	***P***	**Partial R**	***P***
Blood pressure values												
Systolic BP, mmHg	140 (25)	137 (22)	0.064	0.3	0.035	0.6	0.080	0.2	-		0.092	0.2
Diastolic BP, mmHg	86 (15)	87 (13)	-0.038	0.5	-0.031	0.6	-0.008	0.9	-		-0.017	0.8
Lipid values												
T chol, mmol/l	4.7 (0.9)	5.1 (1.2)	**-0.145**	**0.02**	-0.112	0.08	**-0.126**	**0.045**	-0.075	0.2	-0.072	0.3
HDL chol[f], mmol/l	1.48 (1.33)	1.39 (1.32)	0.112	0.07	0.082	0.2	0.094	0.1	-0.001	1.0	0.026	0.7
T chol/HDL chol	3.2 (1.0)	3.7 (1.3)	**-0.180**	**0.003**	**-0.134**	**0.03**	**-0.155**	**0.01**	-0.041	0.5	-0.064	0.4
LDL chol, mmol/l	2.6 (0.8)	3.0 (1.0)	**-0.173**	**0.005**	**-0.133**	**0.04**	**-0.146**	**0.02**	-0.096	0.1	-0.120	0.09
LDL chol/HDL chol[f]	1.68 (1.55)	2.02 (1.59)	**-0.179**	**0.004**	**-0.134**	**0.03**	**-0.147**	**0.02**	-0.070	0.3	-0.110	0.1
Non HDL, mmol/l	3.1 (0.9)	3.6 (1.2)	**-0.190**	**0.002**	**-0.145**	**0.02**	**-0.165**	**0.009**	-0.081	0.2	-0.090	0.2
Trig[f], mmol/l	1.08 (1.70)	1.20 (1.59)	-0.118	0.06	-0.093	0.14	-0.119	0.06	-0.058	0.4	-0.041	0.6
Trig/HDL chol[f]	0.73 (2.02)	0.87 (1.83)	**-0.139**	**0.02**	-0.110	0.08	**-0.135**	**0.03**	-0.046	0.5	-0.046	0.6
Smoking[f], cigarettes/d	0.05 (0.36)	0.15 (0.68)	-0.096	0.1	-		-		-		-	
Glucose [f], mmol/l	5.2 (1.4)	5.5 (1.4)	-0.117	0.06	-0.090	0.2	-		-0.095	0.1	-0.088	0.2
Major RF, number	1.1 (0.8)	1.2 (0.9)	-0.024	0.7	0.010	0.9	0.008	0.9	0.035	0.6	0.023	0.7
10 year risk for CHD [f]	2.5 (3.0)	3.2 (3.2)	-0.103	0.1	-0.090	0.2	-0.057	0.4	-0.042	0.5	-0.012	0.9
10 year risk for CVD [f]	9.3 (2.2)	10.4 (2.4)	-0.050	0.4	-0.012	0.9	0.035	0.6	0.001	1.0	-0.002	1.0
Systemic inflammation												
CRP, mg/l [f]	7.2 (3.1)	6.7 (3.1)	0.024	0.7	0.099	0.1	-		-		-	
Interleukin-6, pg/ml [f]	3.9 (1.9)	6.3 (1.9)	**-0.344**	**<0.0001**	**-0.296**	**<0.0001**	-		-		-	
Atherosclerosis												
cIMT, mm	0.700 (0.085)	0.701 (0.111)	0.025	0.7	0.062	0.4	0.076	0.3	0.013	0.9	0.036	0.7

Results are expressed as mean (SD) or proportions/percentages. Significant associations are shown in bold. [a]Adjusted for age and sex; [b]additionally adjusted for body mass index and waist to height ratio; [c]additionally adjusted for leflunomide use; [d]additionally adjusted for chloroquine use; [e]additionally adjusted for serum C-reactive protein and interleukin-6 concentrations; the number of antihypertensive agents employed and use of statins and oral glucose lowering agents as well as insulin were additionally adjusted for in models that included blood pressure and lipid variables and glucose concentrations, respectively; [f]non-normally distributed variables for which geometric mean (SD) is given. RA, rheumatoid arthritis; BP, blood pressure; CHD, coronary heart disease; cIMT, common carotid intima-media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; HDL chol, high density lipoprotein cholesterol; trig, triglycerides; LDL chol, low density lipoprotein cholesterol; RF, risk factors; T chol, total cholesterol

leflunomide and chloroquine use and systemic inflammation on the associations between RA and cardiovascular risk factors (Model 1 in Table 2) are shown in models 2 to 5. In Model 2, additional adjustment for anthropometric measures consistently attenuated the inverse associations between RA and lipid variables. In Model 3, further adjustment for leflunomide use strengthened the respective associations thereby confirming an adverse effect of leflunomide on serum lipid concentrations. In keeping with the above reported negative borderline relationship between leflunomide use and systolic blood pressure, the association between RA and hypertension was also strengthened and, in fact, significant. In Model 4, additional adjustment for chloroquine use resulted in a complete lack of association between RA and lipid parameters. In Model 5, further adjustment for serum CRP and interleukin-6 concentrations did not materially alter the results in Model 4. The same applied when lifestyle factors were adjusted for (data not shown).

In a separate model, the number of antihypertensives used (Table 1) remained higher in RA compared to non-RA subjects independent of demographic characteristics, life style factors, obesity measures, systemic inflammation and leflunomide use; amongst patients with RA, none of the disease characteristics were related to the number of antihypertensives used (data not shown).

Systemic inflammation in African black subjects with and without RA

In age and sex adjusted analysis, circulating interleukin-6 concentrations were strongly associated with circulating CRP concentrations (partial R = 0.396, $P < 0.0001$) and the presence of RA did not impact on this relationship (interaction $P > 0.1$)

Table 2 further gives serum CRP and interleukin-6 concentrations in the study subjects. Serum CRP concentrations did not differ and the serum interleukin-6 concentrations were lower in RA compared to non-RA subjects ($P = 0.7$ and $P < 0.0001$, respectively, in age and sex adjusted analysis) (Model 1 in Table 2). Adjustment for obesity measures did not materially alter these results (Model 2 in Table 2). Also, further adjustment for alcohol use, cigarettes smoked per day and the use of angiotensin converting enzyme inhibitors that were additional potential confounders in the present context (see analyses below), did not materially alter the relationship between RA and systemic inflammation (data not shown).

The lack of impact of RA on CRP concentrations and reduced interleukin-6 concentrations in patients with RA is unexpected. Therefore, we further measured CRP and interleukin-6 concentrations in 122 African whites with RA that formed part of an investigation that was previously reported by us [52]. We used the same assay as in all subjects and the one employed in non-RA subjects in the present study upon quantifying CRP and interleukin-6 concentrations (see methods), respectively. In African white patients with RA, the geometric mean (SD) CRP and interleukin-6 concentrations were 4.3 (3.7) mg/l and 3.6 (2.2) pg/ml, respectively. CRP concentrations were higher in black compared to white patients ($P = 0.002$ and 0.03 before and after adjustment for confounders (see Table 3)) and those of interleukin-6 were similar in both groups ($P = 0.4$ and 0.4 before and after adjustment for confounders).

Carotid artery atherosclerosis in African black subjects with and without RA

The carotid artery atherosclerosis burden in African black subjects with and without RA is also shown in Table 2. In age and sex adjusted analysis, the cIMT was similar in both groups ($P = 0.7$) (Model 1 in Table 2). Further adjustment for anthropometric measures, leflunomide

Table 3 Associations of potential determinants of systemic inflammation with CRP and interleukin-6 concentrations in all participants

Potential determinant	C-reactive protein[a]				Interleukin-6[a]			
	Age and sex adjusted model		Multivariable adjusted model		Age and sex adjusted model		Multivariable adjusted model	
	Partial R	*P*	Partial R	*P*	Partial R	*P*	Partial R	*P*
Body mass index	**0.240**	**0.0003**	-0.005	0.9	**0.227**	**0.0002**	**0.148**	**0.02**
Waist circumference	**0.318**	**<0.0001**			**0.173**	**0.005**		
Waist/height	**0.302**	**<0.0001**	**0.188**	**0.005**	**0.182**	**0.004**	-0.001	1.0
Waist/hip[a]	**0.163**	**0.01**			0.054	0.39		
Number of cigarettes/day[a]	0.017	0.8	0.034	0.6	**0.128**	**0.04**	**0.130**	**0.04**
Alcohol use	0.065	0.3	0.048	0.5	**0.162**	**0.008**	0.098	0.1
ACE inhibitor use	0.051	0.4	0.056	0.4	**-0.144**	**0.019**	**-0.127**	**0.045**
Model			0.350				0.331	

Significant associations are shown in bold. [a]Non-normally distributed variables that were logarithmically transformed. Except for alcohol use (only in participants without rheumatoid arthritis), none of the relationships differed in black Africans with versus those without rheumatoid arthritis (interaction $P = 0.1$ to 0.9). CRP, C-reactive protein.

and chloroquine use and systemic inflammation did not alter these results (models 2 to 5 in Table 2).

Factors associated with systemic inflammation in African black subjects with and without RA

Table 3 gives the significant associations between the potential determinants of systemic inflammation that were recorded in subjects with and without RA (characteristics shown in Table 1) and serum CRP and interleukin-6 concentrations. In age- and sex-adjusted analysis, each anthropometric measure was associated with CRP concentrations and overall and abdominal obesity measures as well as the number of cigarettes smoked, alcohol use and angiotensin converting enzyme inhibitor therapy were associated with interleukin-6 concentrations. In additional models in which these characteristics (except for waist circumference and waist-hip ratio that were omitted because of co-linearity) were entered together as independent variables, the waist-height ratio remained associated with serum CRP concentrations and the BMI, number of cigarettes smoked per day and angiotensin converting enzyme inhibitor therapy were independently associated with interleukin-6 concentrations. None of the relationships between potential determinants of systemic inflammation and serum CRP and interleukin-6 concentrations differed in black African subjects with compared to those without RA (interaction P = 0.1 to 0.9).

Table 4 shows the analyses of the associations between recorded clinical disease activity and disease severity (deformed joint count) measures and serum CRP and interleukin-6 concentrations in subjects with RA. Both in age and sex adjusted models as well as in models that included additional adjustment for potential confounders (Table 3), there were no significant relationships; the same was true when the respective associations reassessed in subgroups with no or mild disease activity (Table 5) and moderate and high disease activity (Table 7), respectively. In fact, in those with more marked disease activity, a borderline inverse relationship between the swollen joint count and interleukin-6 concentrations was noted. These results were also unexpected. Hence, to ensure that the lack of association between CRP concentrations and clinical disease activity and severity measures is specific to African black patients with RA in our setting, we also assessed the respective relationships in African whites with established RA that formed part of our previously reported investigation [52]. Indeed, in these patients, upon adjustment for demographic characteristics, the log swollen joint count (partial R = 0.536, $P < 0.0001$), log tender joint count (partial R = 0.429, $P < 0.0001$), log doctor disease activity (partial R = 0.628, $P < 0.0001$), patient disease activity (partial R = 0.464, $P < 0.0001$), log CDAI (partial R = 0.580, $P < 0.0001$), CDAI >2.7 (partial R = 0.481, $P < 0.0001$) and log deformed joint count (partial R = 0.254, $P = 0.005$) were each strongly associated with log CRP concentrations. Upon further adjustment for additional potential confounders (Table 3), these relationships remained equally strong (partial R = 0.531, 0.425, 0.614, 0.460, 0.516, 0.462 and 0.284 for log swollen and log tender joint count, log doctor and patient disease activity, log CDAI and CDAI >2.7 and log deformed joint count ($P < 0.003$ for each), respectively).

Table 7 gives the significant associations of serum CRP and interleukin-6 concentrations with the recorded cardiovascular risk factors (Table 2) in African black subjects with and without RA. In age and sex adjusted models, both inflammatory markers were related to metabolic risk that comprised lipid variables. None of the associations between systemic inflammation and cardiovascular risk factors differed in African black subjects with compared to those without RA (interaction P = 0.4 to 0.9).

Relationships between cardiovascular risk factors and carotid artery atherosclerosis in African subjects with and without RA

In age-, sex- and statin therapy-adjusted models, serum low-density lipoprotein (LDL) cholesterol concentrations

Table 4 Relationships of disease activity and severity with systemic inflammation in all 115 African RA patients

Disease activity variable	C-reactive protein[a]				Interleukin-6[a]			
	Age and sex adjusted model		Multivariable adjusted model[b]		Age and sex adjusted model		Multivariable adjusted model[b]	
	Partial R	*P*	Partial R	*P*	Partial R	*P*	Partial R	*P*
Swollen joints[a]	0.081	0.4	0.102	0.3	-0.136	0.2	-0.101	0.3
Tender joints[a]	0.005	1.0	0.009	0.9	-0.029	0.8	-0.012	0.9
Doctor disease activity[a]	0.061	0.5	0.057	0.6	0.077	0.4	0.126	0.2
Patient disease activity	-0.053	0.6	0.082	0.4	0.101	0.3	0.090	0.4
CDAI[a]	0.065	0.5	0.049	0.6	0.083	0.4	0.031	0.8
CDAI >2.7	0.069	0.5	0.088	0.4	0.129	0.2	0.163	0.1
Deformed joints[a]	0.040	0.7	0.103	0.3	-0.027	0.8	-0.016	0.9

[a]Non-normally distributed variables that were logarithmically transformed; [b]additionally adjusted for potential confounders of body mass index, waist:height ratio and angiotensin converting enzyme inhibitors (see Table 3). CDAI, Clinical Disease Activity Index.

Table 5 Relationships of disease activity and severity with systemic inflammation in non- or mildly active RA.

Disease activity variable	C-reactive protein[a]				Interleukin-6[a]			
	Age and sex adjusted model		Multivariable adjusted model[b]		Age and sex adjusted model		Multivariable adjusted model[b]	
	Partial R	*P*	Partial R	*P*	Partial R	*P*	Partial R	*P*
Swollen joints[a]	0.082	0.6	0.063	0.7	-0.189	0.2	-0.147	0.3
Tender joints[a]	-0.067	0.6	-0.100	0.5	-0.173	0.2	-0.168	0.3
Doctor disease activity[a]	0.044	0.8	0.017	0.9	-0.126	0.4	-0.027	0.9
Patient disease activity	-0.148	0.3	-0.139	0.3	0.070	0.6	0.011	0.9
CDAI[a]	-0.034	0.8	-0.060	0.7	-0.143	0.3	-0.116	0.4
Deformed joints[a]	0.071	0.6	0.119	0.4	-0.081	0.6	0.013	0.9

Fifty-four patients had no or mild disease activity (CDAI = 0 to 10). [a]Non-normally distributed variables that were logarithmically transformed; [b]additionally adjusted for potential confounders of body mass index, waist:height ratio and angiotensin converting enzyme inhibitors (see Table 3). CDAI, Clinical Disease Activity Index.

Table 6 Relationships of disease activity and severity with systemic inflammation in moderately or highly active RA

Disease activity variable	C-reactive protein[a]				Interleukin-6[a]			
	Age and sex adjusted model		Multivariable adjusted model[b]		Age and sex adjusted model		Multivariable adjusted model[b]	
	Partial R	*P*	Partial R	*P*	Partial R	*P*	Partial R	*P*
Swollen joints[a]	0.025	0.9	0.113	0.4	-0.260	0.07	-0.246	0.1
Tender joints[a]	0.028	0.8	0.014	0.9	-0.131	0.4	-0.120	0.4
Doctor disease activity[a]	0.100	0.5	0.084	0.6	0.212	0.2	0.232	0.1
Patient disease activity	-0.092	0.5	-0.066	0.7	0.222	0.1	0.225	0.2
CDAI[a]	0.066	0.6	0.111	0.5	0.125	0.4	0.147	0.3
Deformed joints[a]	0.041	0.8	0.028	0.8	0.012	0.9	-0.050	0.7

Sixty-one patients had moderate or high disease activity (CDAI > 10). [a]Non-normally distributed variables that were logarithmically transformed; [b]additionally adjusted for potential confounders of body mass index, waist:height ratio and angiotensin converting enzyme inhibitors (see Table 3). CDAI, Clinical Disease Activity Index.

Table 7 Associations of systemic inflammation with cardiovascular risk factors in RA and non-RA African subjects

Cardiovascular risk factor	C-reactive protein[a]		Interleukin-6[a]	
	Partial R	*P*	Partial R	*P*
HDL chol[a]	**-0.247**	**0.0002**	-0.109	0.08
Chol/HDL chol	**0.208**	**0.002**	0.104	0.10
Triglycerides/HDL chol[a]	**0.170**	**0.01**	**0.147**	**0.02**
LDL chol/HDL chol[a]	**0.202**	**0.002**	0.038	0.5

Relationships were assessed in age and sex adjusted models. Significant associations are shown in bold. HDL, high density lipoprotein; chol, cholesterol; LDL, low density lipoprotein. None of the relationships differed in black Africans versus those without rheumatoid arthritis (interaction $P = 0.4$ to 0.9).

were associated with cIMT (partial R = 0.153, $P = 0.032$). Further adjustment for other traditional risk factors comprising hypertension, diabetes and smoking did not materially alter these associations (R = 0.135, $P = 0.06$). The other recorded cardiovascular risk factors (Table 2) were not associated with cIMT and the relationships between cardiovascular risk factors and cIMT were consistently similar in black African subjects with compared to those without RA (interaction $P > 0.2$).

Discussion

Among African black subjects from a developing population, patients with RA experienced markedly reduced adiposity compared to their non-RA counterparts. RA was not independently associated with hypertension, dyslipidemia, smoking and diabetes and the overall major traditional risk factor burden was similar in RA compared to non-RA subjects. Serum CRP concentrations were not increased in RA and further unrelated to disease activity and severity, a finding that was specific to African black patients with RA. The carotid artery atherosclerosis extent did not differ by RA status. To our knowledge, this is the first study that evaluated the association of RA with cardiovascular risk factors and atherosclerosis in African black persons.

In the present study, non-RA subjects experienced an apparently large systemic inflammation burden with mean circulating CRP and interleukin-6 concentrations of 6.7 mg/l and 6.3 pg/ml, respectively. Of likely relevance in the present context, the pro-inflammatory cytokine interleukin-6 *IL-6*-174 G/G genotype was found 36.5 (95% CI = 8.8 to 159.1) times more frequently in African compared to white Americans [65]. The most striking finding in the current investigation was the

absence of increased systemic inflammation in RA compared to non-RA subjects despite the presence of clinically active disease [63] in >80% of the patients. This is in sharp contrast to the RA associated six- to seven-fold increase in both CRP and interleukin-6 concentrations in a study on mostly white patients with RA, as previously reported by us [21]. In addition, there was an overall lack of impact of RA on the relationships of circulating interleukin-6 and CRP concentrations with their potential determinants and metabolic risk factors. The concentrations of circulating interleukin-6 that constitute the major determinant of hepatic CRP production [12,17] were higher in non-RA compared to RA black Africans even after adjusting for confounders. However, the full impact of disparities in potential confounders including adiposity measures, smoking, alcohol consumption and angiotensin converting enzyme inhibitor use [16,66-68] on the association of RA status with circulating interleukin-6 concentrations may not have been accounted for in multivariable models, particularly given the cross-sectional design of our study.

Our findings have important implications. First, they suggest that interleukin-6 produced in inflamed joints is not released into the circulation in black Africans with established RA. As well, the very low prevalence of extra-articular manifestations among black Africans with RA [52,69] supports the presence of an inflammatory process that is mostly restricted to the joints. Since race specific therapeutic responses to interleukin-6 blockade with tocilizumab were not observed in randomized controlled trials that included black patients, interleukin-6 should be equally important in the pathogenesis of RA induced synovitis in black compared to other subjects [70].

Second, based on reported consistent results that originate in patients with RA from developed populations, a lack of adverse impact of RA on systemic inflammation would be expected to translate in unaltered cardiovascular risk factor profiles and disease [20,21,32,33,71,72]. Indeed, among African black subjects, RA was not related to adverse metabolic risk and atherosclerosis. Furthermore, whereas in patients with RA from developed populations, the associations of traditional cardiovascular risk factors with CVD are weakened due to the substantial contribution of systemic inflammation to cardiovascular mortality [31], in the present study, black Africans with RA experienced similar cardiovascular risk factor-atherosclerosis associations compared to their non-RA counterparts.

Third, our findings could explain the apparent disparities in RA-adiposity relationships among our patients and those that participated in previously reported studies [35-37,73,74]. Thus, patients with RA from developed populations sustain reduced lean body mass and increased adiposity that is mediated mainly by systemic inflammation and results in an overall unaltered or increased BMI and waist circumference, together with a more central fat distribution that enhances cardiovascular metabolic risk [35-37,73,74]. Accordingly, this condition has also been termed 'rheumatoid cachectic obesity' and 'hypercytokinaemic cachexia' [35]. In the present study, RA in black persons was associated with reduced overall and abdominal obesity indices and not with an altered fat distribution as estimated by waist-hip ratio. Waist circumference is determined by abdominal fat and hip circumference by lean mass and subcutaneous fat [75,76]. The waist and hip circumference were reduced to a similar extent in RA compared to non-RA subjects in this study. Reduced adiposity indices partially explained more favorable lipid profiles in RA in mixed regression models and, hence, may protect against CVD. Although systemic inflammation was not increased in African black patients with RA, their cumulative joint inflammation was distinctively large with a mean joint deformity count of 9.7. The joint deformity count is inversely related to BMI, waist and waist-height but not waist-hip ratio in African black women with RA [38] and the same relationships were found in the present investigation (data not shown). Reported findings together with our results therefore indicate that high-grade systemic and joint restricted inflammation may have disparate effects on adiposity and its distribution in RA.

Last, C-reactive protein concentrations should not be relied upon when determining the need for DMARD intensification in African black patients with RA.

Chloroquine, a long standing treatment in rheumatic diseases, can reduce hepatic cholesterol synthesis and increase LDL receptor numbers on fibroblasts and enhances insulin secretion and sensitivity [43-45]. We found that the associations of RA with a range of serum lipid concentrations and their ratios, including the triglycerides-HDL cholesterol ratio that is a marker of insulin resistance [77], were attenuated and no longer significant once chloroquine use was accounted for. Studies aimed at determining the true independent impact of RA on cardiovascular risk factor profiles should consider confounding by RA treatment.

Despite a low smoking prevalence and the small number of cigarettes consumed daily, the 10-year risk for CVD was substantial at approximately 10% in black Africans. These data are reminiscent of an earlier health transition stage that characterizes developing populations [49,50].

As previously reported in developed populations, RA was not associated with an augmented prevalence of hypertension in the present investigation [34]. Further, high frequencies of untreated and uncontrolled hypertension were documented earlier in RA [46] and, in black Africans, these also did not differ by RA status. Notably, however, despite similar blood pressure values

to those in non-RA subjects, patients with RA employed more frequent and twice as many antihypertensive agents, a disparity that remained unexplained in multivariable analysis. Whether and how RA could influence hypertension responsiveness to antihypertensive therapy deserves to be determined in longitudinal studies.

The present study has further limitations. Carotid artery plaques are more strongly associated with coronary heart disease and its risk factors than cIMT that relates more closely to stroke and its determinants [38]. Nevertheless, both cIMT and plaque predict future cardiovascular event rates in RA and non-RA subjects irrespective of ethnicity [78-81]. Serum LDL concentrations were independently associated with cIMT that therefore would be expected to reflect atherosclerosis and coronary heart disease risk in black Africans. As applies to most studies on CVD, many relationships were evaluated. Our main findings each originated in confounder-adjusted multivariable models.

Conclusions

RA associates with markedly reduced overall and abdominal adiposity in black Africans. However, in confounder adjusted analysis, RA did not impact on major traditional cardiovascular risk factor profiles, atherosclerosis extent and their relationships in this population. An absence of interleukin-6 release by inflamed RA joints into the circulation may account for this unaltered cardiovascular risk.

Abbreviations

BMI: body mass index; BP: blood pressure; CDAI: Clinical Disease Activity Index; CHD: coronary heart disease; CI: confidence interval; cIMT: carotid intima-media thickness; CRP: C-reactive protein; CVD: cardiovascular disease; DMARDs: disease modifying drugs for rheumatic disease; HDL: high density lipoprotein; LDL: low density lipoprotein; NSAID: nonsteroidal anti-inflammatory drug; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PHD contributed to the conception and design, performed the statistical analysis and drafted the manuscript. AJW and GRN provided the data in non-RA subjects and contributed to the conception and design, and analysis and interpretation of the data. AS provided the data in RA subjects in whom he also performed the ultrasound examinations and contributed to the conception and design, and revising the manuscript. All authors read and approved the final manuscript.

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Paper 3

In this paper, we compared the (1) atherosclerosis burden and (2) associations of traditional and non-traditional cardiovascular risk factors with atherosclerosis measures between black and white African patients with RA. The atherosclerosis burden was as large in black compared to white African RA patients with a similar carotid intima-media thickness as well as plaque prevalence.

Interaction and stratified analysis produced consistent disparities in cardiovascular risk factor-atherosclerosis relations among black and white African patients with RA. Thus, in white African RA patients, systolic blood pressure was related to both carotid intima-media thickness and plaque; further, the total cholesterol-high density lipoprotein cholesterol ratio and C-reactive protein concentrations were associated with carotid intima-media thickness and extraarticular manifestations were related to carotid plaque. The Framingham score explained 22% of the variation in intima-mediathickness values. By contrast, in black African RA patients, the Arthritis Impact Measurement Scales tension score was associated with both the carotid intima-media thickness and plaque; non-steroidal anti-inflammatory agent use was also related to plaque prevalence in this group but as only 7.4% of them employed the respective medication, this finding needs further

investigation. The Framingham score explained a non-significant ($p = 0.06$) mere 3.2% of the variation in carotid intima-media thickness.

Taken together, traditional and non-traditional cardiovascular risk factors were associated with atherosclerosis in white African RA patients as previously reported in developed populations. By contrast, tension symptoms comprised the only cardiovascular risk factor that was consistently related to atherosclerosis in black African patients with RA. Again, this finding is reminiscent of the presence of an early epidemiological transition stage. These findings argue strongly against the extrapolation of recommendations on cardiovascular disease risk stratification in RA patients from developed populations to those of black African ancestry. Our findings on the Framingham score-atherosclerosis relationships further support this interpretation. The systematic use of vascular imaging may be needed in order to obtain adequate cardiovascular risk stratification in black African RA patients at the present stage.

As the prevalence of excess adiposity is particularly large in black African women, what is the potential contribution of adiposity as assessed by different anthropometric measures, to atherosclerosis in black compared to white Africans with RA?

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The Carotid Artery Atherosclerosis Burden and Its Relation to Cardiovascular Risk Factors in Black and White Africans with Established Rheumatoid Arthritis: A Cross-sectional Study

AHMED SOLOMON, ANGELA J. WOODIWISS, ABU T. ABDOOL-CARRIM, BELINDA A. STEVENS, GAVIN R. NORTON and PATRICK H. DESSEIN

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The Carotid Artery Atherosclerosis Burden and Its Relation to Cardiovascular Risk Factors in Black and White Africans with Established Rheumatoid Arthritis: A Cross-sectional Study

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ABSTRACT. ***Objective.*** Black Africans currently experience a distinctly low frequency of atherosclerotic cardiovascular disease. Whether this protection persists in those with rheumatoid arthritis (RA) is unknown. We compared the carotid atherosclerosis burden and its relationships with cardiovascular (CV) risk factors between Africans with RA from a developing black and developed CV population.

Methods. We performed high resolution B-mode ultrasonography and assessed CV risk factors in 243 patients with established RA, of whom 121 were black and 122 white. Data were analyzed in age, sex, and healthcare center-adjusted regression models.

Results. The mean ± SD common carotid intima-media thickness (cIMT) was 0.694 ± 0.097 mm in black and 0.712 ± 0.136 mm in white patients (adjusted p = 0.8). Plaque prevalence was also similar in black compared to white cases (35.5% and 44.3%, respectively; adjusted OR 0.83, 95% CI 0.32–2.20, p = 0.7). Interactions between population grouping and several CV risk factors were independently associated with cIMT and plaque. In stratified analysis, that is, in each population group separately, risk factors associated with cIMT or/and plaque comprised the systolic blood pressure (p = 0.02), serum cholesterol/high-density lipoprotein cholesterol ratio (p = 0.004), C-reactive protein concentrations (p = 0.01), and the presence of extraarticular manifestations (p = 0.01) in whites but, contrastingly, the Arthritis Impact Measurement Scales tension score (p = 0.04) and use of nonsteroidal antiinflammatory agent (p = 0.03) in black patients. The Framingham score was significantly associated with atherosclerosis only in whites (p < 0.0001).

Conclusion. The carotid atherosclerosis burden is similar in black compared to white Africans with RA, but relationships between modifiable CV risk factors and atherosclerosis vary substantially among Africans with RA. (First Release July 1 2012; J Rheumatol 2012;39:1798–806; doi:10.3899/jrheum.120073)

Key Indexing Terms:
ATHEROSCLEROSIS RHEUMATOID ARTHRITIS DEVELOPING POPULATION
CARDIOVASCULAR RISK FACTORS AFRICANS

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Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease that is recognized to enhance the risk for atherosclerotic cardiovascular disease (CVD) events about 2-fold[1]. The standardized CV mortality ratio is increased by 50% in RA and thereby accounts for most of the excess overall mortality caused by this disease[2].

CVD in RA is brought about by traditional and nontraditional CV risk factors or disease characteristics, particularly inflammation[3,4,5,6,7,8,9,10]. Importantly also in this context, whereas genetic factors contribute substantially to CVD in the population at large[11], the same likely applies in RA. Indeed, genetic polymorphisms that are implicated in inflammatory pathways such as the TNFA-308 (rs1800629)[12] and the CCR5Δ32 variant[13] and metabolic pathways including the acid phosphatase locus 1*C allele[14] were recently shown to be associated with CVD in patients with RA. Further, genes that

influence RA susceptibility can influence CVD[15] and its conventional risk factors in RA[16]. These findings may enable elucidation of the molecular mechanisms involved, discovery of new therapeutic targets, and optimization of risk assessment in RA-related CVD.

Our knowledge of CVD in the general population and even more in persons with chronic inflammatory diseases such as RA largely derives from studies that were performed in developed populations[17,18]. However, ~80% of CVD now arises in middle and low-income groups or in developing countries[17]. Further, the effect of individual CV risk factors on CV events may differ in the developing compared to the developed nations[18,19,20].

South Africa, a sub-Saharan country with 50 million inhabitants, has become the most unequal society in the world[21]. A minority of South Africans follow a westernized lifestyle, live in modern cities, and represent a developed and mostly white population, whereas the majority still follow a more traditional lifestyle, live outside these cities, and typify a developing and predominantly black population[20,22,23]. Accordingly, these populations are at different stages of the epidemiological health transition, and the incidence of CVD is still distinctly uncommon in black compared to white sub-Saharan Africans[18,20,22]. However, whether this protection is present in black Africans in the face of established RA is unknown. The South African Heart Association recommends the European Society of Cardiology and European Atherosclerosis Society guidelines on CV risk assessment and management irrespective of population grouping or socioeconomic factors[24]. In keeping with an earlier epidemiological transition stage, we recently identified several disparities in individual CVD risk factor profiles between blacks and other Africans with RA (whites, Asians, and people of mixed ancestry) but the overall traditional and nontraditional CVD risk burden was similar in both populations[18]. In our present study, we compared the ultrasonographically determined carotid atherosclerosis burden, a predictor of CVD events in the general population and in patients with RA[24,25,26], in black and white Africans with RA. Additionally, we investigated whether disparities exist in the relationships of modifiable CVD risk factors with carotid atherosclerosis between the 2 populations.

MATERIALS AND METHODS

Study populations. We enrolled patients during the period March 23 to November 25, 2009, who met the American College of Rheumatology criteria for RA[27], at the Charlotte Maxeke Johannesburg Academic Hospital (public healthcare) and Milpark Hospital (private healthcare) in Johannesburg (Table 1). None of the recorded data have been reported previously. Only patients that had used disease-modifying agents were included; 4 invited patients refused to participate and those known to be infected with the human immunodeficiency virus (HIV) were excluded. Considering the aims of the investigation, we also excluded patients of mixed ancestry and Asians with RA because they are not consistently at the same epidemiological transition stage as either black or white Africans[20]. The HIV prevalence in South Africans aged 50 years and older is currently 5.7%[28]; and Asians and people of mixed ancestry comprise 11% and 8%, and 8% and 5% of patients with RA in our public and private healthcare centers, respectively[18].

Table 1. African patients (n = 243) with RA by sex and healthcare center.

	Black, n (%)	White, n (%)	p
All participants	121 (49.8)	122 (50.2)	—
Sex			
Women	108 (89.3)	95 (77.9)	
Men	13 (10.7)	27 (22.1)	0.02
Healthcare center			
Public	117 (96.7)	22 (18.0)	
Private	4 (3.3)	100 (82.0)	< 0.0001

RA: rheumatoid arthritis.

Whereas patients attending South African public healthcare centers currently have no access to use of biological agents for RA, this intervention was employed in 10 private-care patients (tumor necrosis factor-α blockade in 9 and rituximab in 1), all whites. Biological and nonbiological disease-modifying antirheumatic drugs (DMARD) were grouped into the same single variable for the purpose of our data analysis. Nonsteroidal antiinflammatory drugs (NSAID) used in black and white patients comprised nonselective cyclooxygenase (COX) inhibitors (indomethacin and ibuprofen) in the former and both traditional NSAID (ibuprofen, diclofenac, and meloxicam) and selective COX-2 inhibitors (celecoxib and etoricoxib) in the latter.

The study was approved by the Ethics Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand. Written informed consent was obtained from each patient.

Assessments. CV risk factors that were assessed are presented in Table 2. Data were missing in < 5% for any of the recorded characteristics. All patients fasted for at least 8 h prior to blood sampling. Hypertension was defined as average systolic blood pressure ≥ 140 mm Hg or/and diastolic blood pressure ≥ 90 mm Hg or/and current use of antihypertensive medications. Serum total cholesterol and low and high-density lipoprotein (LDL, HDL) concentrations were determined by enzymatic assays, serum triglyceride concentrations by the glycerol phosphate oxidase method, and C-reactive protein (CRP) concentrations by nephelometry. Dyslipidemia was diagnosed when the atherogenic index, i.e., cholesterol/HDL cholesterol ratio, was > 4, and the proatherogenic non-HDL concentrations were calculated by subtracting HDL cholesterol from total cholesterol concentrations[18,29,30]. Current smoking status was assessed. Diabetes was defined as plasma glucose concentration ≥ 7 mmol/l or/and use of glucose-lowering agents. We recorded alcohol use (at least 1 unit per month), exercise (at least once per month and including time spent in walking, that is, to reach public transport), marital status, education level (years of education), body mass index (BMI), waist circumference, and the waist-hip ratio. Symptoms of tension and depression were estimated by the Arthritis Impact Measurement Scales (AIMS)[31].

RA characteristics evaluated as potential CV risk factors comprised the rheumatoid factor status, extraarticular manifestations (see below), use of antirheumatic agents including NSAID, prednisone, and number of prescribed DMARD, RA duration, the Disease Activity Score in 28 joints (DAS28), serum CRP concentrations, the Stanford Health Assessment Questionnaire Disability Index, and the number of deformed joints[18,32]. Extraarticular manifestations included current or previously recorded (hospital record review) presence of pericarditis, pleuritis, Felty's syndrome, cutaneous vasculitis, neuropathy, scleritis or episcleritis, retinal vasculitis, glomerulonephritis, vasculitis affecting other organs, amyloidosis, keratoconjunctivitis sicca, xerostomia, Sjögren's syndrome, pulmonary fibrosis, bronchiolitis obliterans organizing pneumonia, cervical myelopathy, and subcutaneous nodules and rheumatoid nodules in other locations[32,33].

Two authors (BAS, AS) performed the carotid artery ultrasound measurements in private and public healthcare patients, respectively. Both operators obtained images of at least 1-cm length of the distal common carotid arteries for measurement of the intima-media thickness of the far wall from an optimal angle of incidence, defined as the longitudinal angle of approach where

Table 2. Cardiovascular risk factor profiles in black compared to white patients with RA. Dichotomous variables are expressed as proportions or percentages and continuous characteristics as mean ± SD. Significant associations are shown in bold type.

Characteristics	Black, n = 121	White, n = 122	OR* (95% CI)
Female sex	89.3	77.9	—
Major conventional CV risk factors			
Hypertension	**71.9**	**45.9**	**2.43 (1.00–5.94)**
T chol/HDL chol > 4	22.2	15.8	1.78 (0.56–5.64)
Smoking	3.3	9.9	0.22 (0.05–1.05)
Diabetes	16.5	7.4	1.78 (0.47–6.65)
Other conventional CV/predisposing risk factors			
Alcohol use	**2.5**	**38.0**	**0.05 (0.01–0.15)**
Exercise	39.7	33.3	0.93 (0.39–2.18)
Marital status			
Unmarried	38.0	7.4	2.88 (0.92–9.05)
Married	37.2	75.4	0.52 (0.22–1.26)
Divorced	8.3	9.0	0.82 (0.19–3.42)
Widowed	16.5	8.2	1.56 (0.38–6.39)
Nonconventional CV risk factors			
Rheumatoid factor-positive	50.5	48.3	1.02 (0.38–2.75)
Extraarticular manifestations	**2.5**	**12.3**	**0.19 (0.05–0.67)**
Antirheumatic agent used			
NSAID	7.4	27.0	3.18 (0.56–18.16)
Prednisone	1.7	3.3	0.50 (0.09–2.78)
Continuous variables, mean ± SD			p*
Age, yrs	55.8 ± 10.1	58.2 ± 11.4	—
Major conventional CV risk factors			
Systolic blood pressure	140 ± 24	128 ± 17	0.5
Diastolic blood pressure	**86 ± 15**	**79 ± 9**	**0.02**
T chol, mmol/l	**4.7 ± 0.9**	**5.0 ± 1.1**	**0.03**
HDL chol†, mmol/l	1.48 ± 1.34	1.61 ± 1.03	0.05
T chol/HDL chol	3.2 ± 1.1	3.2 ± 1.0	0.6
LDL chol, mmol/l	2.6 ± 0.8	2.8 ± 0.9	0.2
Non-HDL chol, mol/l	3.1 ± 0.9	3.3 ± 1.0	0.2
Pack-year history of smoking†, yrs	**0.1 ± 1.7**	**2.8 ± 5.2**	**0.008**
Major risk factors, n	1.2 ± 0.8	0.8 ± 0.7	0.1
Framingham score†	2.6 ± 3.0	2.9 ± 3.0	0.5
Other conventional CV/predisposing risk factors			
Exercise†, hours per wk	0.6 ± 2.0	0.6 ± 2.1	0.2
Education, yrs	**7.4 ± 4.1**	**13.0 ± 2.7**	**0.0002**
BMI, kg/m^2	**29.4 ± 6.6**	**25.6 ± 4.7**	**0.003**
Waist circumference, cm	93.4 ± 13.4	88.8 ± 13.0	0.08
Waist/hip†	0.85 ± 3.65	0.86 ± 1.11	0.6
Triglycerides†, mmol/l	1.08 ± 1.71	1.08 ± 1.51	0.6
AIMS tension†	3.8 ± 1.5	2.8 ± 1.7	0.1
AIMS depression†	3.2 ± 1.5	1.8 ± 1.7	0.1
Nonconventional CV risk factors			
Disease duration, yrs	12.8 ± 9.2	14.3 ± 9.3	0.5
DAS28	4.1 ± 1.3	3.6 ± 1.6	0.3
CRP†, mg/l	7.0 ± 3.1	4.3 ± 3.7	0.9
HAQ score†	0.54 ± 0.41	0.37 ± 0.43	0.5
Deformed joints†	6 ± 2	4 ± 4	0.08
No. DMARD	2.5 ± 1.0	2.2 ± 0.9	0.4

CV: cardiovascular; T: total; chol: cholesterol; BMI: body mass index; AIMS: Arthritis Impact Measurement Scales; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drugs; RA: rheumatoid arthritis; HDL: high-density lipoprotein; NSAID: nonsteroidal antiinflammatory drug; LDL: low-density lipoprotein. * OR and p value for comparisons between black and white Africans after adjustment for age, sex, and healthcare center as well as lipid-lowering and antihypertensive agents in models that include lipid and systolic and diastolic blood pressure variables, respectively. † Logarithmically transformed variables for which geometric means (SD) are given.

both branches of the internal and external carotid artery are visualized simultaneously[34]. They used high-resolution B-mode ultrasound (Image Point, Hewlett Packard, Andover, MA, USA, and SonoCalc IMT, Sonosite Inc., Bothell, WA, USA; used by BAS and AS, respectively) with linear array 7.5-MHz probes. Details of the methodology used by BAS were as reported[3]. The equipment used by AS involved application of a unique semiautomated border detection program that was found to provide highly reproducible results[34]. The intima-media thicknesses in the left and right common carotid artery were measured; carotid intima-media thickness (cIMT) was defined as the mean of these. Carotid artery plaque was defined as a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness value, or demonstrates a thickness of > 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface[35]. Both operators were blinded to the CV risk profiles of the patients. Repeat ultrasound examinations by both operators on 23 patients revealed Spearman correlations between repeat cIMT measurements of 0.983 for BAS and 0.956 for AS, and the correlation between measurements made by BAS and AS was 0.926. Both operators identified carotid artery bulb or/and internal carotid artery plaque in 11 of these 23 patients with full agreement.

Statistical methods. We grouped the CV risk factors into 3 categories[18] (Table 2): (1) the major modifiable conventional risk factors of hypertension, dyslipidemia, smoking, and diabetes that feature in the Framingham score; (2) other CV conventional risk or predisposing factors including alcohol use, exercise, marital status, education level, BMI, waist circumference, waist-hip ratio, serum triglyceride concentrations, and the AIMS tension and depression scores; and (3) nonconventional risk factors consisting of RA characteristics.

Dichotomous variables are expressed as proportions or percentages and continuous variables as mean ± SD. Non-normally distributed characteristics were logarithmically transformed prior to statistical analysis and for these variables geometric means ± SD are given. The selection of potential confounders in multivariate regression models was based on biological plausibility.

Relationships between population grouping, or in the present context, also ethnic grouping (EG) and CV risk factors were investigated in multivariable logistic and linear regression models as appropriate and with consistent adjustment for age, sex, and healthcare center attendance. Prescribed antihypertensive therapy and statin use were further adjusted for when assessing associations with blood pressure and lipid variables, respectively.

The mean ± SD cIMT was compared between black and white patients by the Student t test and in age, sex, and healthcare center-adjusted linear multivariate logistic regression analysis; plaque prevalence was compared in univariate and age, sex, and healthcare center-adjusted multivariate logistic regression models.

To determine whether there were disparities in the relationships of modifiable CV risk factors with atherosclerosis in black compared to white patients, we assessed the associations of interactions between EG and the recorded risk factors with cIMT and plaque in multivariable regression models in which age, sex, and healthcare center and the individual terms were adjusted for, and subsequently performed stratified analysis.

The study was 95% powered to detect a significant ($p < 0.01$) difference in mean cIMT of 0.100 mm (the expected increase per 10-year age increment[36]) in multiple regression analysis with inclusion of 3 covariates between black and white Africans with RA. Statistical computations were made using the GB Stat™ program (Dynamic Microsystems, Silver Spring, MD, USA).

RESULTS

Patient characteristics. Patient characteristics are shown in Tables 1 and 2. A total of 243 patients comprising 121 blacks and 122 whites were investigated. Black patients were more often women ($p = 0.02$) and were on average 2.4 years younger ($p = 0.08$) than their white counterparts. About 97% of black patients and 82% of whites were seen in public and private care, respectively.

Antihypertensives were used more frequently in black patients (54.6% vs 41.8%; OR 1.67, 95% CI 1.00–2.78) and statins more often in whites (36.1% vs 19.0%; OR 2.40, 95% CI 1.33–4.33). In confounder-adjusted analysis (Table 2), compared to whites, black patients experienced a higher prevalence of hypertension and had a higher diastolic blood pressure, but smoked less; their mean serum total cholesterol concentration was lower, but with concurrent numerically lower HDL cholesterol concentrations the total cholesterol/HDL cholesterol ratio was similar. These results translated into an overall major conventional CV risk burden, as estimated by the number of major risk factors and the Framingham score, that was similar in black and white patients. Disparities in other conventional CV/predisposing risk factors (Table 2) included a higher BMI, less frequent alcohol use, and a lower education level in black compared to white patients.

Among the nonconventional or predisposing CV risk factors shown in Table 2, black patients experienced extraarticular manifestations less often than their white counterparts. Although the geometric mean CRP concentrations were substantially higher (2.7 mg/l) in black compared to white patients ($p = 0.002$ in univariate analysis), this difference was not significant ($p = 0.9$) in age, sex, and healthcare center-adjusted analysis.

Carotid atherosclerosis in black and white Africans with RA. The mean cIMT was 0.694 ± 0.097 mm in black and 0.712 ± 0.136 mm in white patients with RA ($p = 0.3$). Forty-three of the black (35.5%) and 54 white patients (44.3%) had plaque ($p = 0.3$). As illustrated in Figure 1, these results were unaltered after adjustment for age, sex, and healthcare center and after further adjustment for disease duration and prednisone use as well as CV risk factors that differed between black and white patients (Table 2) and included hypertension, total and HDL cholesterol, pack-year smoking history, alcohol use, presence of extraarticular manifestations, education level, BMI, and number of deformed joints. The latter models in Figure 1 may be overfitted because 14 independent variables were entered, and hence any real difference between the mean cIMT and plaque prevalence between black and white patients could be disguised. However, when we entered disease duration, prednisone use, hypertension, total and HDL cholesterol, pack-year smoking history, alcohol use, the presence of extraarticular manifestations, education level, BMI, and number of deformed joints as potential confounders, each separately and together with age, sex, and healthcare center in different models, the results remained consistently unaltered: the cIMT remained similar in blacks compared to whites ($p = 0.6$ to 1.0) and population or ethnic grouping (EG) remained unassociated with plaque (OR 0.79 to 0.96, 95% CI 0.32–0.96, 95% CI 1.96–2.62, $p = 0.5$ to 0.9) in each of the models.

Disparities in relationships of modifiable CV risk factors with carotid atherosclerosis in black compared to white patients

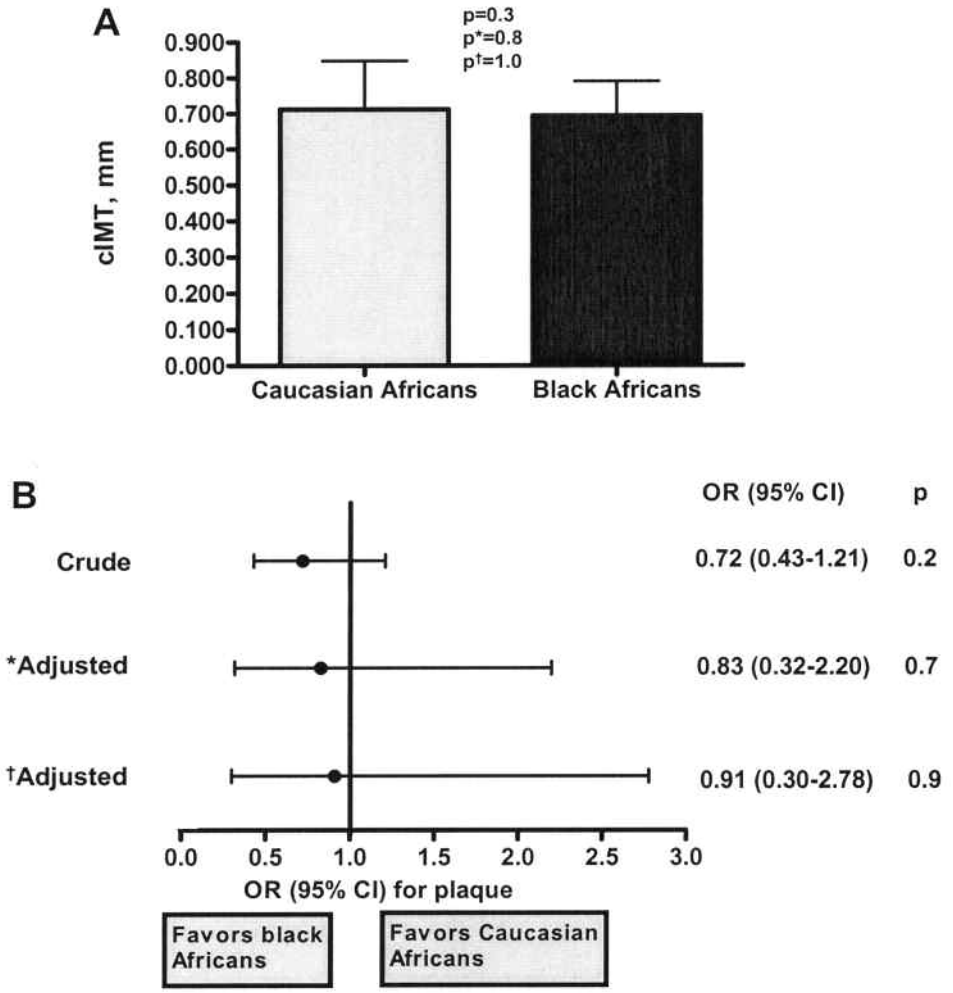

Figure 1. The carotid artery atherosclerosis burden in black and white Africans with rheumatoid arthritis (RA). A. Carotid intima-media thickness (cIMT) in black compared to white patients with RA. B. The association of population or ethnic grouping with carotid artery plaque. Results are expressed as mean (SD) and the corresponding p value in univariate analysis (Student t test) as well as p values in confounder-adjusted linear regression models in panel A, and as OR (95% CI) and the corresponding p values in univariate and confounder-adjusted logistic regression models in panel B. *Adjusted for age, sex, and healthcare center. †Further adjusted for disease duration and prednisone use as well as cardiovascular risk/predisposing factors that differed between black and white patients (Table 2) and included hypertension, total and HDL cholesterol, pack-year smoking history, alcohol use, presence of extraarticular manifestation, education, body mass index, and number of deformed joints.

with RA. In age, sex, and healthcare-adjusted analysis in all patients, these factors were associated with the cIMT: hypertension [partial correlation coefficient in multivariable linear regression model (pr) = 0.13, p = 0.04)], log HDL cholesterol concentrations (pr = –0.16, p = 0.01), LDL cholesterol concentrations (pr = 0.15, p = 0.02), non-HDL cholesterol concentrations (pr = 0.13, p = 0.04), BMI (pr = 0.13, p = 0.04), and DAS28 (pr = 0.13, p = 0.04). No CV risk factors were associated with plaque in all patients.

Interactions between EG and recorded individual CV risk factors (Table 2) that were associated with cIMT in all patients independent of confounders and individual terms are shown in Table 3; they comprised EG × systolic blood pressure, EG × total cholesterol/HDL cholesterol ratio, EG × CRP concentration, and EG × AIMS tension score. In stratified analysis, the systolic blood pressure, total cholesterol/HDL cholesterol, and CRP concentration were associated with the cIMT in white but not in black patients; conversely, the AIMS tension score was related to the cIMT in black but not in white patients. In an additional model, systolic blood pressure (pr = 0.21, p = 0.03), total cholesterol/HDL cholesterol (pr = 0.21, p = 0.03), and CRP concentration (pr = 0.21, p = 0.03) were associated with cIMT in whites, independent of one another and of confounders; further, the association of the AIMS tension score with cIMT among black patients with RA was materially unaltered (pr = 0.18, p = 0.07) after adjustment for socioeconomic factors as potential confounders and comprising marital status, education, alcohol use, and pack-year smoking history.

Table 3. Associations of modifiable CV risk factors with common carotid intima-media thickness (cIMT) in black and white patients with RA separately. Significant associations are shown in bold type.

CV Risk Factor	Black and White Patients Combined Interaction p	Stratified Analysis: Blacks Partial R*	p	Whites Partial R*	p
Systolic blood pressure	**0.005**	–0.06	0.4	**0.24**	**0.01**
Total chol/HDL chol	**0.01**	0.05	0.6	**0.26**	**0.004**
C-reactive protein†	**0.01**	0.11	0.2	**0.24**	**0.01**
AIMS tension†	**0.005**	**0.19**	**0.04**	0.06	0.5

CV: cardiovascular; chol: cholesterol; AIMS: Arthritis Impact Measurement Scales; HDL: high-density lipoprotein. * Partial correlation coefficients in multivariable regression models in which age, sex, and healthcare center were entered as potentially confounding variables. † Log transformed.

Interactions between EG and CV risk factors that were independently associated with carotid artery plaque are shown in Table 4; they comprised EG × systolic blood pressure, EG × extraarticular manifestations, EG × AIMS tension score, and EG × NSAID use. In stratified analysis, systolic blood pressure and presence of extraarticular manifestations were associated with plaque in white but not black patients; conversely, the AIMS tension score and NSAID use were related to plaque in black but not white patients. In additional models, systolic blood pressure (OR per 10-mm Hg increase = 1.37, 95% CI 1.03–1.82, p = 0.03) and the presence of extraarticular manifestations (OR 5.83, 95% CI 1.34–25.39, p = 0.02) in white patients and the AIMS tension score (0 to 10 scale; OR 1.42, 95% CI 1.05–1.92, p = 0.02) and NSAID use (OR 6.75, 95% CI 1.57–39.33, p = 0.03) in black patients were associated with plaque, independent of one another and confounders. Further, among black patients, the association of the AIMS tension score with plaque with RA was materially unaltered (OR 1.31, 95% CI 1.00–1.74, p = 0.05) after adjustment for socioeconomic factors as potential confounders and comprising marital status, education, alcohol use, and pack-year smoking history, and the association of NSAID use with plaque was independent of prednisone and DMARD use.

The analysis revealed that major conventional CV risk factors were related to the cIMT in white but not in black patients. This was confirmed upon assessment of whether the association of overall major conventional CV risk as estimated by the Framingham score with cIMT differed by ethnic group. Thus, the interaction term EG × Framingham score was associated with the cIMT independent of healthcare center and individual terms (p = 0.002; age and sex were not adjusted for in the respective model since these characteristics are used in calculating the Framingham score). In stratified analysis, the Framingham score was significantly associated with cIMT in white (pr = 0.47, p < 0.0001) but not in black (pr = 0.18, p = 0.06) patients.

DISCUSSION

We found the carotid artery atherosclerosis burden sustained by black Africans with established RA was similar to that in whites. An increased cIMT in the presence of hypertension may reflect arterial medial-layer hypertrophy rather than atheroma[37]. The cIMT was, however, similar in African black and white patients independent of a diagnosis of hypertension. Additionally, we found a marked variation in the independent associations between modifiable CV risk factors and atherosclerosis among black and white patients with RA. Our main findings each originated in several multivariable regression models adjusted for confounders. To our knowledge, this is the first study that simultaneously assessed and directly compared the atherosclerosis burden and its relationships with CV

Table 4. Associations of modifiable CV risk factors with carotid artery plaque in black and white patients separately. Significant associations are shown in bold type.

CV Risk Factor	Black and White Patients Combined Interaction p	Stratified Analysis: Blacks OR (95% CI)*	p	Whites OR (95% CI)*	p
Systolic blood pressure/10, range 9–21.3 in black and 9.8–19 in white patients	**0.01**	0.88 (0.74–1.05)	0.2	**1.38 (1.04–1.84)**	**0.02**
Extraarticular manifestations, yes vs no	**0.05**	0.72 (0.05–9.89)	0.8	**5.88 (1.42–24.45)**	**0.01**
AIMS tension†, range 0–10	**0.04**	**1.41 (1.04–1.90)**	**0.02**	0.99 (0.92–1.06)	0.9
NSAID use, yes vs no	**0.02**	**5.97 (1.60–23.85)**	**0.03**	1.00 (0.97–1.02)	0.4

CV: cardiovascular; AIMS: Arthritis Impact Measurement Scales; NSAID: nonsteroidal antiinflammatory drug. * Adjusted for age, sex, and healthcare center. † Log transformed and normalized to a 0 to 10 range.

risk factors between patients with RA that belong to a developing and a developed population.

The acquisition of western lifestyles resulting in emerging CVD risk factors and events was recently documented in non-RA black Africans[18,22]. Nevertheless, CVD is still confirmed in only 6% of black South Africans that present to hospital with heart disease[38]. Our finding of a similar atherosclerosis burden in black and white patients with RA confirms that in the presence of RA, protection against CVD, mediated by the earlier epidemiological transition stage, may be absent in black Africans[18].

Because hypertension was more frequent and the mean atherogenic index and CRP concentrations were similar in black compared to white patients in our study, it is particularly striking that the respective risk factors as well as the Framingham score were associated with atherosclerosis in whites only. This finding has 2 potential implications. First, major conventional CV risk factors and systemic inflammation may not be reliable in estimating CVD risk in black Africans that have developed established RA. This is in sharp contrast with reported findings in studies that were performed in developed populations and are congruous with our current results obtained in whites[3,4,5,6,7,8,9,10]. Because ultrasonographically identified atherosclerosis including both carotid cIMT and plaque was shown to predict CVD events not only in non-RA subjects but also in patients with RA and independent of population origin[25,26,39], our results suggest that the use of direct vascular imaging may be more frequently indicated in optimal CV risk assessment in patients with RA from developing populations. Second, atherogenesis in black Africans with RA needs further investigation. The absence of associations of hypertension and dyslipidemia with atherosclerosis among black Africans with RA in our analysis does not exclude a role of major conventional risk factors in atherogenesis. Rather, because black Africans are currently undergoing a rapid socioeconomic transition[18,20,22], upon reaching a mean age of 56 years as applied to those enrolled in our study, they are likely to sustain a shorter lifetime exposure to unhealthy lifestyles that could have contributed to our findings. Equally relevant, we recently reported that, compared to British white subjects, non-RA black Africans experience much greater aortic reflective waves and hence possibly greater aortic blood pressure values for a given brachial blood pressure[40], and black Africans have reduced nocturnal blood pressure dipping that may produce target organ effects independent of conventional blood pressure[41]. Finally, we found that CRP concentrations were associated with atherosclerosis only in white Africans with RA. Interestingly, we recently documented prevalent high CRP concentrations in non-RA black Africans that were also not independently related to CVD risk as assessed by increases in aortic pulse pressure, the component waves, or the determinants of central pulse pressure[42]. Taken together, the potential contributions of major conventional risk factors and systemic inflammation to atherogenesis in black Africans with RA require assessment in future longitudinal studies and possibly central rather than brachial blood pressure evaluation[40], the use of ambulatory 24-hour day and night blood pressure recording[41], and direct measurement of inflamed joint-derived circulating cytokine concentrations[43,44,45].

We found that the presence of extraarticular manifestations that reflect RA severity[46] was independently associated with atherosclerosis in whites only. This disease characteristic was previously shown to be associated with atherosclerosis[47] and to predict CV mortality in RA[46]. However, in keeping with an earlier report[48], extraarticular disease was distinctly uncommon in black Africans with RA (2.5% vs 12.3% in whites; adjusted OR 0.19), and therefore a larger study may be required to adequately assess its potential influence on atherogenesis in patients with RA from this population.

Vascular reactivity to psychological stress is enhanced in black compared to white subjects and is associated with an increased susceptibility to atherosclerosis and incident CV events[49,50,51]. Stress reduction was shown to reduce carotid atherosclerosis and CV mortality in black Americans[52]. In our investigation, the AIMS tension score was independently associated with both the cIMT and plaque in black Africans with RA and not in whites; and in multivariable analysis, marital status, low education level, and smoking and alcohol use did not materially alter this relationship. Our results support the presence of an enhanced interconnectedness between mental and physical health[23] that should be considered in optimal CVD prevention in black Africans with RA.

Selective COX-2 inhibition can enhance thrombosis risk and the development of hypertension[53]. However, the use of both traditional NSAID and selective COX-2 inhibitors increases CV event rates[54]. Variable effects of these agents in terms of atheroma development were reported in animal studies[53]. In our cohort, traditional NSAID use independently increased the OR for plaque 6-fold in black Africans with RA.

In addition to an earlier epidemiological health transition stage in black compared to white Africans, genetic differences between patients with RA from the 2 ethnic groups may alternatively or additionally support our findings. Indeed, in studies that included black and white populations, a different ethnic distribution of genetic polymorphisms that are associated with CVD, hypertension, and circulating lipid and CRP concentrations was found[55,56,57,58,59,60]. Further, specific patterns of associations between genetic variations in beta-adrenoreceptors and not only cold and but also psychological stress have been reported in young black individuals[61]. Finally, the potential importance of documented variations in CVD-related COX polymorphisms among white and black Americans[62] deserves further study.

Compared to their white counterparts, black Africans with RA experience a similar burden of carotid atherosclerosis. These findings call for intensive CV risk management irrespective of epidemiological transition stage or population ori-

gin in patients with RA. However, relationships between cross-sectionally recorded modifiable risk factors and atherosclerosis vary considerably among Africans with RA. Longitudinal studies and possibly other than conventional CV risk factor evaluations are needed to further elucidate atherogenesis and optimal CV risk assessment in black Africans with RA.

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Paper 4

A range of anthropometric measures and their association with atherosclerosis were compared between black and white African RA women in paper 4. The atherosclerosis burden was similar in both groups. The body mass index and waist-to-height ratio were markedly larger in black African RA women. Irrespective of population origin, body mass index was associated with blood pressure whereas abdominal adiposity measures were related to lipid concentrations; both generalized and abdominal adiposity measures were associated with fasting plasma glucose levels.

Upon interaction and stratified analysis, consistent disparities in adiposity measures-atherosclerosis relations were found. In white African women, body mass index was associated with carotid intima-media thickness and waist-to-hip ratio related to plaque. These associations were explained metabolic risk factors. Interestingly in this regard, carotid intima-media thickness relates to stroke and its risk factors whereas waist-to-hip ratio is associated with ischemic heart disease and its risk factors.

In contrast to our findings in whites,none of the anthropometric measures were associated with atherosclerosis in black African RA patients. In fact, the odds ratio was 1.00 to 1.03 with extremely narrow confidence intervals for the adiposity-carotid plaque relations in black African patients with RA.

This study revealed a large excess adiposity burden but this did not translate into any association with atherosclerosis in black African RA women. We also showed for the first time that body mass index and waist-to-hip ratio can assist in atherosclerotic cardiovascular risk stratification in white women with RA.

The National Cholesterol Education Program Adult Treatment Panel III metabolic syndrome definition summarizes excess adiposity together with its complications. What is its potential impact on atherosclerosis in black compared to white African women with RA?

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RESEARCH ARTICLE Open Access

Obesity and carotid atherosclerosis in African black and Caucasian women with established rheumatoid arthritis: a cross-sectional study

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Abstract

Introduction: Reported findings on the relationship between adiposity and atherosclerotic cardiovascular disease (ACVD) risk in rheumatoid arthritis (RA) are contradictory and originate in developed populations. Approximately 80% of ACVD now occurs in developing countries. We aimed to ascertain the associations of clinical obesity measures with metabolic cardiovascular risk and atherosclerosis in African women with RA from a developing black and developed Caucasian population.

Methods: The associations of body mass index (BMI) as an indicator of overall adiposity and waist circumference and waist-to-height and waist-to-hip ratios as abdominal obesity indices with metabolic risk factors and high resolution B-mode ultrasound-determined carotid artery atherosclerosis were assessed in multivariate regression models in 203 African women with established RA; 108 were black and 95 Caucasian.

Results: BMI and waist-to-height ratio were higher in African black compared to Caucasian women (29.9 (6.6) versus 25.3 (4.9) kg/m^2, $P = 0.002$ and 0.59 (0.09) versus 0.53 (0.08), $P = 0.01$, respectively). Interactions between population origin and anthropometric measures were not related to metabolic risk factors but were associated with atherosclerosis, independent of confounders and individual terms. In all patients, BMI was related to systolic and diastolic blood pressure but not with serum lipid concentrations whereas abdominal obesity indices were associated with serum lipid concentrations but not with blood pressure values; obesity measures that were associated with plasma glucose concentrations comprised BMI, waist circumference and waist-to-height ratio ($P < 0.05$ in multiple confounder adjusted analysis). In African Caucasian women, BMI was associated with common carotid artery intima-media thickness (standardized β (95% confidence interval (CI)) = 0.21 (0.03 to 0.38)) and waist-to-hip ratio with plaque (odds ratio (OR) (95% CI) = 1.83 (1.03 to 3.25) for one standard deviation (SD) increase). These relationships were independent of multiple non-metabolic risk factors and explained by metabolic risk factors. In African black women with RA, none of the obesity measures was related to atherosclerosis.

Conclusions: Obesity in women with RA from developing groups of black African descent does not as yet translate into atheroma. In Caucasian women with RA that belong to developed populations, BMI and waist-to-hip ratio should be considered in ACVD risk assessment.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory and potentially destructive joint disease that enhances the risk for atherosclerotic cardiovascular disease (ACVD) event rates two fold [1]. ACVD death rates are increased by 50% and responsible for most of the excess mortality in RA [2]. Traditional and nontraditional cardiovascular risk factors as well as genetic polymorphisms were each reported to be associated with cardiovascular disease in RA [3-12].

The role of excess adiposity in ACVD and cardiovascular risk assessment among persons with RA has become a controversial issue. Whereas adiposity as assessed by the body mass index (BMI) and waist circumference was shown to be independently associated with enhanced

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metabolic cardiovascular risk [13,14], a paradoxical inverse relationship between the BMI and ACVD and overall mortality were reported in RA [15,16]. The increased ACVD risk associated with a low BMI in patients with RA could be explained by chronic inflammation and inactivity mediated reduced lean mass and particularly muscle mass in the presence of increased body fat accumulation, a condition known as rheumatoid cachexia [15-17]. Alternatively, Stavropoulos-Kalinoglou and colleagues recently proposed that a paradoxical epidemiological association between survival outcomes and cardiovascular risk factors such as obesity as well as analytical deficiencies in some of the previous studies may account for the reported seemingly contradictory observations on the potential impact of adiposity on cardiovascular risk in RA [18]. Importantly in the present context, BMI constitutes the only obesity measure in RA studies on cardiovascular morbidity and mortality [18]. However, BMI does not discriminate between body fat percentage and lean mass [19] and predicts cardiovascular disease less effectively than measures of central obesity [20-22] in non-RA subjects. To the best of our knowledge, the relative role of different clinical obesity measures in the assessment of ACVD risk in RA has not been reported.

Reported data on atherogenesis in the general population and diseases such as RA derive almost exclusively from developed populations [23,24]. Nevertheless, approximately 80% of ACVD now arises in low income or developing countries. In South Africa, a sub-Saharan country, a minority of citizens consist of an overall affluent, developed and mostly Caucasian population whereas the majority are socially and economically disadvantaged, at an earlier epidemiological health transition stage with consequent different cardiovascular risk factor profiles and disease presentation and mostly of black African ancestry [25-27]. A markedly high prevalence of obesity has been increasingly reported especially in black South African women [28,29]. Still, ACVD event rates remain distinctly low in black Africans [25-27,30]. These findings suggest that in populations that are at an earlier epidemiological transition stage, obesity may not as yet translate into atheroma. Whether this apparent lack of association between excess adiposity and ACVD is present in persons with RA from developing populations, is currently unknown. In the present study, we determined disparities in the relationships of obesity measures with atherosclerosis between women with RA from a developing black compared to a developed Caucasian population. In addition, we examined the potential role of different clinical obesity measures including BMI, waist circumference and waist-to-height and waist-to-hip ratios in assessing metabolic cardiovascular risk and ultrasonographically determined carotid artery atherosclerosis among women with RA.

Materials and methods

Study populations

We enrolled African black and Caucasian patients who met the American College of Rheumatology criteria for RA [31] at the Charlotte Maxeke Johannesburg Academic Hospital (public healthcare) and Milpark Hospital (private healthcare) in Johannesburg. None of the data have been reported previously. Four invited patients refused to enroll. Only 13 black African men with RA participated and hence to avoid confounding of the data analyses by gender differences between black and Caucasian patients with RA, the data analysis was performed in women only. Patients who had used disease modifying agents, that is, persons with established RA, were included and those known to be infected with HIV were excluded. The study was approved by the Ethics Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand. Written informed consent was obtained from each patient.

Assessments

Using methods previously reported by us [3,14], we assessed sociodemographic characteristics, lifestyle factors, systolic and diastolic blood pressure, serum lipid and glucose concentrations, RA characteristics, markers of systemic inflammation including the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentrations and other potential cardiovascular risk factors comprising years of education, thyroid status and hormone replacement therapy. Exercise included hours spent in walking (for example, to reach public transportation). Data were missing in fewer than 5% for any of the recorded variables. Serum lipid and plasma glucose concentrations were determined on fasting blood samples using standard laboratory methods.

BAS (see acknowledgements) and AS performed the carotid artery ultrasound measurements in private and public healthcare patients, respectively. Both operators obtained images of at least 1 cm length of the distal common carotid arteries for measurement of the intima-media thickness of the far wall from an optimal angle of incidence defined as the longitudinal angle of approach where both branches of the internal and external carotid artery are visualized simultaneously [32] and with high resolution B-mode ultrasound (Image Point, Hewlett Packard, Andover, MA, USA and SonoCalc IMT, Sonosite Inc, Bothell, Wash, USA used by BAS and AS, respectively) employing linear array 7.5 MHz probes. The details of the methodology used by BAS were reported previously [3]. The equipment used by AS involves the application of a unique semi-automated border detection program that was previously found to provide highly reproducible results [32]. The intima-media thicknesses in the left and right common carotid artery were

measured and the carotid intima-media thickness (cIMT) was defined as the mean of these. Carotid artery plaque was defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness value, or demonstrates a thickness of > 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface [33]. Both operators were blinded to the cardiovascular risk profiles of the patients. Repeat ultrasound examinations by both operators on 23 patients revealed Spearman correlations between repeat cIMT measurements of 0.983 and 0.956 for BAS and AS, respectively, and the correlation between measurements made by BAS and AS was 0.926. Both operators identified carotid artery bulb or/and internal carotid artery plaque in 11 of these 23 patients with full inter-observer agreement.

Height and weight were measured with participants wearing light clothing and no shoes and the BMI was calculated using these parameters. Waist circumference was measured at the umbilical level and hip at the level of the largest circumference. The adiposity measures included in our main data analysis comprised BMI as an indicator of overall obesity and waist circumference and waist-to-height and waist-to-hip ratios as abdominal obesity indices, respectively [20-22]. The relationships between waist-to-height ratio and incident ACVD and diabetes are reportedly most consistent across different population groups [22].

Statistical analysis

Continuous variables are reported as mean (SD) and categorical variables as proportions or percentages. Non-normally distributed characteristics were logarithmically transformed prior to statistical analysis and for these variables geometric means (SD) are given.

Disparities in sociodemographic features between African black and Caucasian women were compared using the Student t-test and univariate logistic regression analysis as appropriate. Relationships of population grouping (PG) with baseline characteristics, cIMT and carotid artery plaque and anthropometric measures were investigated in multivariate logistic and linear regression models as appropriate and with consistent adjusting for age and healthcare center attendance as well as lipid lowering, antihypertensive and glucose lowering agents in models that included lipid, systolic and diastolic blood pressure and glucose variables, respectively.

Disparities in the relationships of obesity measures with metabolic risk factors and with atherosclerosis in African black compared to Caucasian women were identified by assessing the associations of interactions between PG and obesity measures with metabolic risk factors and cIMT and plaque, respectively, in confounder and individual term adjusted multivariate regression models; when significant interactions were present, stratified analysis was performed.

Finally, we determined whether associations of obesity measures with carotid atherosclerosis as identified in the above mentioned analyses were independent of multiple non-metabolic risk factors and explained by metabolic risk factors in additional multivariate regression models.

Statistical computations were made using the GB Stat™ program (Dynamic Microsystems, Inc, Silverspring, Maryland, USA).

Results

Baseline characteristics and atherosclerosis in African black compared to Caucasian women with RA

Baseline characteristics and carotid atherosclerosis in African black and Caucasian women with RA are shown in Table 1. African black women were on average 2.1 years younger ($P = 0.2$) than their Caucasian counterparts. Approximately 97% of African black women and 80% of Caucasian women attended the public and private healthcare center, respectively ($P < 0.0001$). As compared to African Caucasian women and in confounder adjusted analysis, black women with RA had a smaller pack year history of smoking, used alcohol less often, exercised less, had lower total and HDL cholesterol concentrations but similar LDL cholesterol, triglycerides and non-HDL cholesterol concentrations as well as cholesterol÷HDL cholesterol and triglycerides÷HDL cholesterol ratios, higher plasma glucose concentrations, more deformed joints, higher ESRs and lower educational levels. Ever prednisone use was similar in African black and Caucasian women in univariate ($P = 0.94$) and adjusted analysis ($P = 0.08$, see Table 1). The small proportion of current prednisone users reflects our previously reported increasing avoidance of this intervention [24].

Anthropometric measures in African black compared to Caucasian women with RA

The anthropometric measures in African black and Caucasian women with RA are shown in Table 2. In age and healthcare center adjusted analysis, African black women had higher body weight, BMI and waist-to-height ratio compared to their Caucasian counterparts; by contrast, height, waist circumference, hip circumference and the waist-to-hip ratio were similar in both groups.

Relationships of obesity measures with metabolic risk factors in African black and Caucasian women with RA

The relationships between obesity measures and metabolic risk factors in all women with RA are shown in Table 3. Potentially confounding characteristics that were included as independent variables in the respective regression models comprised age, healthcare center, lifestyle factors (smoking variable was pack-year history of

Table 1 Baseline characteristics and atherosclerosis in Caucasian and black women with RA

Characteristic	Caucasian women (*n* = 95)	Black women (*n* = 108)	*P*[a]
Sociodemographics			
Age, years	57.5 (11.7)	55.4 (10.0)	...
Public healthcare (%)	18.9	97.2	...
Lifestyle factors			
Pack year history smoking, n	2.4 (5.0)	0.1 (1.5)	0.003
Current smoking (%)	9.6	1.9	0.04
Never smoking (%)	90.7	58.5	0.01
Former smoking (%)	31.9	8.4	0.01
Alcohol use (%)	34.0	1.9	< 0.0001
Exercise, hours per week[b], n	0.7 (2.1)	0.6 (1.9)	0.04
Blood pressure			
Systolic blood pressure, mmHg	128 (17)	140 (24)	0.5
Diastolic blood pressure, mmHg	78 (9)	85 (15)	0.1
Lipids			
Total cholesterol, mmol/l	5.1 (1.0)	4.7 (0.9)	0.02
LDL cholesterol, mmol/l	2.8 (0.9)	2.6 (0.8)	0.5
HDL cholesterol[b], mmol/l	1.7 (1.3)	1.5 (1.3)	0.002
Cholesterol÷HDL cholesterol	3.1 (1.0)	3.3 (1.1)	0.1
Triglycerides[b], mmol/l	1.1 (1.5)	1.1 (1.7)	0.8
Triglycerides÷HDL cholesterol[b]	0.6 (1.8)	0.7 (2.1)	0.1
Non-HDL cholesterol	3.3 (1.0)	3.2 (0.9)	0.5
Glucose[b], mmol/l	4.7 (1.2)	5.2 (1.4)	0.02
Diabetes mellitus (%)	4.2	16.7	0.3
RA characteristics			
Disease duration, years	12.7 (9.1)	14.8 (9.4)	0.6
Rheumatoid factor positive (%)	73.4	75.9	0.8
DAS28	3.5 (1.5)	4.1 (1.3)	0.5
Deformed joints[b], n	4 (4)	7 (3)	0.05
Prednisone use ever (%)	43.2	42.6	0.08
Current prednisone use (%)	4.2	1.9	0.07
Current DMARD, n	2.1 (0.9)	2.5 (1.0)	0.4
Current methotrexate use (%)	77.9	91.7	0.9
Current chloroquine use (%)	47.4	77.8	0.2
Systemic inflammation			
Erythrocyte sedimentation rate[b], mm/hr	7 (3)	21 (3)	0.007
C-reactive protein[b], mg/l	3.9 (3.6)	7.5 (3.1)	0.5
Cardiovascular drugs			
Antihypertensive agent use (%)	43.2	55.6	0.07
Oral glucose lowering agent use (%)	4.2	13.9	0.03
Insulin use (%)	1.1	2.0	0.6
Statin use (%)	36.8	18.5	0.03
Ezetimibe use (%)	2.1	0	...
Other			
Education, years	12.7 (2.7)	7.5 (4.1)	0.002
Hypothyroidism[c] (%)	34.7	6.5	0.2
Hormone replacement therapy (%)	17.9	5.6	0.8
Atherosclerosis			
cIMT, mm	0.689 (0.117)	0.691 (0.099)	0.6
Plaque (%)	36.8	35.2	0.5

Results are expressed as mean (SD) or proportions/percentages. [a]*P* for comparison between black and Caucasian women with RA after adjustment for age and healthcare as well as lipid lowering and antihypertensive agents in models that include lipid and blood pressure variables, respectively; [b]non-normally distributed variable for which geometric mean (SD) is given; [c] includes subclinical and overt hypothyroidism and diagnosed when serum thyrotropin level was > 4.94 mU/L or when thyroid hormone replacement therapy was used. cIMT, common carotid artery intima-thickness; DAS28, Disease Activity Score in 28 joints; DMARD, disease modifying agents for rheumatic disease; n, number of; RA, rheumatoid arthritis.

Table 2 Anthropometric measures in Caucasian and black women with RA

Anthropometric measures	Caucasian women (n = 95)	Black women	P^a (n = 108)
Height, cm	163 (7)	159 (7)	0.08
Body weight, kg	67.2 (15.2)	75.8 (16.3)	0.03
BMI, kg/m^2	25.3 (4.9)	29.9 (6.6)	0.002
Waist circumference, cm	87 (13)	94 (14)	0.06
Waist÷height	0.53 (0.08)	0.59 (0.09)	0.01
Hip circumference[b]	101 (1)	110 (1)	0.2
Waist÷hip	0.84 (0.08)	0.85 (1.12)	0.4

Results are expressed as mean (SD). [a]P-value adjusted for age and healthcare center; [b] non-normally distributed variable for which geometric mean (SD) is given. BMI, body mass index; RA, rheumatoid arthritis.

smoking), current disease activity (DAS28), cumulative disease activity (deformed joints), prednisone use, hypothyroidism and hormone replacement therapy as well as antihypertensive, lipid and glucose lowering agents upon entering of blood pressure, lipid and glucose parameters, respectively. Interactions between PG and obesity measures were consistently unrelated to metabolic risk factors and therefore no stratified analysis was performed. BMI was associated with blood pressure variables but not with serum lipid concentrations. By contrast, waist circumference and waist-to-height and waist-to-hip ratios were related to serum lipid concentrations but not to blood pressure values. Obesity measures that were associated with plasma glucose concentrations comprised BMI, waist circumference and waist-to-height ratio.

The selection of confounders modeled in the analysis shown in Table 3 was based on biological plausibility and not data driven. The associations of these characteristics with obesity measures in African black and Caucasian women are shown in Table 4. Age, smoking history, deformed joints and cardiovascular drugs were each associated with obesity measures in African black or/and Caucasian women. Additionally, there were several disparities in these relationships between African black and Caucasian participants. Age was associated with a high waist-to-hip ratio and smoking with a high BMI, waist circumference and waist-to-height ratio in African Caucasian but not in black women. By contrast, the number of deformed joints was associated with a low BMI, waist circumference and waist-to-height ratio in African black but not in Caucasian women.

Relationships of obesity measures with carotid artery atherosclerosis in African black and Caucasian women with RA

Due to consistent differences in the relationships of obesity measures with cIMT and carotid artery plaque between African black and Caucasian women with RA (see below), the respective measures were not associated with atherosclerosis upon analysis of the data in all patients or African black and Caucasian women combined.

Results of age and health care adjusted stratified analyses for cIMT are shown in Figure 1. The association of waist-to-height ratio with cIMT differed in African black compared to Caucasian women (P for interaction < 0.003). BMI was significantly related to cIMT in African Caucasian women. By contrast, none of the obesity measures were associated with cIMT among African black women.

Results of age and health care adjusted stratified analyses for plaque are shown in Figure 2. The associations of each obesity measure with carotid artery plaque differed in African black compared to Caucasian women (P for interaction < 0.05). Waist-to-hip ratio was significantly related to carotid artery plaque in African Caucasian women whereas none of the obesity measures were associated with carotid artery plaque in black women.

Impact of adjustment for multiple non-metabolic and metabolic risk factors on anthropometric measure - atherosclerosis relations in African Caucasian women with RA

As shown in the Figures, upon adjustment for age, healthcare center and non-metabolic risk factors including lifestyle factors (smoking variable was pack-year

Table 3 Associations between obesity measures and metabolic risk factors in 203 African women with RA

Metabolic risk factor	Obesity measure			
	BMI	Waist	Waist÷height	Log waist÷hip
Systolic blood pressure	**0.23 (0.09 to 0.37)[a]**	0.11 (-0.01 to 0.25)	0.09 (-0.06 to 0.24)	-0.05 (-0.16 to 0.07)
Diastolic blood pressure	**0.29 (0.15 to 0.43)[b]**	0.13 (-0.13 to 0.28)	-0.05 (-0.18 to 0.26)	0.10 (-0.05 to 0.09)
Log triglycerides	0.11 (-0.06 to 0.25)	**0.27 (0.14 to 0.41)[b]**	**0.28 (0.13 to 0.43)[b]**	0.14 (0.00 to 0.29)
Log HDL cholesterol	-0.02 (-0.19 to 0.14)	**-0.22 (-0.33 to -0.08)[b]**	**-0.20 (-0.36 to -0.04)[a]**	**-0.21 (-0.35 to -0.07)[b]**
Log glucose	**0.16 (0.02 to 0.27)[a]**	**0.15 (0.01 to 0.30)[a]**	**0.18 (0.04 to 0.33)[a]**	0.02 (-0.10 to 0.13)

Results are expressed as standardized regression coefficients (95% confidence interval) in multivariable models in which age, healthcare center, lifestyle factors, current disease activity (DAS28), cumulative disease activity (log deformed joints), prednisone use, hypothyroidism and hormone replacement therapy as well as antihypertensive, lipid and glucose lowering agents upon entering of blood pressure, lipid and glucose parameters as independent variables, respectively, were controlled for. Significant associations are shown in bold. [a]P-value < 0.05; [b]P-value < 0.01. BMI, body mass index; HDL, high-density lipoprotein; Log, logarithmically transformed.

Table 4 Associations between obesity measures and non-metabolic risk factors in African black and Caucasian women with RA

Non-metabolic risk factor	Obesity measure									
	BMI			Waist			Waist÷height			
	Black	Caucasian	Interaction *P*-value	Black	Caucasian	Interaction *P*-value	Black	Caucasian	Interaction *P*-value	Black
Age	-0.09	-0.10	0.9	-0.10	-0.01	0.4	-0.04	0.10	0.6	-0.09
Public healthcare	-0.05	0.07	0.4	-0.08	-0.01	0.3	-0.04	0.13	0.4	-0.07
L py history smoking	-0.16	**0.22**[a]	**0.03**	-0.14	**0.27**[a]	0.05	-0.15	**0.25**[a]	**0.048**	0.08
Alcohol use	0.07	0.05	0.08	0.06	0.07	**0.04**	0.03	0.06	0.08	-0.08
Exercise	-0.00	-0.07	0.7	0.05	-0.12	0.2	0.06	-0.16	0.1	-0.03
DAS28	-0.06	0.19	0.2	0.03	0.11	0.5	0.03	0.16	0.4	-0.04
L deformed joints	**-0.25**[a]	-0.15	0.2	**-0.32**[b]	-0.06	**0.01**	**-0.28**[b]	-0.08	**0.036**	-0.11
Prednisone use	-0.10	-0.07	0.6	-0.15	0.02	0.2	-0.16	-0.05	0.5	-0.09
Hypothyroidism	-0.11	0.16	0.1	0.04	0.08	0.9	-0.04	0.11	0.4	0.05
HRT	0.04	-0.06	0.6	-0.02	-0.07	0.8	-0.04	-0.07	0.9	-0.09
Anti-HTA use	0.15	**0.35**[b]	0.5	**0.23**[a]	**0.30**[†]	0.5	0.19	**0.29**[b]	0.6	0.00
Statin use	0.10	**0.30**[b]	0.4	0.10	**0.29**[b]	0.8	0.05	**0.28**[b]	0.2	0.06
Ezetimibe use	...	0.17	...	...	0.08	...	...	0.11	...	...
OHA use	**0.27**[b]	**0.25**[a]	0.5	**0.31**[b]	**0.25**[a]	0.5	**0.29**[b]	**0.26**[a]	0.7	0.00
Insulin therapy	**0.25**[b]	-0.05	0.06	**0.26**[a]	-0.03	0.07	**0.30**[b]	-0.05	**0.042**	0.09

Results are expressed as standardized regression coefficients in univariate analysis for the relationships between obesity measures and age and public healthcare and in age and p for the associations between obesity measures and the other non-metabolic risk factor measures. Significant associations are shown in bold. [a]*P*-value < 0.05, [b]*P*-value < 0.01. BMI, Activity Score in 28 joints; HRT, hormone replacement therapy; HTA, hypertensive agent; Log, logarithmically transformed; L, logarithmically transformed; OHA, oral hypoglycemic a

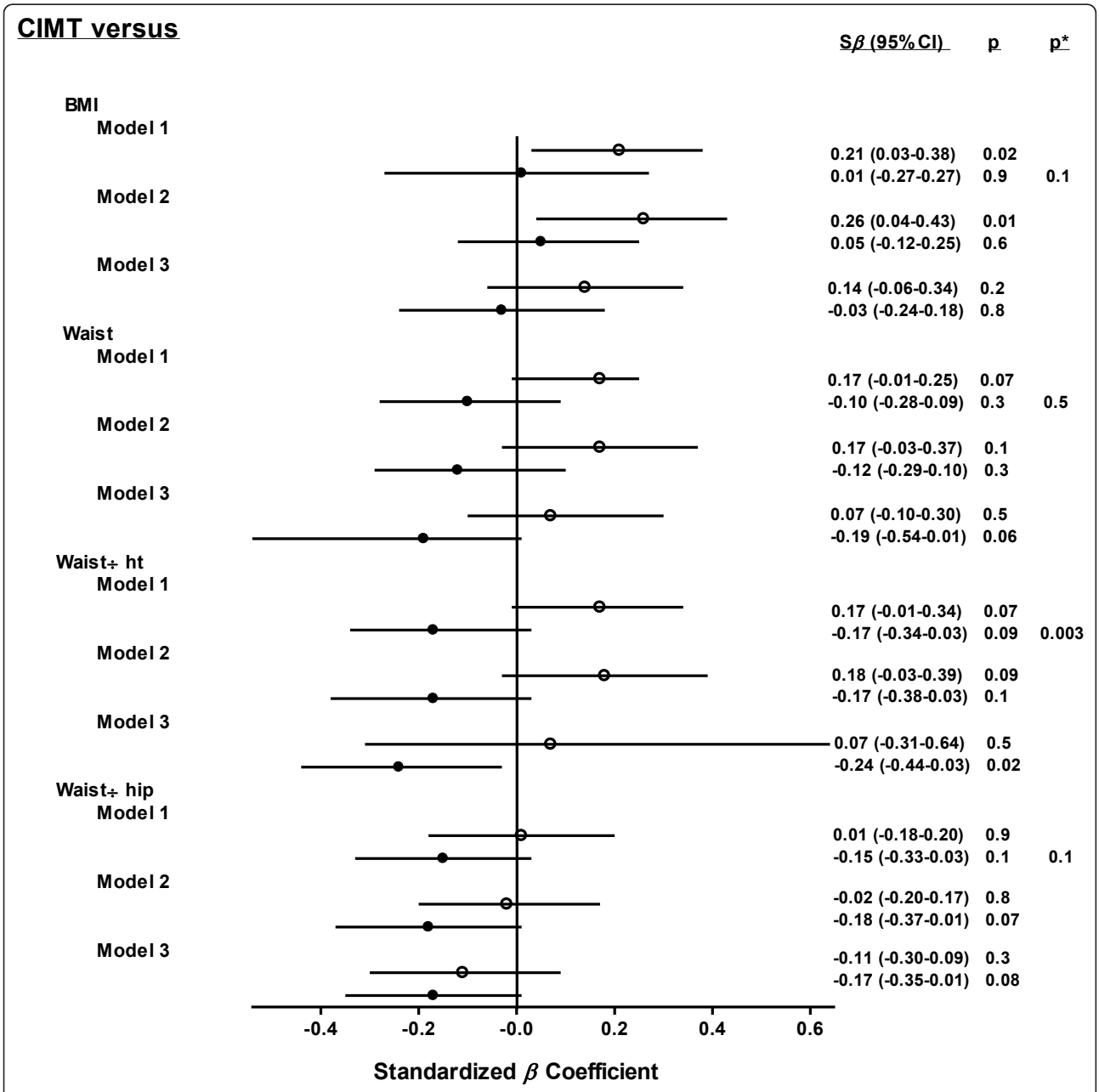

Figure 1 Obesity measure - carotid intima-media thickness relations in African women with RA. Disparities in the relationships of obesity measures with ultrasonographically determined carotid artery intima-media thickness between black and Caucasian women with RA after adjustment for age and healthcare (model 1), age, healthcare and non-metabolic risk factors including lifestyle factors, current disease activity (DAS28), cumulative disease activity (deformed joints), prednisone use, hypothyroidism, hormone replacement therapy and cardiovascular drug use (model 2) and age, healthcare center and metabolic risk factors comprising systolic and diastolic blood pressure and HDL cholesterol, triglyceride and glucose concentrations (model 3). Open and closed circles and their horizontal crossing lines represent the odds ratios and 95% confidence intervals for the relationships in Caucasian and black women, respectively. BMI, body mass index; CI, confidence interval; cIMT, carotid intima-media thickness; DAS28, Disease Activity Score in 28 joints; HDL, high density liporotein; ht, height; RA, rheumatoid arthritis; Sβ, standardized regression coefficient.

history of smoking), current disease activity (DAS28), cumulative disease activity (deformed joints), prednisone use, hypothyroidism, hormone replacement therapy and use of cardiovascular drugs, the associations of BMI with cIMT (Figure 1) and of waist-to-hip ratio with carotid plaque (Figure 2) were not materially altered. By contrast, upon adjusting for sociodemographic characteristics and metabolic risk factors comprising systolic

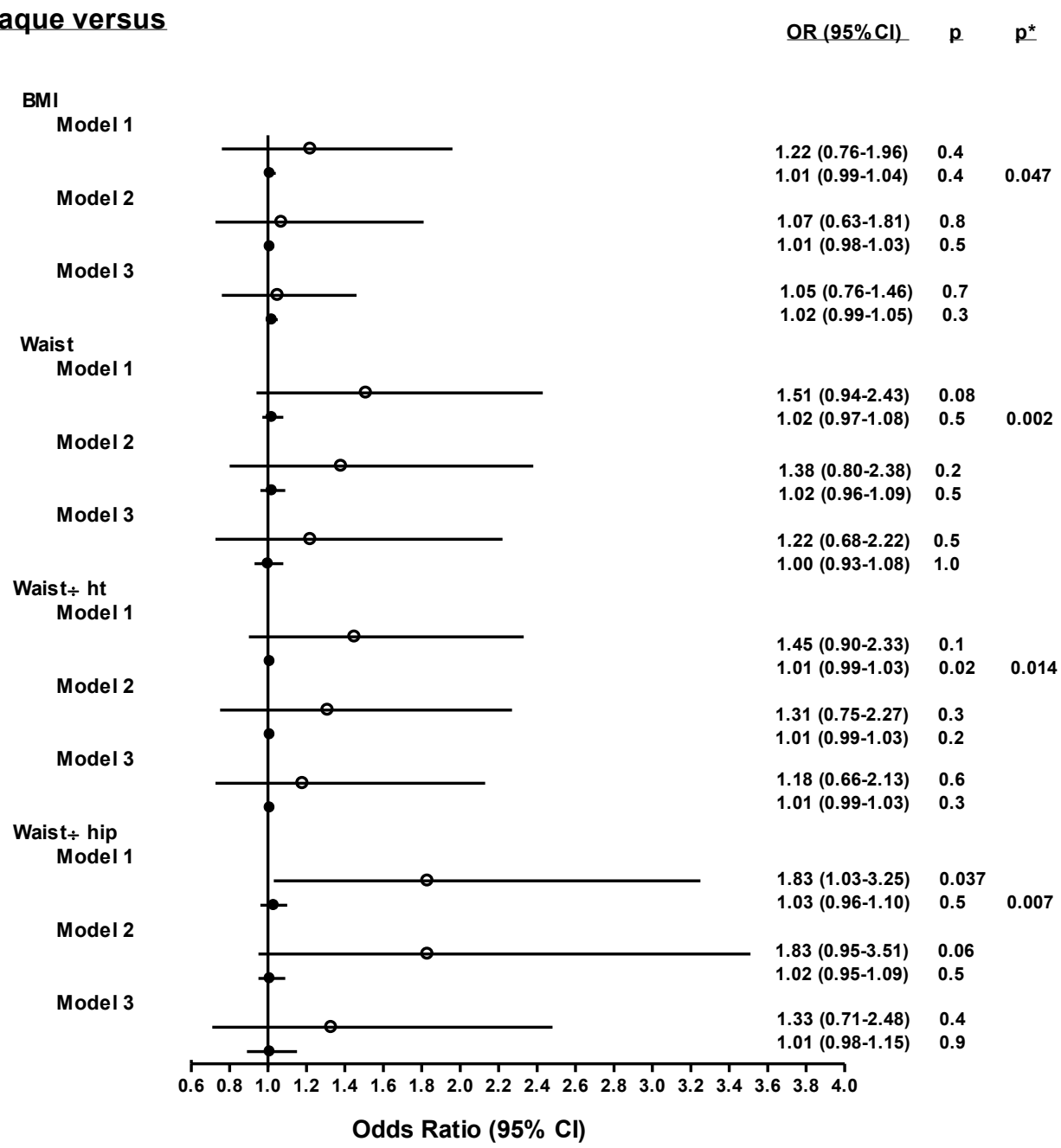

Figure 2 Obesity measure - carotid plaque relations in African women with RA. Disparities in the relationships of obesity measures with ultrasonographically determined carotid artery plaque between black and Caucasian women with RA after adjustment for age and healthcare (model 1), age, healthcare and non-metabolic risk factors including lifestyle factors, current disease activity (DAS28), cumulative disease activity (deformed joints), prednisone use, hypothyroidism, hormone replacement therapy and cardiovascular drug use (model 2) and age, healthcare center and metabolic risk factors comprising systolic and diastolic blood pressure and HDL cholesterol, triglyceride and glucose concentrations (model 3). Open and closed circles and their horizontal crossing lines represent the odds ratios and 95% confidence intervals for the relationships in Caucasian and black women, respectively. BMI, body mass index; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; HDL, high density liporotein; ht, height; OR, odds ratio; RA, rheumatoid arthritis.

and diastolic blood pressure and HDL cholesterol, triglyceride and glucose concentrations, the associations of BMI with cIMT and waist-to-hip ratio with plaque were markedly attenuated. Further, in African black women, a high waist-to-height ratio was significantly associated with a small cIMT (Figure 1).

Discussion

In this study, African black women with RA that form part of a developing population sustained a markedly increased adiposity burden compared to their Caucasian counterparts. The associations of obesity measures with metabolic risk factors were as strong in African black compared to Caucasian women with RA. By contrast, obesity measures were not related to carotid atherosclerosis in African black women with RA whereas BMI and the waist-to-hip ratio were associated with atherosclerosis among Caucasian women who belong to a developed population and these relationships were explained by metabolic risk factors.

Relationships between adiposity measures and cardiovascular risk and disease could be expected to be stronger in patients with RA compared to non-RA subjects. In non-RA subjects, a high BMI can reflect an increased body fat mass or a large muscle mass, factors that are each associated with opposite outcomes in cardiovascular disease [19]. However, Stavropoulos-Kalinoglou and colleagues recently reported that patients with RA experience a 4.3% increase in body fat mass for a given BMI compared to healthy individuals [34]. This is most probably attributable to the presence of rheumatoid cachexia that affects nearly two thirds of patients with RA [15-17,34].

The most striking finding in our analysis was revealed upon analyzing the associations of obesity measures with carotid artery plaque among African black women with RA. For each of the adiposity measures, the OR for plaque per 1 SD increase in obesity measure was between 1.00 and 1.03 and the 5 to 95% confidence intervals were very small (see Figure 2). This evident consistent lack of relationships between obesity measures and atherosclerosis could not be attributed to reduced metabolic cardiovascular risk in African black women with RA. Indeed, BMI and waist-to-height ratio were higher in African black compared to Caucasian women and the associations of obesity measures with metabolic risk factors were similar in both groups. Ultrasonographically determined carotid artery plaque is associated with a 10-year cardiovascular event rate risk of 39% in non-RA subjects [35] and reportedly predicts incident ACVD in patients with RA irrespective of population origin [36,37]. Our findings indicate that excess adiposity in patients with RA from developing groups of black African descent does not as yet translate in severe atherosclerosis as reflected by the presence of plaque (see below). Alternatively or additionally, genetic differences between the African black and Caucasian populations may underlie our findings. Indeed, in studies that included African black and European subjects, a differential ethnic distribution of genetic polymorphisms that are associated with obesity [38] as well as those related to cardiovascular disease [39] were found. Either way, our results are congruous with the distinctly low ACVD event rates despite highly prevalent obesity as reported in non-RA African black women [25-30]. Further, the data analysis in the present study indicates that the presence of RA does not alter this current absence of adiposity related atheroma.

Our observation that obesity measures were also not associated with increased cIMT among African black women with RA further substantiates the absence of excess adiposity-related atherogenesis in this patient population. In addition, the waist-to-height and waist-to-hip ratios tended (P = 0.09 and 0.1, respectively) to be negatively associated with cIMT and the waist-to-height ratio was significantly (P = 0.02) and negatively associated with cIMT upon adjustment for metabolic risk factors. This finding is reminiscent of the reported paradoxical inverse relationships between BMI and ACVD mortality as reported in patients with RA from developed populations [15]. Important potential confounders in this context are smoking and the use of cardiovascular drugs [18]. The latter variables did not alter the relationships of waist-to-height and waist-to-hip ratios with cIMT in the present investigation.

The burden of atherosclerosis was as extensive in African black compared to Caucasian women with RA in this study. These results indicate that systematic cardiovascular risk assessment should be performed irrespective of adiposity extent in African black women with RA.

Published reports on the associations between obesity measures and atherosclerosis in patients with RA, even in those that form part of developed populations, are limited. In African Caucasian women with RA, we found relationships of obesity measures with cIMT and internal carotid artery and carotid artery bulb plaque. cIMT and plaque constitute different phenotypes of atherosclerosis and are biologically and genetically distinct [40-45]. The cIMT constitutes approximately 80% media and approximately 20% intima [41]. Intima-media thickening results mostly from adaptive responses of medial cells to blood pressure and age [41] and is associated with stroke risk factors and stroke prevalence [43-45]. On the other hand, carotid artery plaque occurs as a consequence of intimal pathology [40] and reflects an advanced stage of atherosclerosis that is more closely related to coronary artery disease risk factors and coronary heart disease prevalence [41,43]. Importantly also in the present context, the INTERHEART study investigators found that waist-to-hip ratio was more strongly associated with myocardial infarction than BMI [21] whereas in another recent large study performed in Finland and reported by Hu and colleagues, BMI but not waist-to-hip ratio enhanced the risk for stroke among female participants [46]. Our results in

African Caucasian women with established RA are in keeping with these reported findings in that BMI was associated with blood pressure and cIMT whereas waist-to-hip ratio was related to lipids and plaque. In addition, metabolic cardiovascular risk factors explained the relationships of adiposity measures with carotid atherosclerosis thereby supporting the presence of an obesity effect. A differential effect among the individual metabolic risk factors on the associations of BMI with cIMT and waist-to-hip ratio with plaque could not be assessed as lipid characteristics and blood pressure variables were collinear (data not shown). Taken together, our results indicate that in patients with established RA from a developed population, BMI and waist-to-hip ratio are associated with different metabolic risk factor profiles, reflect different aspects of carotid artery atherosclerosis and, therefore, both can be helpful in ACVD risk assessment.

Our study has further limitations. Our patients were exclusively women and the cross-sectional design of our investigation precludes drawing inferences on the direction of causality. Further, characteristics that can be important in the present context and were not recorded include menopausal status and cumulative prednisone dose. Also, clinical measures of abdominal obesity do not distinguish between visceral and subcutaneous fat. Imaging studies (for example, computerized tomography) will be needed to determine the relative impact of visceral as compared to deep and superficial subcutaneous fat at the abdominal level on atherogenesis in patients with RA [47,48]. Visceral fat is particularly strongly associated with ACVD risk [20-22]. Circulating triglyceride concentrations reflect visceral fat mass [29] and these did not differ in African black compared to Caucasian women with RA in the current investigation. Finally, as applies in previously reported investigations on cardiovascular risk in non-RA as well as RA subjects, many relationships were evaluated. However, our main findings each originate in confounder adjusted multivariable regression models.

Conclusions

Although women with established RA from developing groups of African descent experience a larger obesity burden compared to their Caucasian counterparts, this is currently not as yet associated with enhanced carotid atherosclerosis. Additionally and contrastingly, we report for the first time evidence that supports the use of clinical obesity measures including BMI and waist-to-hip ratio in the assessment of ACVD and risk among Caucasian women with established RA from a developed population.

Abbreviations

ACVD: atherosclerotic cardiovascular disease; β: regression coefficient; BMI: body mass index; CI: confidence interval; cIMT: carotid intima-media thickness; CRP: C-reactive protein; DAS 28: disease activity in 28 joints; DMARD: disease modifying drugs for rheumatic disease; ESR: erythrocyte sedimentation rate; HDL: high density lipoprotein; LDL: low density lipoprotein; PG: population grouping; OR: odds ratio; RA: rheumatoid arthritis; S and Std: standardized; SD: standard deviation.

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Authors' contributions

AS contributed to the conception and design, data acquisition, interpretation of the data and revising the manuscript and performed the carotid ultrasound examinations in public healthcare patients. GRN and AJW contributed to the conception and design and analysis and interpretation of the data. PHD contributed to the conception and design and data acquisition, performed the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Paper 5

Metabolic syndrome definitions and their components are associated with atherosclerosis in patients with RA from developed populations. The metabolic syndrome as presently defined comprises abdominal obesity and its metabolic complications. In paper 5, we used this tool to further investigate whether the metabolic risk burden and its association with atherosclerosis differs among black and white African women with RA.

The metabolic syndrome prevalence was 30.8% and 9.7% in black and white African women with RA, respectively ($p = 0.009$). The mean number of metabolic syndrome criteria was 2.1 in black compared to 1.3 in white Africans with RA ($p = 0.03$). Except for the triglyceride criterion, all other criteria were numerically more prevalent in black African RA women; the difference in the metabolic syndrome high density lipoprotein cholesterol concentration criterion prevalence was statistically significant ($p = 0.036$).

In white African RA women, the metabolic syndrome definition was associated with carotid intima-media thickness and the triglyceride criterion and number of criteria were associated with plaque.

In black African RA women, only the blood pressure criterion was associated with carotid intima-media thickness. Moreover, arterial intima-

media thickening represents mostly age and blood pressure induced hypertrophy of medial cells rather than atherosclerosis.

Taken together, compared to their white counterparts, black African women with RA currently experience a much larger metabolic risk burden, which is further also not associated with atherosclerosis. Cardiovascular risk management should be applied irrespective of metabolic risk factor profiles in this RA population.

Metabolic cardiovascular risk burden and atherosclerosis in African black and Caucasian women with rheumatoid arthritis: a cross-sectional study

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Abstract

Objectives

The impact of metabolic risk factors on atherosclerotic cardiovascular disease (ACVD) in patients with rheumatoid arthritis (RA) from developing populations is currently unknown. We examined the relationships of the metabolic syndrome (MetS) and its components with carotid artery atherosclerosis in African women with rheumatoid arthritis (RA) from a developing black and developed Caucasian population.

Methods

We assessed the associations of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) defined MetS and its criteria with high resolution B-mode ultrasound determined common carotid artery intima-media thickness (cIMT) and carotid artery plaque in multivariable regression models in 104 black and 93 Caucasian women with RA.

Results

The MetS prevalence was 30.8% in black compared to 9.7% in Caucasian women with RA (adjusted odds ratio [95% confidence interval]=10.11 [1.76–58.03] [p=0.009]). Population origin impacted on the relationships of metabolic risk factors with atherosclerosis. In Caucasian women, the MetS was associated with cIMT (p=0.036) and MetS triglycerides and the number of MetS criteria were each associated with both cIMT (p=0.01 and p=0.028, respectively) and plaque (p=0.049 and p=0.02, respectively); by contrast, in black women, MetS blood pressure was related to cIMT (p=0.04).

Conclusion

A high overall metabolic cardiovascular risk burden as disclosed by markedly prevalent MetS in women with RA from developing groups of black African descent was not associated with atherosclerosis. This calls for systematic rigorous cardiovascular risk management irrespective of metabolic risk factor profiles in African black women with RA.

Key words

metabolic syndrome, rheumatoid arthritis, developing population

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that doubles the risk for atherosclerotic cardiovascular disease (ACVD) events (1). ACVD death rates are increased by 50% and account for most of the excess overall mortality in RA (2).

Conventional and non-conventional cardiovascular risk factors or RA characteristics and genetic polymorphisms are associated with ACVD in RA (3-15). Additionally, the RA characteristics of disease activity and treatment with traditional disease modifying drugs, biological agents and corticosteroids can impact on the metabolic syndrome (MetS) and its features including insulin resistance, visceral adiposity and circulating lipid concentrations (16-26). We and others have recently reported that metabolic risk factors are independently associated with both carotid and coronary artery atherosclerosis in RA (18, 20, 27).

Our knowledge on atherogenesis in RA originates almost exclusively in developed populations (28, 29). However, developing populations are not immune to RA (29) and ~80% of ACVD now arises in middle and low income or developing countries (28) in which ACVD risk factor profiles and their impact on atherogenesis are dissimilar (29, 31, 32). Optimal strategies in ACVD risk assessment and prevention in patients with RA from developing populations await delineation.

South Africa is a sub-Saharan country that has become the most unequal society in the world (33). A minority of its inhabitants represents an overall affluent, developed and mostly African Caucasian population, whereas the majority is socially and economically disadvantaged, at an earlier epidemiological health transition stage with consequent different cardiovascular risk factor profiles and disease presentation and consists mostly of an African black population (32, 34, 35). A distinctly high prevalence of obesity that further impacts substantially on blood pressure and glucose and lipid metabolism has been increasingly documented particularly in black South African women (36, 37). Despite this, ACVD event rates remain distinctly low in black Africans (32, 34) with ischemic heart disease currently being confirmed in only 6% of South African black patients that present to hospital with heart disease (38). These findings suggest that in populations that are at an earlier epidemiological health transition stage, metabolic cardiovascular risk factors may not as yet translate into atherosclerosis. Furthermore, whether this apparent lack of association between metabolic cardiovascular risk and ACVD is present in persons from developing populations that have RA, is currently unknown.

The MetS is a multidimensional risk factor for ACVD and diabetes (39). The US National Cholesterol Education Program (NCEP) describes the MetS as the metabolic complications of obesity (39). In the present study, we examined whether or not disparities exist between the relationships of the NCEP-MetS and its individual components with ultrasonographically determined carotid atherosclerosis (18, 27, 40, 41) in women with RA from a developing black compared to a developed Caucasian population.

Materials and methods

Study populations

Study participants comprised consecutively recruited African black and Caucasian women with RA (42, 43) at the Charlotte Maxeke Johannesburg Academic Hospital (public healthcare) and Milpark Hospital (private healthcare) in Johannesburg. None of the data were previously reported. Only 13 African black men with RA participated and, hence, to avoid confounding of the data analysis by gender differences, our research question was addressed in women only. We included women that had used disease modifying agents and, therefore, had established RA. Four invited patients refused to participate and those known to be infected with Human Immunodeficiency Virus (HIV) were excluded. Whereas HIV infection status is currently systematically recorded in our African black patients with patient refusal rates of ~1%, this is not done routinely in our Caucasian patients in view of the distinctly low

prevalence of HIV infection in such subjects. The study was approved by Ethics Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand. Written informed consent was obtained from each patient.

Assessments

Using methods as previously reported by us (18, 29, 35, 43, 44), we assessed sociodemographic characteristics, lifestyle factors, body mass index (BMI), systolic and diastolic blood pressure, diabetes mellitus status, RA characteristics, markers of systemic inflammation including the erythrocyte sedimentation rate (ESR) and serum C-reactive protein concentrations (CRP) and other potential cardiovascular risk factors comprising years of education, the Arthritis Impact Measurement Scales (AIMS) depression score, thyroid status and hormone replacement therapy. Exercise included hours spent in walking (*e.g.* to reach public transport). Data were missing in less than 5% of any of the recorded variables. Serum lipid and plasma glucose concentrations were determined on fasting blood samples and using standard laboratory methods (18, 29, 35, 43, 44).

B.A. Stevens (BAS) (see *Acknowledgement*) and A. Solomon (AS) performed the carotid artery ultrasound measurements in private and public healthcare patients, respectively. Both operators obtained images of at least 1cm length of the distal common carotid arteries for measurement of the intima-media thickness of the far wall from an optimal angle of incidence defined as the longitudinal angle of approach where both branches of the internal and external carotid artery are visualised simultaneously (45) and with high resolution B-mode ultrasound (Image Point, Hewlett Packard, Andover, MA, USA and SonoCalc IMT, Sonosite Inc, Bothell, Wash, USA used by BAS and AS, respectively) employing linear array 7.5 MHz probes. The details of the methodology used by BAS were reported previously (3). The equipment used by AS involves the application of a unique semi-automated border detection programme that was previously found to provide highly reproducible results (45). The intima-media thicknesses in the left and right common carotid artery were measured and the carotid intima-media thickness (cIMT) was defined as the mean of these. Carotid artery plaque was defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness value, or demonstrates a thickness of >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface (46). Both operators were blinded to the cardiovascular risk profiles of the patients. Repeat ultrasound examinations by both operators on 23 patients revealed Spearman correlations between repeat cIMT measurements of 0.983 and 0.956 for BAS and AS, respectively, and the correlation between measurements made by BAS and AS was 0.926. Both operators identified carotid artery bulb or/and internal carotid artery plaque in 11 of these 23 patients with full agreement.

We classified patients as having the NCEP-MetS using the criteria as updated by the American Heart Association and the National Heart, Lung and Blood Institute in 2005 (39). The NCEP identifies women as having the MetS when 3 or more of the following criteria are present: a) waist circumference ≥88 cm; b) triglycerides ≥1.7 mmol/l or drug treatment for elevated triglycerides; c) HDL-cholesterol <1.3 mmol/l or drug treatment for reduced HDL-cholesterol; d) systolic blood pressure ≥130 mm Hg or/and diastolic blood pressure ≥85 mm Hg or drug treatment for hypertension; and e) fasting glucose >5.5 mmol/l or drug treatment for elevated glucose.

Statistical analysis

Continuous variables are reported as mean (SD) and dichotomous variables as proportions or percentages. Non-normally distributed characteristics were logarithmically transformed prior to statistical analysis and for these variables geometric means (SD) are given. Differences in sociodemographic features between black and Caucasian Africans were compared using the Student *t*-test and univariate logistic regression analysis as appropriate. Relationships between population grouping (PG) and baseline characteristics, the cIMT and carotid artery plaque and the metabolic syndrome and its components as well as the associations of the MetS definition with baseline characteristics in black and Caucasian women with RA were investigated in multivariable logistic and linear regression models as appropriate and with consistent adjusting for age and healthcare centre attendance.

To determine whether there were disparities in the relationships of metabolic risk factors with atherosclerosis in African black compared to Caucasian patients, we assessed the associations of interactions between PG and the respective risk factors with cIMT and plaque in age, healthcare centre and individual term adjusted multivariate regression models and, subsequently, performed stratified analysis.

Statistical computations were made using the GB Stat™ programme (Dynamic Microsystems, Inc, Silverspring, Maryland, USA).

Results

Baseline characteristics and atherosclerosis in African black compared to Caucasian women with RA

Baseline characteristics and carotid artery atherosclerosis in African Caucasian and black women with RA are shown in Table I. Black women were on average 1.9 years younger (p=0.2) than Caucasian women. Approximately 97% of black women and 83% Caucasians were seen in public and private care, respectively (p<0.0001). As compared to their Caucasian counterparts and in sociodemographic characteristic adjusted analysis, black women with RA had a smaller pack year history smoking, used alcohol less often and had a higher BMI and lower serum total and HDL cholesterol concentrations but similar total cholesterol÷HDL cholesterol ratios, a higher ESR and lower educational level. The atherosclerosis burden was similar in black and Caucasian patients with RA. Antihypertensive medications, oral glucose lowering agents, insulin, statins and ezetimibe were used in 43.0 and 54.8 (p=0.1), 4.3 and 14.4 (p=0.02), 1.1 and

Table I. Recorded characteristics in African Caucasian and black women with RA.

Characteristics	Caucasian women (n=93)	Black women (n=104)	*p*-value*
Sociodemographics			
Age, years	57.3 (11.8)	55.4 (10.0)	…
Public healthcare (%)	16.7	96.6	…
Lifestyle factors			
Pack year history smoking†, n	2.5 (4.0)	0.1 (1.5)	0.002
Alcohol use (%)	34.8	1.9	<0.0001
Exercise, hours per week†, n	0.7 (2.1)	1.6 (1.9)	0.01
BMI, kg/m^2	25.4 (4.9)	30.0 (6.6)	0.0008
Blood pressure			
Systolic blood pressure, mm Hg	129 (17)	140 (24)	0.8
Diastolic blood pressure, mm Hg	78 (9)	85 (14)	0.2
Lipids			
Total cholesterol, mmol/l	5.1 (1.0)	4.7 (0.9)	0.03
LDL cholesterol, mmol/l	2.8 (0.9)	2.6 (0.8)	0.5
HDL cholesterol†, mmol/l	1.7 (1.3)	1.5 (1.3)	0.002
Total cholesterol÷HDL cholesterol	3.1 (1.0)	3.3 (1.1)	0.1
Triglycerides†, mmol/l	1.1 (1.5)	1.1 (1.7)	0.9
Triglycerides÷HDL cholesterol†	0.6 (1.8)	0.7 (2.1)	0.1
Non-HDL cholesterol	3.3 (1.0)	3.2 (1.0)	0.1
Diabetes mellitus (%)	4.3	17.3	0.5
RA characteristics			
Disease duration, years	14.6 (8.7)	12.9 (9.2)	0.9
Rheumatoid factor positive (%)	73.9	76.0	1.0
DAS28	3.5 (1.5)	4.2 (1.3)	0.5
Deformed joints†, n	3 (4)	7 (3)	0.1
Prednisone ever (%)	41.9	43.3	0.2
Current DMARD, n	2.1 (1.0)	2.5 (1.0)	0.3
Current methotrexate use (%)	78.5	92.3	0.7
Current chloroquine use (%)	46.2	77.9	0.1
Systemic inflammation			
Erythrocyte sedimentation rate†, mm/hr	7 (3)	21 (3)	0.007
C-reactive protein†, mg/l	3.8 (3.5)	7.5 (3.1)	0.2
Other			
Education, years	12.8 (2.7)	7.5 (4.1)	0.002
AIMS depression†	1.9 (1.8)	3.3 (1.6)	0.07
Hypothyroidism‡ (%)	35.5	5.8	0.1
Hormone replacement therapy (%)	18.3	5.8	0.9
Atherosclerosis			
CIMT, mm	0.689 (0.118)	0.691 (0.096)	0.7
Plaque (%)	35.5	35.6	0.2

Results are expressed as mean (SD) unless indicated otherwise.
*p-value for comparisons between African black and Caucasian women after adjustment for age and healthcare as well as lipid lowering and antihypertensive agents in models that include lipid and blood pressure variables, respectively. †Non-normally distributed variable for which geometric mean (SD) is given. ‡It includes subclinical and overt hypothyroidism and diagnosed when thyrotropin level was >4.94 mU/L or when thyroid hormone replacement therapy was used. RA: rheumatoid arthritis; BMI: body mass index; DAS28: disease activity score in 28 joints; DMARD: disease modifying agents for rheumatic disease; AIMS: arthritis impact measurement scales; CIMT: common carotid artery intima-media thickness.

1.9 (p=0.6), 36.6 and 19.2 (p=0.007) and 2.2 and 0% of Caucasian and black women, respectively.

Metabolic risk factors in African black compared to Caucasian women with RA

The metabolic syndrome characteristics in African black and Caucasian women with RA are shown in Table II. The MetS prevalence was 9.7% in Caucasians and 30.8 % in black women with RA. Each of the individual MetS components was numerically markedly more prevalent in black compared to Caucasian women. In age and healthcare centre attendance adjusted analysis, black women with RA sustained an odds ratio for having MetS HDL cholesterol and meeting sufficient criteria for the NCEP MetS definition of 6.1 and 10.1, respectively. Moreover, the number of metabolic syndrome criteria was significantly larger in black compared to Caucasian Africans with RA.

Characteristics of African black and Caucasian women with RA by MetS status

The characteristics in African black and Caucasian women with RA who had and who did not have MetS are shown in Table III. Sociodemographic characteristics did not significantly differ in both black and Caucasian women with and without the MetS (p≥0.08). In sociodemographic characteristic adjusted analysis, the MetS was associated with the BMI, serum triglyceride and non-HDL cholesterol concentrations and the total cholesterol÷HDL cholesterol and triglyceride÷HDL cholesterol ratios in black and Caucasian women; the MetS was further associated with a high pack year history smoking, systolic and diastolic blood pressure, the DAS28 and AIMS depression score in Caucasian women and with low serum HDL cholesterol concentrations in black women with RA.

Relationships between metabolic risk factors and carotid artery atherosclerosis in African black and Caucasian women with RA

In sociodemographic characteristic adjusted analysis, MetS blood pressure and the number of metabolic syndrome criteria were associated with the cIMT in all African women with RA (standardised [S] β [95% CI]=0.18 [0.04–0.31], p=0.01 and S β=0.14 [0.00–0.35], p=0.04, respectively). The metabolic syndrome and each of its components were not associated with carotid artery plaque in all black and Caucasian women with RA.

Interactions between PG and metabolic syndrome features that were associated with cIMT in all women with RA independent of age, healthcare centre and individual terms comprised PG x the MetS triglycerides (p=0.034) and PG x the MetS definition (p=0.02). Disparities in the relationships of metabolic cardiovascular risk with cIMT in black compared to Caucasian women in stratified analysis are shown in Table

Table II. Metabolic syndrome criteria in African Caucasian and black women with RA.

MetS characteristics	Caucasian women (n=93)	Black women (n=104)	OR* (95% CI)
MetS waist	33.3	64.7	2.47 (0.92–6.60)
MetS blood pressure	59.1.5	83.7	1.45 (0.45–4.68)
MetS HDL-cholesterol	15.1	21.2	6.14 (1.11–33.92)†
MetS triglycerides	11.8	17.3	0.82 (0.23–2.92)
MetS glucose	5.4	20.2	2.73 (0.52–14.36)
MetS definition	9.7	30.8	10.11 (1.76–58.03)‡
Continuous variable	Caucasian women mean (SD)	Black women mean (SD)	*p*-value*
MetS criteria, n	1.3 (1.0)	2.1 (1.1)	0.03

Dichotomous variables are expressed as proportions or percentages. *Odds ratio and *p*-value for comparisons between African black and Caucasian African women after adjustment for age, sex and healthcare centres. †*p*=0.036. ‡*p*=0.009. RA: rheumatoid arthritis; MetS: metabolic syndrome; HDL: high-density lipoprotein.

IV. MetS triglycerides, the MetS definition and the number of MetS criteria were associated with cIMT in Caucasian women, whereas MetS blood pressure was associated with cIMT in black women with RA.

Interactions between PG and metabolic syndrome features that were associated with plaque in all women with RA independent of age, healthcare centre and individual terms comprised PG x the MetS waist (*p*=0.01), PG x the number of Mets criteria (*p*=0.02) and PG x the MetS definition (*p*=0.05). Disparities in the relationships of metabolic cardiovascular risk with plaque in black compared to Caucasian women in stratified analysis are shown in Table V. MetS triglycerides and the number of MetS criteria were associated with plaque in Caucasian women, whereas none of the metabolic risk factors was related to plaque in black women with RA.

Baseline recorded characteristics that are potential non-metabolic risk factors and differed between African black and Caucasian women with RA (Table I) included life style factors (pack year history smoking, alcohol use and exercise), the ESR and years of education. In separate models amongst African Black women with RA and in which age and healthcare centre together with these characteristics were adjusted for, MetS waist, MetS HDL cholesterol, MetS triglycerides, MetS glucose and the MetS definition and number of MetS criteria remained unrelated with cIMT (S β=-0.05, *p*=0.6, S β=0.09, p=0.4, S β=0.03, *p*=0.8, S β=-0.10, *p*=0.3, S β=-0.07, *p*=0.5 and S β=0.06, *p*=0.6, respectively) and plaque (odds ratio [OR] [95% confidence interval CI]=1.02 [0.93–1.11], *p*=0.8 ,OR (95%CI)=0.46 [0.13–1.63], *p*=0.5 ,OR (95% CI)=1.23 [0.36–4.21], *p*=0.8, OR (95%CI)=1.23 [0.39–4.20], *p*=0.7 , OR (95%CI)=0.63 [0.21–1.86], *p*=0.4 and OR [95%CI]=0.78 [0.50–1.24], p=0.3, respectively), whereas MetS blood pressure remained associated with cIMT (S β=0.19, *p*=0.049) and unassociated with plaque (OR [95%CI]=1.97 [0.47–8.24], *p*=0.4).

In patients with RA from developed populations, systemic inflammation can explain the association of metabolic risk with atherosclerosis (20). In additional models amongst Caucasian women with RA in which age and healthcare centre together with the DAS28, C-reactive protein concentrations and the ESR were adjusted for, MetS triglycerides were no longer significantly associated with plaque (OR [95%CI]=4.59 [0.71–29.60], *p*=0.1), but the MetS remained related to cIMT (S β=0.17, *p*=0.05) and the number of MetS criteria was still associated with cIMT (S β=0.21, *p*=0.027) and plaque (OR [95%CI]=2.14 [1.12–4.06], *p*=0.02).

Discussion

In this study, African black women with RA experienced a markedly increased metabolic risk factor burden compared to their Caucasian counterparts. However, although MetS blood pressure was related to cIMT, overall metabolic risk as reflected by the MetS and number of its components were not associated with carotid atherosclerosis in black women with RA. In contrast, overall metabolic risk was consistently related to carotid atherosclerosis independently of sociodemographic characteristics in Caucasian women with RA. As applies to previously reported studies that examined cardiovascular risk in non-RA and RA subjects, many relationships were assessed. However, our main findings were each produced in confounder adjusted multivariable analysis. To our knowledge, this is the first study that simultaneously assessed and directly compared the relationships of metabolic cardiovascular risk with atherosclerosis between patients with RA that belong to a developing and developed population.

African black women with RA used numerically more often antihypertensive agents than their Caucasian counterparts, in the present study. This would appear to further support our observation that MetS blood pressure is associated with carotid atherosclerosis in black but not Caucasian African women with RA, since antihypertensive agents reduce adverse cardiovascular outcomes. However, the association between MetS blood pressure and cIMT in African black women with RA should be interpreted with caution. CIMT and plaque represent different aspects of arterial pathology and are biologically and genetically distinct (47-52). The cIMT constitutes ~80% media and ~20% intima (48). Intima-media thickening results mostly from adaptive responses of medial cells to blood pressure and age and associates mostly with stroke risk factors and stroke, whereas carotid artery plaque arises as a consequence of intimal pathology and reflects an advanced stage of atherosclerosis that is more closely associated with coronary artery disease risk factors and ischemic heart disease prevalence (48-50). Therefore, the most striking and important finding in the present study is the consistent lack of relationships of metabolic cardiovascular risk factors with plaque as well as the lack of associations of the respec-

Table III. Recorded characteristics in African Caucasian and black women with RA with and without metabolic syndrome.

Characteristics	Caucasian women			Black women		
	MetS (n=9)	no MetS (n=84)	*p*-value*	MetS (n=32)	no MetS (n=72)	*p*-value*
Sociodemographics						
Age, years	59.2 (14.5)	57.1 (11.5)	…	55.7 (9.5)	55.3 (10.3)	…
Public healthcare (%)	22.2	16.7	…	97.1	90.6	…
Lifestyle factors						
Pack year history smoking†, n	13.3 (5.6)	0.12 (4.7)	0.009	0.1 (1.4)	0.1 (1.5)	0.9
Alcohol use (%)	50.0	33.3	0.4	6.3	0.0	1.0
Exercise, hours per week†, n	0.7 (1.9)	0.5 (2.0)	0.5	0.5 (2.9)	0.8 (2.1)	0.3
BMI, kg/m^2	30.9 (4.5)	24.8 (4.6)	0.0003	32.5 (6.4)	28.9 (6.4)	0.01
Blood pressure						
Systolic blood pressure, mm Hg	150 (17)	126 (16)	<0.0001	141 (23)	139 (24)	0.7
Diastolic blood pressure, mm Hg	85 (13)	77 (8)	0.01	87 (13)	84 (15)	0.3
Lipids						
Total cholesterol, mmol/l	5.7 (1.5)	5.1 (1.0)	0.1	4.8 (1.0)	4.7 (0.8)	0.5
LDL cholesterol, mmol/l	3.0 (1.0)	2.8 (0.9)	0.6	2.7 (0.9)	2.6 (0.7)	0.6
HDL cholesterol†, mmol/l	1.5 (1.5)	1.8 (1.3)	0.1	1.2 (1.3)	1.6 (1.2)	<0.0001
Total cholesterol÷HDL cholesterol	3.9 (1.4)	3.0 (0.9)	0.009	4.1 (1.3)	2.9 (0.7)	<0.0001
Triglycerides†, mmol/l	2.1 (1.7)	1.0 (1.4)	<0.0001	1.7 (1.8)	0.9 (1.4)	<0.0001
Triglycerides÷HDL cholesterol†	1.4 (2.1)	0.6 (1.6)	<0.0001	1.4 (2.0)	0.5 (1.6)	<0.0001
Non-HDL cholesterol	4.0 (1.2)	3.3 (1.0)	0.03	3.5 (1.0)	3.0 (0.8)	0.006
Diabetes mellitus (%)	33.3	1.2	0.004	43.8	5.6	<0.0001
RA characteristics						
Disease duration, years	16.7 (9.0)	14.4 (8.7)	0.5	13.6 (9.9)	12.6 (8.9)	0.9
Rheumatoid factor positive (%)	88.9	72.3	0.3	75.0	76.4	0.9
DAS28	4.5 (1.7)	3.4 (1.5)	0.05	4.4 (1.3)	4.1 (1.3)	0.1
Deformed joints†, n	3 (4)	3 (4)	0.8	5 (3)	6 (3)	0.6
Prednisone ever (%)	33.3	42.9	0.5	34.4	47.2	0.2
Current DMARD, n	1.6 (0.9)	2.2 (0.9)	0.06	2.6 (0.8)	2.5 (1.1)	0.9
Current methotrexate use (%)	55.6	81.0	0.06	90.6	93.1	1.0
Current chloroquine use (%)	22.2	48.8	0.1	75.0	79.1	0.7
Systemic inflammation						
ESR†, mm/hr	13 (3)	7 (3)	0.09	25 (3)	19 (3)	0.2
C-reactive protein†, mg/l	8.2 (3.1)	3.5 (3.4)	0.06	9.0 (3.6)	6.9 (2.8)	0.2
Other						
Education, years	12.7 (2.1)	12.8 (2.7)	0.8	8.3 (4.2)	7.1 (4.0)	0.6
AIMS depression†	4.1 (1.5)	2.8 (1.7)	0.04	3.4 (1.4)	3.3 (1.6)	0.7
Hypothyroidism‡ (%)	55.6	33.3	0.1	6.3	5.6	0.6
Hormone replacement therapy (%)	22.2	17.9	0.7	9.4	4.2	0.2

Results are expressed as mean (SD) unless indicated otherwise.
*p-value for comparisons between African black and Caucasian women after adjustment for age, sex and healthcare.
†Non-normally distributed variable for which geometric mean (SD) is given. ‡It includes subclinical and overt hypothyroidism and diagnosed when thyrotropin level was >4.94 mU/L or when thyroid hormone replacement therapy was used. RA: rheumatoid arthritis; MetS: metabolic syndrome; BMI: body mass index, DAS28: disease activity score in 28 joints, DMARD: disease modifying agents for rheumatic disease, ESR: erythrocyte sedimentation rate; AIMS: arthritis impact measurement scales; CIMT: common carotid artery intima-media thickness.

tive risk factors, other than MetS blood pressure, with cIMT in African black women with RA, particularly in the face of an overall metabolic risk factor burden that was larger than in their Caucasian counterparts. Ultrasonographically determined carotid artery plaque is associated with a 10-year cardiovascular event rate risk of 39% in non-RA subjects (53) and reportedly predicts incident ACVD in patients with RA irrespective of population origin (40, 41). Taken together, our results indicate that metabolic risk factors in women with RA from developing groups of African descent do not as yet translate in severe atherosclerosis. Indeed, our findings are congruous with the distinctly low ACVD event rates (32-34, 38) despite the recent acquisition of more prevalent obesity, hypertension and diabetes in African black compared to Caucasian non-RA subjects (54). Furthermore, our data analysis indicates that the presence of RA does not alter the absence of metabolic risk factor related ACVD. Ultimately, metabolic risk may enhance atherogenesis in such persons, but only a longitudinal study will answer this question.

The burden of atherosclerosis was as large in African black compared to Caucasian women with RA in this study. Our results therefore indicate that rigorous systematic cardiovascular risk assessment should be performed irrespectively of metabolic risk factor profiles in African black women with RA.

Caucasian patients in the present investigation had a lower BMI and less frequent abdominal obesity and, consequently, a smaller MetS prevalence

Table IV. Relationships of MetS characteristics with carotid artery intima-media thickness in African Caucasian and black women with RA.

	Caucasian women		Black women	
MetS characteristic	S β (95% CI)*	*p*-value	S β (95% CI)*	*p*-value
MetS waist	0.07 (-0.11–0.26)	0.4	-0.05 (-0.25–0.15)	0.6
MetS blood pressure	0.14 (-0.09–0.37)	0.2	0.20 (0.01–0.40)	0.04
MetS HDL cholesterol	0.11 (-0.08–0.28)	0.2	0.07 (-0.10–0.21)	0.4
MetS triglycerides	0.24 (0.05–0.39)	0.01	0.01 (-0.13–0.16)	0.9
MetS glucose	-0.01 (-0.19–0.11)	0.6	-0.10 (-0.23–0.06)	0.3
MetS definition	0.19 (0.01–0.35)	0.036	-0.08 (-0.24–0.08)	0.4
MetS criteria, n	0.21 (0.02–0.35)	0.028	0.04 (-0.10–0.20)	0.7

*Adjusted for age and healthcare centere. MetS: metabolic syndrome; S: standardised; β: regression coefficient; CI: confidence intervals; HDL: high-density lipoprotein.

Table V. Relationships of MetS characteristics with carotid artery plaque in African Caucasian and black women with RA.

	Caucasian women		Black women	
MetS characteristic	OR (95% CI)*	*p*-value	OR (95% CI)*	*p*-value
MetS waist	2.17 (0.79–5.93)	0.1	1.03 (0.94–1.12)	0.6
MetS blood pressure	1.19 (0.41–3.45)	0.7	1.60 (0.44–5.91)	0.5
MetS HDL cholesterol	2.91 (0.77–11.01)	0.1	0.44 (0.13–1.51)	0.2
MetS triglycerides	5.30 (0.99–28.46)	0.049	1.14 (0.36–3.59)	0.8
MetS glucose	1.93 (0.24–15.80)	0.5	1.12 (0.38–3.30)	0.8
MetS definition	4.74 (0.81–27.73)	0.08	0.58 (0.21–1.61)	0.3
MetS criteria, n	1.89 (1.09–3.26)	0.02	0.80 (0.53–1.23)	0.3

*Adjusted for age and healthcare centre. MetS: metabolic syndrome; OR: odds ratio; CI: confidence intervals; HDL: high-density lipoprotein.

compared to those in published reports on metabolic risk in RA from the US (20, 24) and Europe (19, 21). Nevertheless, our results in Caucasians add to the available evidence that substantiates a role for metabolic risk in atherogenesis and cardiovascular risk assessment amongst patients with RA from developed populations (16-25). This includes the association of metabolic risk with systemic inflammation in that the DAS28 was, and the ESR and C-reactive protein concentrations tended to be higher in Caucasians with compared to those without the MetS in adjusted analysis. However, whereas systemic inflammation and disease activity explained the association between metabolic risk and coronary atherosclerosis in a study from the US by Chung *et al*. that included patients with both early- and long-standing RA (20), we found that the respective relationship was not materially altered by, and mostly independent of non-metabolic risk factors. This discrepancy is likely due to the fact that only patients with established treated RA were included in our study. Since lipid lowering agents decrease adverse cardiovascular outcomes, the fact that this intervention was more frequently employed in African Caucasian than in black women with RA further supports the presence of a relationship between MetS triglycerides and carotid atherosclerosis in the former but not the latter group.

Our study has further limitations. Our patients were exclusively women, the cross-sectional design of our investigation precludes drawing inferences on the direction of causality and the presence of less strong relationships between MetS characteristics and atherosclerosis than those found in our study may have eluded identification in view of our relatively small patient sample. Furthermore, we have recently reported that, compared to British Caucasians, non-RA black Africans experience much greater aortic reflective waves (54) and, therefore, possibly greater aortic blood pressure values for a given brachial blood pressure and, black Africans have reduced nocturnal blood pressure dipping that may produce target organ effects independently of conventional blood pressure (56). Consequently, central rather than brachial blood pressure evaluation and the use of ambulatory 24-hour day and night blood pressure recording may be required to adequately investigate the impact of the respective metabolic risk factor on atherogenesis in black Africans with RA.

Conclusion

In contrast to their African Caucasian counterparts, black women with RA experience a markedly increased metabolic risk factor burden that is however currently as yet not likely to be associated with atherosclerosis. The potential role of metabolic risk factors in atherogenesis in African black women with RA requires further assessment in longitudinal studies. Meanwhile, since the atherosclerosis extent was not reduced in African black compared to Caucasian women in the present study, our findings call for systematic cardiovascular risk management irrespective of metabolic risk factor profiles in African black women with RA.

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Paper 6

The previous 5 papers revealed that none of the risk factors that are currently recommended in cardiovascular risk stratification among patients with RA, are associated with atherosclerosis in black Africans with this disease. Another potential candidate in this context is a reduced glomerular filtration rate or chronic kidney disease. Indeed, as stated in the introduction of this thesis, reduced kidney function is an independent cardiovascular risk factor and may be more prevalent in black Africans than in developed populations.

Paper 6 compares the frequency of reduced kidney function and its association with (1) endothelial activation that comprises the earliest stage in atherogenesis upon exposure to cardiovascular risk factors, as well as (2) atherosclerosis among black and white Africans with RA. Nine reported estimated glomerular filtration rate equations were calculated.

A Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate of <90 ml/min/1.73 m^2 was identified in 49.1% of black and 30.6% of white African patients with RA ($p = 0.004$). In white Africans with RA, estimated glomerular filtration rate was related to endothelial activation. By contrast, in black RA patients, all except the Modification of Diet in Renal Disease equation were associated to a similar extent with carotid intima-media thickness, and plaque ($p = 0.0003$ to 0.08) in Receiver Operating Characteristic

curve analysis. Based on optimal estimated glomerular filtration rate cut-off values with sensitivities and specificities ranging from 42 to 60% and 70 to 91%, respectively, a low estimated glomerular filtration rate increased the odds ratio for plaque 2.2 to 4.0 fold. The respective optimal cut-off values ranged from 49 ml/min/1.73 $m^2$for the Cockroft-Gault equation to 82 ml/min/1.73 m^2 for the Chronic KidneyDisease Epidemiology Collaboration.

In conclusion, except for the Modification of Diet in Renal Disease equation, other estimated glomerular filtration rate equations comprise the first reported easily and in fact routinely available cardiovascular risk marker shown to be useful in cardiovascular disease risk stratification in black Africans with RA.

PLOS ONE

RESEARCH ARTICLE

Kidney Function, Endothelial Activation and Atherosclerosis in Black and White Africans with Rheumatoid Arthritis

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Abstract

Objective

To determine whether kidney function independently relates to endothelial activation and ultrasound determined carotid atherosclerosis in black and white Africans with rheumatoid arthritis (RA).

Methods

We calculated the Jelliffe, 5 Cockcroft-Gault equations, Salazar-Corcoran, Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (EGFR) equations in 233 (112 black) RA patients.

Results

The CKD-EPI eGFR was $<$90 ml/min/1.73m^2 in 49.1% and 30.6% of black and white patients, respectively (odds ratio (95% confidence interval) = 2.19 (1.28–3.75), p = 0.004). EGFRs were overall consistently associated with monocyte chemoattractant protein-1 and angiopoietin 2 concentrations in white patients, and with carotid intima-media thickness and plaque in black participants. Amongst black patients, plaque prevalence was 36.7% and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve was not associated with plaque presence for the MDRD equation (p = 0.3), whereas the respective relationship was significant or borderline significant (p = 0.003 to 0.08) and of similar extent (p$>$0.1 for comparisons of AUC (SE)) for the other 8 equations. Based on optimal eGFR cut-off values with sensitivities and specificities ranging from 42 to 60% and 70 to 91%

Competing Interests: The authors have declared that no competing interests exist.

respectively, as determined in ROC curve analysis, a low eGFR increased the odds ratio for plaque 2.2 to 4.0 fold.

Conclusion

Reduced kidney function is independently associated with atherosclerosis and endothelial activation in black and white Africans with RA, respectively. CKD is highly prevalent in black Africans with RA. Apart from the MDRD, eGFR equations are useful in predicting carotid plaque presence, a coronary heart disease equivalent, amongst black African RA patients.

Introduction

In 1974, Lindner and colleagues [1] reported that atherosclerotic coronary heart disease (CHD) risk is increased in patients on dialysis. However, dialyzed patients experience increased mortality due to sudden death and heart failure more frequently than from atherosclerotic CHD [2]. Endothelial cell dysfunction comprises a central mechanism in the genesis of the different cardiovascular dysfunction aspects in chronic kidney disease (CKD) [2]. Mild renal impairment elevates cardiovascular disease (CVD) risk [3].

Patients with RA sustain an increased risk of CVD [4,5]. Reduced kidney function development is enhanced in patients with RA compared to non-RA persons and increases the risk of cardiovascular events in RA [6,7]. The potential impact of impaired kidney function on atherogenic mechanisms including endothelial activation and atherosclerosis in RA requires elucidation.

Both traditional and nontraditional cardiovascular risk factors are associated with prevalent and incident CVD in RA [8]. Accordingly, currently reported recommendations on CVD risk stratification in RA include the use of multiple traditional risk factor assessment equations such as the Framingham score and the Systematic COronary Risk Evaluation score (SCORE) in combination with consideration of RA characteristics [9]. Nevertheless, up to 85% of white RA patients considered to be at moderate CVD risk according to the latter approach were reported to have carotid artery plaque [10], which represents a CHD equivalent [11,12]. Importantly in the present context, we recently found that both traditional cardiovascular risk factors and RA characteristics were related to atherosclerosis in white but consistently not in black Africans with RA, this despite a similar atherosclerosis burden amongst the 2 groups [13–15]. Taken together, these findings call for additional easily available and reliable CVD risk markers in white and even more so in black patients with RA.

Creatinine concentrations are unreliable and creatinine clearance is no longer recommended to estimate kidney function as timed urine collections are cumbersome and prone to error [16]. The iothalamate, EDTA, diethylene triamine pentaacetic acid or iohexol clearance most accurately estimate glomerular filtration rate (GFR) [16]. However, performing these investigations is expensive and complex and not recommended in routine clinical practice [16].

The initially reported Jelliffe estimated glomerular filtration (eGFR) equation in 1973 was a landmark in the assessment of kidney function [17]. Subsequently, a large series of other equations calculated from serum creatinine concentrations as well as age and sex with or without the inclusion of anthropometric measures or race were reported. Amongst these, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) is most recent and was most extensively validated [18]. Both The Modification of Diet in Renal disease (MDRD) [19] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were also validated in

non-RA black Africans [20]. To date, only the Cockcroft-Gault (C-G) actual body weight equation has been validated in a small cohort of white RA patients [21]. The MDRD was reported to be less accurate than the C-G actual body weight as a measure of creatinine clearance in RA [22]. A further complicating factor in patients with RA is that they experience excess body fat for a given body mass index (BMI) and reduced muscle mass [23], which can result in an overestimation of kidney function [24–26]. In this regard, the Salazar-Corcoran equation and the substitution of actual body weight by various other weight measures in the C-G equation can improve kidney function evaluation in persons with an altered adiposity status [24–26].

In view of these considerations, we evaluated the independent relations of 9 different eGFR equation values with endothelial activation and atherosclerosis in black and white Africans with RA. We further aimed at determining the accuracy of eGFR equation results in identifying patients with carotid plaque or high risk atherosclerosis.

Patients and Methods

Patients

The present study was conducted according to the principles outlined in the Helsinki declaration. The Human Research Ethics Committee (Medical) from the University of the Witwatersrand in Johannesburg, South Africa approved the protocol (approval number: M06-07-33). Participants gave informed, written consent.

This was a two-center based prospective study, comprising consecutive patients. Two hundred and thirty three African patients (112 black and 121 white) that met the 1987 American College of Rheumatology [27] and 2010 American College of Rheumatology/European League against Rheumatism (EULAR) criteria for RA [28] were enrolled at the Charlotte Maxeke Johannesburg (n = 129) and Milpark Hospital (n = 104) in Johannesburg. All invited participants agreed to participate. Data were missing in fewer than 5% of any of the recorded characteristics.

Baseline characteristics

Were assessed baseline characteristics using previously reported methods (13–15). Briefly, we recorded demographic features, and anthropometric characteristics including height, weight and waist and hip circumference were measured employing standard approaches. The body mass index (BMI) was calculated and abdominal obesity and fat distribution were estimated by waist circumference and waist-hip ratio respectively. We recorded disease duration and rheumatoid factor status. Anti-cyclic citrullinated peptide antibody concentrations were not consistently evaluated and therefore not included in the analysis. Disease activity was assessed by the Clinical Disease Activity Index (CDAI) and the Disease Activity Score in 28 joints (DAS28). Extra-articular manifestations included the current or previously recorded (hospital record review) presence of pericarditis, pleuritis, Felty's syndrome, cutaneous vasculitis, neuropathy, scleritis or episcleritis, retinal vasculitis, glomerulonephritis, vasculitis affecting other organs, amyloidosis, keratoconjunctivitis sicca, xerostomia, Sjogren's syndrome, pulmonary fibrosis, bronchiolitis obliterans organizing pneumonia, cervical myelopathy, subcutaneous nodules and rheumatoid nodules in other locations. C-reactive protein concentrations were determined using immunoturbidimetric methods. Standard laboratory blood tests of erythrocyte sedimentation rate, lipids and glucose were performed.

We recorded current smoking status and systolic and diastolic blood pressure. Hypertension was defined as an average systolic blood pressure $\geq$140 or/and diastolic blood pressure $\geq$90 mmHg or/and current use of antihypertensive medications. Dyslipidemia was diagnosed when the atherogenic index, i.e. the cholesterol-HDL cholesterol ratio, was >4. Diabetes was

identified when glucose lowering agents were used or the fasting plasma glucose was ≥7 mmol/l. The Framingham score was calculated using algorithms [12].

Endothelial activation

We measured early endothelial activation molecule concentrations including those of soluble E-selectin, vascular cell adhesion molecule-1 (VCAM-1), ICAM-1and monocyte chemoattractant protein-1 (MCP-1), as well as angiopoietin 2 and using solid-phase sandwich ELISA (Quantikine®HS, R & D Systems, Inc., Minneapolis, MN, USA). Their lower detection limits were 0.009 ng/l, 0.6 ng/l, 0.096 ng/l, 5.0 pg/ml and 1.2 pg/ml respectively; their inter- and intra-assay coefficients of variation were 7.9 and 5.8, 7.0 and 3.1, 5.5 and 4.6, 5.7 and 5.8, and 8.9 and 5.9% respectively.

Atherosclerosis

BAS (see acknowledgement) and AS performed the carotid artery ultrasound measurements in private and public healthcare patients, respectively. Both operators obtained images of at least 1cm length of the distal common carotid arteries for measurement of the intima-media thickness of the far wall from an optimal angle of incidence defined as the longitudinal angle of approach where both branches of the internal and external carotid artery are visualized simultaneously [29] and with high resolution B-mode ultrasound (Image Point, Hewlett Packard, Andover, MA, USA and SonoCalc IMT, Sonosite Inc, Bothell, Wash, USA used by BAS and AS, respectively) employing linear array 7.5 MHz probes. The details of the methodology used by BAS were reported previously [30]. The equipment used by AS involves the application of a unique semi-automated border detection program that was previously found to provide highly reproducible results [29]. The intima-media thicknesses in the left and right common carotid artery were measured and the cIMT was defined as the mean of these. Carotid artery plaque was defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima-media thickness value, or demonstrates a thickness of >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface [31]. Both operators were blinded to the cardiovascular risk profiles of the patients. Repeat ultrasound examinations by both operators on 23 patients revealed Spearman correlations between repeat cIMT measurements of 0.983 and 0.956 for BAS and AS, respectively, and the correlation between measurements made by BAS and AS was 0.926. Both operators identified carotid artery bulb or/and internal carotid artery plaque in 11 of these 23 patients with full agreement.

Kidney function

Serum creatinine concentrations were measured using the kinetic alkaline picrate method. In the 129 patients enrolled at the Charlotte Maxeke Johannesburg Academic Hospital, the Advia Chemistry systems (Siemens) was used with calibration traceable to isotope dilution mass spectrometry (IDMS); in the other 104 patients that were recruited at the Milpark Hospital, the Multiconstituent Calibrator (Architect) was employed which, at that time, was not traceable to IDMS. The non-IDMS and IDMS traceable values were inter-converted using the following equations: IDMS serum creatinine = (non-IDMS serum creatinine—0.067)/1.065 and non-IDMS serum creatinine = IDMS serum creatinine x 1.065 + 0.067 [32]. IDMS serum creatinine values were used in the CKD-EPI equation and non-IDMS results were employed in the other equations, as was defined when these equations were initially formulated [17–26]. Table 1 gives the 9 different eGFR equations [17–26] that were evaluated in the present study. The MDRD was calculated based on 4 variables [19]. The ethnicity factor as recommended in black

Table 1. Estimated glomerular filtration rate equations.

Jelliffe	Men: (98–0.8 x (age—20)) / Scr; women: (98–0.8 x (age—20)) / Scr x 0.9
Cockcroft Gault ABW	Men: ((140—age) x ABW) / (Scr x 72); women: ((140—age) x ABW) / (Scr x 72) x 0.85
Cockcroft Gault IBW	Men: ((140—age) x IBW) / (Scr x 72); women: ((140—age) x IBW) / (Scr x 72) x 0.85; with IBW = 50 kg + (0.906 x (height-152.4)) in men and 45.5 kg + (0.906 x (height-152.4)) in women
Cockcroft Gault LBW	Men: ((140—age) x LBW) / (Scr x 72); women: ((140—age) x LBW) / (Scr x 72) x 0.85; with LBW = (9270 x ABW) / (6680 + (216 x BMI)) in men and (9270 x ABW) / (8780 + (244 x BMI)) in women
Cockcroft Gault ADBW	Men: ((140—age) x ADBW) / (Scr x 72); women: ((140—age) x ADBW) / (Scr x 72) x 0.85; with ADBW = IBW + (0.4 x (ABW—IBW))
Cockcroft Gault NBW	Men: (140—age) / Scr; women: (140—age) / Scr x 0.85
Salazar-Corcoran	Men: ((137—age x ((0.285 x weight) + (12.1 x height^2))) / (51 x Scr); women: ((146—age x ((0.287 x weight) + (9.74 x height^2))) / (60 x Scr)
MDRD	Men: 186 x Scr$^{-1.154}$ x age$^{-0.203}$; women: 186 x Scr$^{-1.154}$ x age$^{-0.203}$ 0.742
CKD-EPI	Women when Scr $\leq$0.7: 144 x (Scr / 0.7)$^{-0.329}$ x 0.993^{age} and when Scr $>$0.7: 144 x (Scr / 0.7)$^{-1.209}$ x 0.993^{age}; men when Scr $\leq$0.9: 141 x (Scr 0.9) $^{-0.411}$ x 0.993^{age} and when Scr $>$0.9: 141 x (Scr / 0.9)$^{-1.209}$ x 0.993^{age}

Ideal body weight was calculated using the formula by Devine (34) with height measured in centimeters. In the Salazar-Corcoran equation, weight is expressed in kilogram and height in meter.
Scr = serum creatinine, AWB = actual body weight, IBW = ideal body weight, LBW = lean body Weight, ADBW = adjusted body weight, NBW = no body weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

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Americans when calculating the MDRD and CKD-EPI was not applied in the present study as its use results in an overestimation of kidney function in black Africans living in our region [20].

Data analysis

Dichotomous variables are expressed as proportions or percentages and continuous variables as mean (SD) or median (interquartile range) when non-normally distributed. Non-normally distributed characteristics were also logarithmically transformed prior to their inclusion in multivariable statistical analysis.

The recorded characteristics were compared between black and white patients using the Student t test, Mann-Whitney U or univariate logistic regression analysis as appropriate. To identify potential confounding variables in subsequent analysis, we assessed the associations of baseline characteristics with eGFR equations at $p \leq 0.2$ in demographic characteristic adjusted linear regression models.

The independent relationships of eGFR equations with endothelial activation molecule concentrations and cIMT were identified in confounder adjusted linear regression models; independent associations between eGFR equations and carotid plaque were evaluated in logistic regression models.

When consistent independent relations were found between eGFR equations and plaque, sensitivity versus false positive frequency (1-specificity) for predicting plaque presence with eGFR levels was analyzed employing receiver operator characteristic (ROC) curves. The predictive accuracy of eGFR equations was evaluated by the area under the curve (AUC). In this analysis, we accounted for potential confounding by traditional CVD risk factors and RA

characteristics by including as a covariate the Framingham score, this with the application of the EULAR multiplier of 1.5 in patients with 2 of 3 criteria comprising of (1) a disease duration >10 years, (2) rheumatoid factor positivity, and (3) the presence of extraarticular manifestation(s) and thereby giving the modified (m) Framingham score (9). To determine the optimal cut-off values of eGFR values in predicting plaque presence, we calculated the Youden index using the following formula: sensitivity + specificity − 1, with the maximum obtained value corresponding to the optimal cut-off point [33]. Positive and negative predictive values were determined by applying Bayes' theorem [34]. We then reassessed the associations of eGFRs with plaque using the obtained cut-off values in mFramingham score adjusted logistic regression models.

Statistical computations were made using the GB Stat program (Dynamic Microsystems, Inc, Silverspring, Maryland, USA) and SPSS software, version 21 (SPSS, Armonk, NY, USA). Significance was set at $p<0.05$.

Results

Baseline characteristics

Table 2 gives the baseline characteristics and their comparisons between those obtained in black and white patients with RA. As compared to whites, black participants were more often women, experienced a larger adiposity burden, more active and severe RA except for less frequent extraarticular manifestations and more prevalent hypertension and diabetes. The mean (SD) Framingham score was 6 (7) and 5 (7) in black and white patients, respectively. However, this characteristic was non-normally distributed with similar median (interquartile range) values of only 2 (1–5) and 3 (1–6) in the respective groups.

Endothelial activation and atherosclerosis

E-selectin and angiopoietin 2 concentrations were larger and ICAM-1 and MCP-1 levels lower in black compared to white patients with RA. CIMT values and plaque frequency were similar in both groups.

Kidney function

Table 2 also gives measures of kidney function in all, black and white patients. As previously reported in non-RA subjects [32], in all patients, IDMS creatinine concentrations were on average 13% smaller than those of non-IDMS creatinine. The mean (SD) C-G actual body weight and CKD-EPI eGFR values were similar (91 (28) ml/min versus 93 (17) ml/min/m^2, $p = 0.2$). Application of the other equations produced consistently lower values ($p<0.05$ for comparisons with CKD-EPI eGFR), as also reported in non-RA subjects [24–26,35].

The non-IDMS and IDMS creatinine concentrations were higher in black compared to white patients. Kidney function as estimated by the C-G actual body weight equation was similar in both groups whereas application of each of the other 8 equations revealed reduced values in black compared to white patients. Taken together, as the C-G actual body weight equation overestimates kidney function in obese persons [24–26] and black patients experienced excess adiposity compared to whites (see Table 2), overall, these results indicate that renal function is impaired in the former compared to the latter group. In this regard also, CKD as defined by a CKD-EPI eGFR of <90 ml/min/m^2 (3,18) was present in 49.1% and 30.6% of black and white RA patients, respectively; black population origin was associated with CKD (odds ratio (95% CI) for CKD = 2.19 (1.28–3.75), $p = 0.004$). Amongst all patients, the eGFR was mildly (60 to

Table 2. Recorded characteristics in all 233 and 112 black and 121 white patients with RA.

Demographic characteristics	All patients	Black	White	p
Age (years)	57.1 (10.8)	55.7 (10.1)	58.3 (11.4)	0.06
Female sex	82.8	**88.4**	**77.7**	**0.03**
Anthropometry				
Body mass index (kg/m^2)	27.4 (6.0)	**29.3 (6.6)**	**25.6 (6.6)**	**<0.0001**
Body mass index ≥25 (kg/m^2)	58.8	**69.6**	**48.8**	**0.001**
Waist circumference (cm)	91 (13)	**93 (13)**	**89 (13)**	**0.01**
Waist/hip	0.86 (0.80–0.92)	0.85 (0.80–0.90)	0.87 (0.80–0.93)	0.2
Cardiovascular agents				
Antihypertensives	46.8	52.7	41.3	0.08
Statins	28.3	**19.6**	**36.4**	**0.005**
Ezetimibe	0.9	0	1.7	. . .
Oral glucose lowering agents	7.7	**12.5**	**3.3**	**0.01**
Insulin	1.7	1.8	1.7	0.9
RA characteristics				
Disease duration (years)	13.6 (9.3)	12.9 (9.2)	14.3 (9.4)	0.3
Rheumatoid factor positive	76.7	78.5	75.0	0.5
Clinical Disease Activity Index	7.2 (2.0–13.7)	**10.3 (4.0–15.5)**	**5.1 (0.7–11.7)**	**0.0001**
Disease Activity Score in 28 joints	3.9 (1.5)	**4.1 (1.3)**	**3.6 (1.6)**	**0.01**
Erythrocyte sedimentation rate (mm/hr)	12 (5–27)	**21 (9–31)**	**7 (3–14)**	**<0.0001**
C-reactive protein (mg/l)	5.1 (2.1–12.5)	**7.0 (4.0–13.8)**	**3.8 (1.5–10.6)**	**0.002**
Deformed joints (number)	6 (0–15)	**8 (3–14)**	**4 (0–17)**	**0.03**
Extraarticular manifestation(s)	7.7	**2.7**	**12.4**	**0.01**
Synthetic modifying agents				
Methotrexate	83.7	**90.2**	**77.7**	**0.01**
Chloroquine	66.1	**79.5**	**53.7**	**<0.0001**
Leflunomide	30.9	**22.3**	**38.8**	**0.007**
Sulphasalazine	18.5	**24.1**	**13.2**	**0.03**
Azathioprine	14.2	16.1	12.4	0.4
Tetracycline	12.0	10.7	13.2	0.6
Cyclophosphamide	3.0	5.4	0.8	0.08
Penicillamine	3.4	4.5	2.5	0.4
Number	2.4 (1.0)	**2.5 (1.0)**	**2.2 (0.9)**	**0.01**
Prednisone use	2.6	1.8	3.3	0.5
Tumor necrosis factor- blockade	3.9	0	7.4	. . .
NSAID	17.6	**7.1**	**27.3**	**0.0002**
Conventional CV risk factors				
Hypertension	57.5	**70.5**	**45.5**	**0.0001**
Systolic blood pressure (mmHg)	133 (21)	**139 (24)**	**128 (16)**	**0.0001**
Diastolic blood pressure (mmHg)	82 (12)	**86 (14)**	**79 (9)**	**<0.0001**
Total cholesterol (mM)	4.8 (1.0)	**4.7 (0.9)**	**5.0 (1.1)**	**0.02**
HDL cholesterol (mM)	1.5 (1.3–1.9)	1.5 (1.3–1.8)	1.6 (1.3–2.0)	0.07
LDL cholesterol (mM)	2.7 (0.9)	2.6 (0.8)	2.8 (0.9)	0.09
Triglycerides (mM)	1.0 (0.8–1.4)	1.0 (0.8–1.4)	1.0 (0.8–1.4)	0.6
Cholesterol/HDL cholesterol	3.2 (1.1)	3.3 (1.1)	3.2 (1.0)	0.5
Cholesterol/HDL cholesterol>4	19.7	23.9	16.0	0.1
Non-HDL cholesterol (mM)	3.2 (1.0)	3.1 (0.9)	3.3 (1.0)	0.2
Diabetes	12.5	**17.9**	**7.4**	**0.002**

(*Continued*)

Table 2. (*Continued*)

Demographic characteristics	All patients	Black	White	p
Glucose (mM)	4.7 (4.4–5.2)	**4.9 (4.5–5.4)**	**4.7 (4.4–5.1)**	**0.02**
Smoking, current	6.9	3.6	10.0	0.07
Framingham score	2 (1–6)	2 (1–5)	3 (1–6)	0.4
Endothelial activation				
Early endothelial activation				
E-selectin (ng/ml)	38.6 (18.4)	**41.6 (19.8)**	**35.7 (16.5)**	**0.02**
VCAM-1 (ng/ml)	834 (664–1,048)	835 (696–1,043)	828 (635–1,033)	0.5
ICAM-1 (ng/ml)	277 (214–353)	**247 (173–317)**	**305 (251–385)**	**<0.0001**
MCP-1 (pg/ml)	427 (265–683)	**351 (223–679)**	**476 (334–684)**	**0.009**
Angiopoietin 2 (pg/ml)	2,502 (2,044–3,307)	**2,681 (2,232–3,566)**	**2,366 (1,924–3,130)**	**0.002**
Carotid atherosclerosis				
Intima-media thickness (mm)	0.709 (0.111)	0.703 (0.090))	0.715 (0.130)	0.4
Plaque	40.3	36.7	43.8	0.2
Creatinine (mg/dl)				
Non IDMS traceable	0.82 (0.72–0.96)	**0.87 (0.75–0.89)**	**0.79 (0.67–0.92)**	**0.006**
IDMS traceable	0.71 (0.61–0.84)	**0.76 (0.64–0.86)**	**0.68 (0.57–0.80)**	**0.006**
EGFR equations				
Jelliffe (ml/min)	79 (22)	**76 (19)**	**82 (24)**	**0.003**
C-G ACBW (ml/min)	91 (28)	90 (27)	92 (30)	0.2
C-G IBW (ml/min)	71 (23)	**65 (20)**	**77 (24)**	**<0.0001**
C-G ADBW (ml/min)	79 (23)	**75 (20)**	**83 (25)**	**0.0002**
C-G LBW (ml/min)	57 (17)	**54 (14)**	**59 (20)**	**0.001**
C-G NBW (ml/min)	91 (25)	**87 (22)**	**94 (28)**	**0.0003**
Salazar-Corcoran (ml/min)	89 (25)	**85 (22)**	**93 (28)**	**0.0003**
MDRD (ml/min/1.73 m^2)	84 (24)	**78 (20)**	**89 (27)**	**0.0003**
CKD-EPI (ml/min/1.73 m^2)	93 (17)	**90 (17)**	**95 (17)**	**0.0005**

Results are expressed as mean (SD), median (interquartile range) or proportion as appropriate.

Significant relations are shown in bold.

RA = rheumatoid arthritis, NSAID = non steroidal antiinflammatory agents, VCAM-1 = vascular adhesion molecule-1, ICAM-1 = intercellular adhesion molecule-1, MCP-1 = monocyte chemoattractant protein-1, IDMS = isotope dilution mass spectrometry, eGFR = estimated glomerular filtration rate, C-G = Cockcroft-Gault, AWB = actual body weight, IBW = ideal body weight, ADBW = adjusted body weight, LBW = lean body weight, NBW = no body weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

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89 ml/min/m^2 (stage 2 CKD)) and moderately (30 to 59 ml/min/m^2 (stage 3 CKD)) reduced in 84 (36.1%) and 8 (3.4%) (4 black and 4 white) RA participants, respectively.

Baseline characteristics associated with kidney function

Associations between baseline characteristics and eGFR equations at $p \leq 0.2$ are shown in S1 Table. Demographic characteristics, adiposity indices, RA characteristics and traditional CVD risk factors were related to kidney function equations. The Framingham score was significantly associated with 7 of the eGFR equations and was included in subsequent analysis to account for potential confounding by traditional CVD risk factors.

Table 3. EGFR formulas and endothelial activation in all, black, white, normal weight and obese patients with RA.

	All patients		Black patients		White patients	
	MCP-1	Angiopoietin 2	MCP-1	Angiopoietin 2	MCP-1	Angiopoietin 2
EGFR equation	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**
Jelliffe	**–0.002 (0.001); 0.04**	–0.001 (0.001); 0.2	–0.001 (0.002); 0.6	0.001 (0.001); 0.4	**–0.003 (0.001); 0.02**	–0.001 (0.001); 0.2
C-G ACBW	–0.002 (0.001); 0.05	–0.001 (0.001); 0.05	–0.000 (0.002); 0.8	–0.000 (0.001); 0.8	**–0.003 (0.001); 0.01**	**–0.002 (0.001); 0.04**
C-G IBW	–0.002 (0.001); 0.07	**–0.001 (0.001); 0.02**	0.000 (0.002); 0.9	–0.000 (0.001); 0.6	**–0.003 (0.001); 0.009**	**–0.002 (0.001); 0.03**
C-G ADBW	–0.002 (0.001); 0.06	**–0.001 (0.001); 0.03**	–0.000 (0.002); 1.0	–0.000 (0.001); 0.7	**–0.003 (0.001); 0.009**	**–0.002 (0.001); 0.04**
C-G LBW	**–0.003 (0.001); 0.04**	**–0.002 (0.001); 0.006**	–0.000 (0.002); 0.9	–0.001 (0.001); 0.3	**–0.004 (0.001); 0.008**	**–0.003 (0.001); 0.01**
C-G NBW	**–0.002 (0.001); 0.04**	–0.001 (0.001); 0.1	–0.001 (0.002); 0.6	–0.000 (0.001); 0.6	**–0.002 (0.001); 0.02**	–0.001 (0.001); 0.2
Salazar-Corcoran	–0.002 (0.001); 0.06	**–0.001 (0.001); 0.04**	–0.000 (0.002); 1.0	–0.000 (0.001); 0.8	**–0.003 (0.001); 0.009**	**–0.002 (0.001); 0.04**
MDRD	–0.002 (0.001); 0.05	–0.001 (0.001); 0.2	–0.000 (0.002); 0.9	0.000 (0.001); 1.0	**–0.002 (0.001); 0.02**	–0.001 (0.001); 0.3
CKD-EPI	**–0.003 (0.001); 0.01**	**–0.002 (0.001); 0.04**	–0.002 (0.002); 0.4	–0.000 (0.001); 1.0	**–0.004 (0.002); 0.008**	**–0.003 (0.001); 0.04**

Data were analyzed in BMI, Framingham score, ethnicity, deformed joints, CDAI, chloroquine, leflunomide, penicillamine, prednisone and non-steroidal antiinflammatory agent use adjusted linear regression models.

Significant relations are shown in bold.

EGFR = estimated glomerular filtration rate, RA = rheumatoid arthritis, MCP-1 = monocyte chemoattractant protein-1, C-G = Cockcroft-Gault, AWB = actual body weight, IBW = ideal body weight, ADBW = adjusted body weight, LBW = lean body weight, NBW = no body weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

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Kidney function and endothelial activation

Table 3 gives the independent relations of the eGFR equations with the endothelial activation markers MCP-1 and angiopoietin 2. In all patients, 4 eGFR equations were related to MCP-1 and 5 of them to angiopoietin 2. In stratified analysis, eGFR equations were not associated with endothelial activation amongst black Africans; by contrast, in whites, all equations were associated with MCP-1 concentrations and all except the Jelliffe, C-G no body weight and MDRD equation were related to angiopoietin 2 levels. Kidney function was unrelated to E-selectin, VCAM-1 and ICAM-1 concentrations (see S2 Table).

Kidney function and atherosclerosis

Table 4 gives the independent relations of eGFR equations with atherosclerosis. In all patients, the Jelliffe, C-G ideal body weight, C-G no body weight, Salazar-Corcoran and CKD-EPI equations were associated with cIMT, and the Jelliffe, C-G no body weight and CKD-EPI equations with plaque. In stratified analysis, all except the MDRD equation were related to cIMT and all equations were associated with plaque in black patients; a 1 SD increase in eGFR was associated with an odds ratio of 0.34 (C-G actual body weight) to 0.45 (MDRD) for plaque. By contrast, no associations between eGFR equations and atherosclerosis were found in whites.

As shown in Fig. 1, to estimate the accuracy of eGFR levels in the independent prediction of plaque presence amongst black patients with RA, we performed ROC curve analysis with the inclusion of the mFramingham score as a covariate. The mean (SD) and median (interquartile

Table 4. Associations of EGFR with carotid intima-media thickness and plaque (per 1 SD increase in eGFR) in all, black and white patients with RA.

	All patients		Black patients		White patients	
	CIMT	plaque	CIMT	plaque	CIMT	plaque
EGFR equation	**β (SE); p**	**OR (95% CI); p**	**β (SE); p**	**OR (95% CI); p**	**β (SE); p**	**OR (95% CI); p**
Jelliffe	**–0.001 (0.000); 0.005**	**0.65 (0.47–0.89); 0.008**	**–0.002 (0.000); 0.002**	**0.38 (0.20–0.69); 0.001**	–0.001 (0.000); 0.3	0.88 (0.59–1.31); 0.5
C-G ACBW	–0.001(0.000); 0.06	0.73 (0.52–1.02); 0.07	**–0.001 (0.000); 0.006**	**0.34 (0.17–0.67); 0.001**	–0.000 (0.000); 0.5	1.04 (0.67–1.63); 0.8
C-G IBW	**–0.001(0.000); 0.04**	0.74 (0.54–1.01); 0.06	**–0.001 (0.000); 0.003**	**0.37 (0.20–0.70); 0.002**	–0.000 (0.000); 0.5	1.00 (0.98–1.02); 0.8
C-G ADBW	–0.001 (0.000); 0.05	0.75 (0.55–1.01); 0.06	**–0.001 (0.000); 0.004**	**0.38 (0.21–0.69); 0.001**	–0.000 (0.000); 0.5	1.05 (0.71–1.55); 0.8
C-G LBW	–0.001 (0.000); 0.1	0.84 (0.62–1.13); 0.8	**–0.002 (0.001); 0.01**	**0.39 (0.21–0.72); 0.002**	–0.000 (0.001); 0.6	1.21 (0.82–1.80); 0.3
C-G NBW	**–0.001 (0.000); 0.006**	**0.66 (0.48–0.90); 0.009**	**–0.001 (0.000); 0.001**	**0.39 (0.20–0.68); 0.001**	–0.000 (0.000); 0.3	0.91 (0.61–1.36); 0.6
Salazar-Corcoran	**–0.0001 (0.000); 0.04**	0.74 (0.55–1.00); 0.05	**–0.001 (0.000); 0.003**	**0.38 (0.21–0.70); 0.001**	–0.000 (0.000); 0.5	1.04(0.70–1.54); 0.8
MDRD	–0.000 (0.000); 0.3	0.94 (0.69–1.27); 0.7	–0.001 (0.000); 0.06	**0.45 (0.24–0.84); 0.01**	–0.000 (0.000); 1.0	1.42 (0.94–2.13); 0.09
CKD-EPI	**–0.001 (0.001); 0.005**	**0.68 (0.50–0.91); 0.01**	**–0.002 (0.000); 0.004**	**0.44 (0.26–0.73); 0.001**	–0.000 (0.001); 0.2	0.94 (0.61–1.45); 0.8

Data were analyzed in BMI, Framingham score, ethnicity, deformed joints, CDAI, chloroquine, leflunomide, penicillamine, prednisone and non-steroidal antiinflammatory agent use adjusted linear or logistic regression models for cIMT and plaque, respectively.

Significant relations are shown in bold.

EGFR = estimated glomerular filtration rate, SD = standard deviation, RA = rheumatoid arthritis, cIMT = carotid intima-media thickness, C-G = Cockcroft-Gault, AWB = actual body weight, IBW = ideal body weight, ADBW = adjusted body weight, LBW = lean body weight, NBW = no body Weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

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range) mFramingham scores were 6 (9) and 2 (1–8) in black African patients with RA. The area under the curve (AUC) of the ROC curve was not associated with plaque presence for the MDRD (p = 0.3) whereas the respective relation was significant or borderline significant and of similar extent (p>0.1 for comparisons of AUC (SE)) for the other 8 equations. The AUC of the ROC curve was consistently not associated with plaque presence for the mFramingham score.

To determine the optimal cut-off values for the eGFR equations in determining plaque presence we calculated the Youden index [33]. The obtained values and their corresponding sensitivity, specificity, and positive and negative predictive values as determined by applying Bayes' theorem [34] are given in Table 5. EGFR values below these cut-off levels were significantly or borderline significantly associated with plaque with odds ratios ranging from 2.22 to 4.00.

In 108 of the black patients with RA, IDMS traceable creatinine concentrations were obtained. As shown in S3 Table in a sensitivity analysis performed amongst these patients, the associations of eGFR equations with plaque were consistently numerically stronger with lower odds ratios than in the whole group (Table 4), irrespective of whether conversion of IDMS creatinine to non-IDMS creatinine results was performed (the first 8 equations) or not (the CKD-EPI equation). This suggests that the use of converted creatinine results in eGFR equations does not affect their associations with CVD risk in RA.

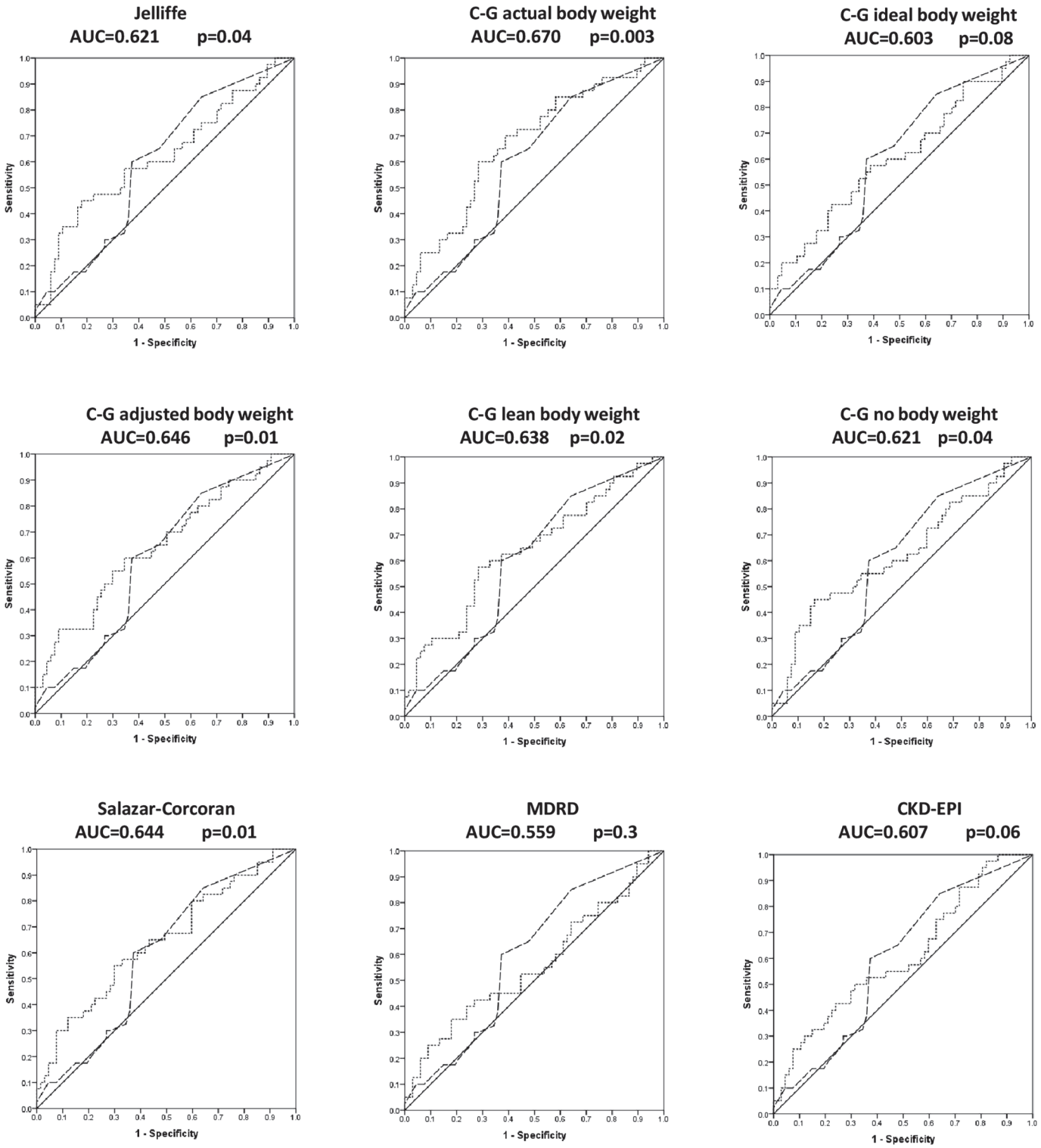

Fig 1. Receiver operator characteristic curves showing the accuracy of the eGFR equations (AUCs shown as dotted lines) in predicting plaque presence independent of the mFramingham score (AUCs shown as dashed lines). The *P* values given are for the AUC-plaque associations. The mFramingham score was consistently unrelated to plaque presence (AUC = 0.596 (*P* = 0.1) in each analysis). EGFR = estimated glomerular filtration rate; AUC = area under the curve; C-G = Cockcroft-Gault; MDRD = Modification of Diet in Renal Disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

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Table 5. Optimal cut-off EGFR values in ROC curves with corresponding characteristics and associations with plaque in black patients with RA.

EGFR	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR (95% CI) *	p*
Jelliffe	64	45	82	24	72	**3.61 (1.43–9.11)**	**0.007**
C-G ACBW	85	60	70	34	75	**3.36 (1.46–7.75)**	**0.004**
C-G IBW	54	42	88	22	72	2.22 (0.95–5.21)	0.07
C-G ADBW	68	55	81	29	75	**2.72 (1.19–6.20)**	**0.02**
C-G LBW	49	58	79	30	76	**3.31 (1.45–7.55)**	**0.005**
C-G NBW	73	45	84	24	72	**4.00 (1.57–10.17)**	**0.004**
Salazar-Corcoran	79	55	81	29	75	**2.72 (1.19–6.22)**	**0.02**
MDRD	64	35	91	18	70	2.49 (1.00–6.18)	0.05
CKD-EPI	82	42	91	21	73	2.22 (0.95–5.22)	0.07

Significant associations are shown in bold.

EGFR = estimated glomerular filtration rate, ROC = receiver operator characteristic, RA = rheumatoid arthritis, PPV = positive predictive value, NPV = negative predictive value, OR = odds ratio, CI = confidence interval, C-G = Cockcroft-Gault, AWB = actual body weight, IBW = ideal body weight, ADBW = adjusted body weight, LBW = lean body weight, NBW = no body weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

*Associations were assessed in modified Framingham score adjusted logistic regression models.

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Metabolic risk factors and kidney function in black compared to white patients with RA

In the present study, metabolic risk factors including not only BMI but also hypertension and diabetes were more adverse in black compared to white patients with RA (Table 2) and, at the same time, associated with kidney function (S1 Table). Both BMI and 5 of the eGFR equations as used in the present study contain body weight. Hence, as was previously reported in non-RA subjects, positive associations between body weight and kidney function as estimated by the respective equations is expected [36]. However, this does not accurately represent a 'cardio-renal' relationship [36]. As shown in S4 Table File after adjustment for metabolic risk in multivariable linear regression models, eGFR equations that did not contain anthropometric measures (Jelliffe, C-G no body weight, MDRD and CKD-EPI) no longer differed amongst both groups. BMI had a strong attenuating effect on the race-eGFR equation relation.

Discussion

Although ~80% of cardiovascular disease now occurs in low or middle income countries, data on cardiovascular risk management mostly originate in developed populations [13–15]. The present study revealed that reduced kidney function as assessed by previously reported eGFR equations for use in clinical settings, is independently associated with increased atherosclerosis in black Africans with RA. EGFR equations comprise the first reported easily and in fact routinely available cardiovascular risk marker shown to be useful in CVD risk stratification amongst RA patients from black African ancestry. Indeed, in ROC curve analysis, apart from the MDRD, eGFR equation results that fell below optimal cutoff values with sensitivities, specificities and positive and negative predictive values ranging from 42 to 60%, 70 to 91%, 21 to 34% and 72 to 76% respectively, increased the odds ratio for plaque 2.2 to 4 fold. The relatively high specificities and negative predictive values suggest that African black RA patients with non-reduction in eGFR are unlikely to have plaque, whereas the low positive predictive values are expected as the prevalence of plaque was, although clinically relevant, numerically low at 36.7%. Carotid plaque represents very high CVD risk that generally requires the preventive use

of CVD drugs in both non-RA and RA subjects [8,11,12,37,38]. The AUC of the ROC curve for the C-G actual body weight-plaque relations was as large as those recently reported for rheumatoid factor and anti-cyclic citrullinated peptide-radiographic progression relation amongst patients with early RA [39]. Our results are also congruent with our reported finding that major traditional cardiovascular risk factors as well as previously investigated disease characteristics are not related to atherosclerosis in black Africans with RA, as the mFramingham was not related to plaque in these patients [13–15].

An independent association of eGFR equation values with the endothelial activation markers MCP-1 and angiopoietin 2 concentrations was found in white Africans with RA. Increased production of MCP-1 and angiopoietin 2 was reported and is linked to inflammation and implicated in the enhanced CVD risk amongst non-RA CKD patients [40–42]. Angiopoietin 2 concentrations also predict mortality in CKD [42]. Recently, angiopoietin 2 was shown to impact proliferation and apoptosis of cardiac endothelial cells and promote mesenchymal transition thereby leading to cardiac fibrosis [41] and capillary rarefaction. These processes increase the susceptibility to arrhythmias and ischemic injury in CKD [2,41].

The disparities in kidney function-CVD relations amongst black and white Africans with RA in the present investigation require further exploration. In this regard however, black Africans experienced markedly reduced kidney function with a 2.2 fold risk of CKD when compared to whites. Kidney function was reported to decrease more rapidly with age in black persons [43]. The most important causes of CKD are hypertension and diabetes [2,4]. Additionally, obesity is associated with glomerular hyperfiltration that mediates glomerular sclerosis [44,45]. This together with the impact of obesity on other CKD risk factors including metabolic parameters and renin angiotensin system and sympathetic nervous system activation engenders reduced kidney function over time in obese subjects (44,45). In this study, disparities in kidney function amongst black and white Africans with RA were explained by more adverse metabolic risk factor profiles in the former group, particularly obesity and to a lesser extent hypertension and diabetes. Interestingly, BMI but not hypertension and diabetes, was recently also shown to associate with kidney function reduction development in a predominantly white RA cohort [4]. Compared to the present investigation, kidney function was more impaired in previous studies that documented its impact on incident cardiovascular events in RA [6,7].

We assessed kidney function using 9 different equations [17–26]. The association of the obtained results with endothelial activation was consistent across these different measures amongst white RA patients. Overall, the same applied to the relations of the different equations with atherosclerosis in black patients with RA. Nevertheless, the AUC of the ROC curve for the MDRD equation was not associated with plaque presence amongst black patients with RA. Our results suggest that the application of any of the other 8 assessed equations as examined in the present study is more reliable and therefore preferable to the MDRD equation for CVD risk stratification amongst black RA patients.

Can a single EGFR equation be recommended in the management of patients with RA? Kidney function evaluation is important for drug dosing [46], CKD staging in delineating renoprotective intervention strategies to prevent end stage renal disease [16], and CVD risk stratification and management [3]. Whereas only the C-G actual body weight was previously validated in white patients with RA (21), the CKD-EPI equation is currently most recommended in CKD staging in non-RA subjects. The C-G equations have become the standard for drug dosing. Nevertheless, recent recommendations from the National Kidney Education Program suggest that both the C-G and CKD-EPI equations can be used for drug dosing [46]. In the present investigation, application of the C-G actual body weight and CKD-EPI equations produced equivalent eGFR values that were further similarly associated with atherosclerosis in black patients and endothelial activation in whites. Calculation of the CKD-EPI equation does

not require information on body weight measurements, which is mostly not available to reporting laboratories. Taken together, although the CKD-EPI equation awaits validation in patients with RA, our results suggest that its recommended use in non-RA subjects can be extended to the RA population. Notably, anthropometric measures are also not include in the C-G no body weight equation and a recent meta-analysis showed that amongst C-G equations, the C-G no body weight equation most closely estimates creatinine clearance in non-RA patients [26].

A limitation of the present study is its cross-sectional design, thereby precluding drawing inferences on the direction of causality. Kidney function was defined by estimating equations. A large number of potential confounders were included in the models on plaque in Table 4. When we re-assessed the associations of kidney function with plaque using a summary score of traditional and non-traditional cardiovascular risk factors being the mFramingham score, as currently recommended for CVD risk stratification amongst patients with RA (9) and as a single covariate in the analysis, the results were consistent (Table 5).

Perspectives

Impaired kidney function is frequent and should therefore be routinely ascertained in RA patients. A C-G ACBW equation result of <85 ml/min, C-G NBW of <73 ml/min or CKD-EPI of <82 ml/min comprises a useful surrogate marker of high risk subclinical atherosclerosis in black African patients with RA. This finding can help in determining the need for enhanced CVD risk stratification by carotid ultrasound [8,11,12] or, intensified risk management with cardiovascular drugs including statins in black African RA patients who have no access to cardiovascular imaging.

Conclusions

CKD is twice as prevalent in black compared to white Africans with RA. Reduced kidney function is independently associated with atherosclerosis and endothelial activation in black and white Africans with RA, respectively. Apart from the MDRD, eGFR equations are useful in CVD risk stratification in black African RA patients.

Supporting Information

S1 Table. Baseline characteristics that were associated with estimated glomerular filtration rate equations at p≤0.2.
(DOC)

S2 Table. Associations of EGFR equations with early endothelial activation molecule concentrations in all and black and white patients.
(DOC)

S3 Table. Associations of EGFR with carotid intima-media thickness and plaque (per 1 SD increase in eGFR) in 108 black patients with IDMS traceable creatinine results.
(DOC)

S4 Table. EGFR equations without anthropometric measures in black compared to white RA patients after adjustment for metabolic risk.
(DOC)

S1 Dataset.
(XLS)

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Author Contributions

Conceived and designed the experiments: PHD H-CH MAG-G. Performed the experiments: PHD LT AS. Analyzed the data: PHD LT AMEM AJW GRN. Contributed reagents/materials/analysis tools: PHD AJW GRN. Wrote the paper: PHD. Revised the manuscript critically for important intellectual content: PHD H-CH LT AMEM AJW GRN AS MAG-G. Provided final approval of the version to be published: PHD H-CH LT AMEN AJW GRN AS MAG-G. Agreed to be accountable for all aspects of the work: PHD H-CH LT AMEM AJW GRN AS MAG-G.

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S1 Table. Baseline characteristics that were associated with estimated glomerular filtration rate equations at p≤0.2.

	Jelliffe	CG ACBW	CG IBW	CG ADBW	CG LBW	CG NBW	Salazar-C	SMDRD	CKD-EPI
Characteristic	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**
Age	**-1.006 (0.116); <0.0001**	**-1.388 (0.149); <0.0001**	**-1.119 (0.110); <0.0001**	**-1.227 (0.113); <0.0001**	**-0.855 (0.081); <0.0001**	**-1.194 (0.134); <0.0001**	**-1.304 (0.126); <0.0001**	**-0.459 (0.143); 0.002**	**-0.781 (0.093); <0.0001**
Female sex	6.128 (3.329); 0.07	**-8.958 (4.297); 0.04**	**-18.132 (3.150); <0.0001**	**-14.463 (3.261); <0.0001**	**-19.790 (2.329); <0.0001**	2.140 (3.841); 0.6	**-12.475 (3.635); 0.0007**	-6.856 (4.122); 0.1	-3.155 (2.671); 0.2
Black race	**-9.254 (2.509); 0.0003**	-4.146 (3.239); 0.2	**-12.640 (2.374); <0.0001**	**-9.242 (2.458); 0.0002**	**-5.811 (1.756); 0.002**	**-10.623 (2.895); 0.0003**	**-9.908 (2.740); 0.0004**	**-11.472 (3.107); 0.0003**	**-7.094 (2.013); 0.0005**
BMI	**-0.695 (0.213); 0.001**	**2.375 (0.235); <0.0001**	**-0.792 (0.201); 0.0001**	**0.475 (0.212); 0.02**	**0.541 (0.149); 0.0004**	**-0.804 (0.247); 0.001**	**0.481 (0.237); 0.04**	**-0.842 (0.266); 0.002**	**-0.439 (0.173); 0.01**
Waist	**-0.213 (0.095); 0.03**	**0.997 (0.105); <0.0001**	-0.129 (0.090); 0.2	**0.322 (0.092); 0.0005**	**0.300 (0.064); <0.0001**	**-0.244 (0.110); 0.03**	**0.323 (0.103); 0.002**	**-0.242 (0.118); 0.04**	-0.147 (0.076); 0.05
Log CDAI	3.784 (2.704); 0.2	0.605 (3.506); 0.9	1.357 (2.569); 0.6	0.605 (3.506); 0.9	0.882 (1.899); 0.6	4.410 (3.120); 0.1	1.673 (2.964); 0.6	5.546 (3.343); 0.1	2.540 (2.172); 0.2
Log deformed joints	-0.359 (2.424); 0.9	**-8.630 (3.076); 0.005**	-0.896 (2.293); 0.7	-3.991 (2.360); 0.09	**-3.467 (1.681); 0.04**	-0.438 (2.797); 0.9	-4.148 (2.633); 0.1	-0.312 (3.002); 0.9	-0.460 (1.944); 0.8
Chloroquine use	**-8.887 (2.739); 0.001**	-6.489 (3.591); 0.07	**-6.228 (2.619); 0.02**	**-6.332 (2.712); 0.02**	**-4.967 (1.932); 0.01**	**-10.353 (3.159); 0.001**	**-7.489 (3.019); 0.01**	**-10.929 (3.393); 0.01**	**-6.984 (2.199); 0.002**
Leflunomide use	**5.588 (2.736); 0.04**	3.912 (3.554); 0.3	3.858 (2.600); 0.1	3.880 (2.693); 0.1	3.015 (1.921); 0.1	**6.489 (3.156); 0.04**	4.714 (2.999); 0.1	6.461 (3.392); 0.06	3.690 (2.201); 0.1
Penicillamine use	10.180 (6.792); 0.1	**25.633 (8.646); 0.003**	6.821 (6.444); 0.3	**14.346 (6.620); 0.03**	**11.193 (4.718); 0.02**	11.746 (7.837); 0.1	**15.851 (7.380); 0.03**	12.860 (8.410); 0.1	7.120 (5.456); 0.2
NSAID use	4.180 (3.364); 0.2	7.504 (4.329); 0.08	3.698 (3.185); 0.2	5.220 (3.289); 0.1	3.604 (2.350); 0.1	4.697 (3.883); 0.2	5.974 (3.665); 0.1	5.502 (4.165); 0.2	2.744 (2.702); 0.3
Prednisone use	**19.014 (7.752); 0.01**	15.390 (10.087); 0.1	**14.741 (7.368); 0.04**	15.000 (7.630); 0.05	10.190 (5.454); 0.06	**21.788 (8.946); 0.01**	**17.553 (8.497); 0.04**	**23.909 (9.596); 0.01**	12.469 (6.246); 0.05
Hypertension	**-6.246 (2.637); 0.02**	5.446 (3.427); 0.1	4.846 (2.506); 0.05	-0.729 (2.615); 0.8	0.471 (1.868); 0.8	**-7.112 (3.044); 0.02**	-1.189 (2.914); 0.7	**-7.718 (3.266); 0.02**	**-4.513 (2.121); 0.03**
Systolic BP	-0.076 (-0.062); 0.2	**0.169 (0.079); 0.03**	-0.063 (0.058); 0.3	0.030 (0.061); 0.6	0.035 (0.043); 0.4	-0.087 (0.071); 0.2	0.028 (0.068); 0.7	-0.097 (0.076); 0.2	-0.067 (0.049); 0.2
Diastolic BP	-0.104 (0.107); 0.3	**0.406 (0.136); 0.003**	-0.053 (0.101); 0.6	0.131 (0.105); 0.2	0.123 (0.074); 0.1	-0.117 (0.123); 0.3	0.131 (0.117); 0.3	-0.134 (0.132); 0.3	-0.108 (0.086); 0.2

S1 Table Continued. Baseline characteristics that were associated with estimated glomerular filtration rate equations at $P \leq 0.2$.

	Jelliffe	CG ACBW	CG IBW	CG ADBW	CG LBW	CG NBW	Salazar-C	SMDRD	CKD-EPI
Characteristic	β (SE); p	β (SE); p	β (SE); p	β (SE); p	β (SE); p	β (SE); p	β (SE); p	β (SE); p	β (SE); P
HDL cholesterol*	9.728 (9.827); 0.3	-6.195 (12.707); 0.6	8.557 (9.303); 0.4	2.677 (9.648); 0.8	0.568 (6.892); 0.9	11.658 (11.337); 0.3	3.966 (10.752); 0.7	12.140 (12.170); 0.3	11.314 (7.865); 0.2
Triglycerides*	-10.312 (6.009); 0.9	3.689 (7.804); 0.6	-9.124 (5.691); 0.1	-4.036 (35.920); 0.5	-1.599 (4.231); 0.7	-11.861 (6.934); 0.09	-4.604 (6.598); 0.5	-12.718 (7.442); 0.09	-7.799 (4.824); 0.1
Diabetes	-6.254 (3.790); 0.1	4.091 (4.914); 0.4	**-8.394 (3.565); 0.02**	-3.400 (3.729); 0.4	-1.682 (2.665); 0.5	-7.343 (4.372); 0.09	-3.782 (4.156); 0.4	-7.525 (4.695); 0.1	-4.813 (3.042); 0.1
Glucose*	-13.212 (10.548); 0.2	14.923 (13.629); 0.3	-17.187 (9.952); 0.09	-4.435 (10.367); 0.7	-0.975 (7.407); 0.9	-15.550 (12.170); 0.2	-4.929 (11.556); 0.7	-18.546 (13.051); 0.2	-6.992 (8.480); 0.4
Smoking	*.083 (4.923); 0.07	3.172 (6.400); 0.6	**10.271 (4.645); 0.03**	7.439 (4.835); 0.1	5.425 (3.452); 0.1	10.808 (5.679); 0.06	8.577 (5.387); 0.1	**12.717 (6.085); 0.04**	6.255 (3.958); 0.1
Framingham*	**-15.344 (2.886); <0.0001**	**9.355 (3.927); 0.02**	**-6.319 (3.057); 0.04**	**-7.540 (3.162); 0.02**	-1.107 (2.404); 0.6	**-16.100 (3.359); <0.0001**	**-9.295 (3.433); 0.007**	-3.914 (3.319); 0.2	**-8.527 (2.337); 0.0003**

Associations were assessed in demographic characteristic adjusted linear multivariable regression models.

C-G = Cockcroft-Gault, AWB = actual body weight, IBW = ideal body weight, ADBW = adjusted body weight, LBW = lean body weight, NBW = no body weight, Salazar-C = Salazar-Corcoran, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, BMI = body mass index, log = logarithmically transformed, CDAI = Clinical Disease Activity Index, NSAID = non steroidal antiinflammatory agents, BP = blood pressure, HDL = high density lipoprotein.

S2 Table. Associations of EGFR equations with early endothelial activation molecule concentrations in all and black and white patients.

	All patients			Black patients			White patients		
	E-selectin	**VCAM-1**	**ICAM-1**	**E-selectin**	**VCAM-1**	**ICAM-1**	**E-selectin**	**VCAM-1**	**ICAM-1**
EGFR equation	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**	**β (SE); p**
Jelliffe	-0.088 (0.067); 0.2	-0.001 (0.001); 0.05	-0.001 (0.001); 0.09	0.047 (0.119); 0.7	-0.001 (0.001); 0.3	-0.000 (0.001); 0.6	-0.122 (0.082); 0.1	-0.001 (0.001); 0.08	-0.001 (0.001); 0.08
CG ACBW	-0.043 (0.057); 0.4	-0.001 (0.000); 0.08	-0.001 (0.001); 0.07	0.007 (0.099); 0.9	-0.001 (0.001); 0.2	-0.001 (0.001); 0.4	-0.036 (0.069); 0.6	-0.001 (0.001); 0.2	-0.001 (0.001); 0.1
C-G IBW	-0.043 (0.063); 0.5	-0.001 (0.001); 0.2	-0.001 (0.001); 0.06	0.017 (0.113); 0.9	-0.001 (0.001); 0.4	-0.001 (0.001); 0.6	-0.027 (0.076); 0.7	-0.001 (0.001); 0.3	-0.001 (0.001); 0.1
C-G ADBW	-0.044 (0.061); 0.5	-0.001 (0.000); 0.1	-0.001 (0.001); 0.07	0.013 (0.108); 0.9	-0.001 (0.001); 0.3	-0.001 (0.001); 0.5	-0.031 (0.074); 0.7	-0.001 (0.001); 0.3	-0.001 (0.001); 0.1
C-G LBW	-0.069 (0.081); 0.4	-0.001 (0.001); 0.2	-0.001 (0.001); 0.1	-0.028 (0.150); 0.9	-0.001 (0.001); 0.2	-0.001 (0.001); 0.6	-0.042 (0.096); 0.7	-0.001 (0.001; 0.3	-0.001 (0.001); 0.2
C-G NBW	-0.076 (0.058); 0.2	-0.001 (0.000); 0.05	-0.001 (0.001); 0.1	0.029 (0.102); 0.8	-0.001 (0.001); 0.3	-0.000 (0.001); 0.7	-0.101 (0.070); 0.2	-0.001 (0.001); 0.09	-0.001 (0.001); 0.09
Salazar-Corcoran	-0.045 (0.056); 0.4	-0.001 (0.000); 0.1	-0.001 (0.001); 0.07	0.017 (0.099); 0.9	-0.001 (0.001); 0.2	-0.001 (0.001); 0.5	-0.040 (0.068); 0.6	-0.001 (0.001); 0.2	-0.001 (0.001); 0.1
MDRD	-0.097 (0.059); 0.1	-0.001 (0.000); 0.05	-0.001 (0.001); 0.1	-0.012 (0.110); 0.9	-0.001 (0.001); 0.4	-0.000 (0.001);0.7	-0.114 (0.068); 0.1	-0.001 (0.001); 0.07	-0.001 (0.001); 0.08
CKD-EPI	-0.069 (0.082); 0.4	-0.001 (0.001); 0.09	-0.001 (0.001); 0.2	0.029 (0.130); 0.8	-0.001 (0.001); 0.1	-0.000 (0.001); 0.9	-0.097 (0.109); 0.4	-0.001 (0.001); 0.2	-0.001 (0.001); 0.2

Data were analyzed in BMI, Framingham score, ethnicity, deformed joints, CDAI, chloroquine, leflunomide, penicillamine, prednisone and non-steroidal antiinflammatory agent use adjusted linear regression models.
Significant relations are shown in bold.
EGFR = estimated glomerular filtration rate, RA = rheumatoid arthritis, VCAM-1 = vascular adhesion molecule-1, ICAM-1 = intercellular adhesion molecule-1, C-G = Cockroft-Gault, AWB = actual body weight, IBW = ideal body weight, ADBW = adjusted body weight, LBW = lean body weight, NBW = no body weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

S3 Table. Associations of EGFR with carotid intima-media thickness and plaque (per 1 SD increase in eGFR) in 108 black patients with IDMS traceable creatinine results.

	CIMT		**Plaque**	
EGFR equation	**β (SE)**	**p**	**OR (95% CI)**	**p**
Jelliffe	**-0.002 (0.001)**	**0.004**	**0.34 (0.18-0.65)**	**0.001**
C-G ACBW	**-0.001 (0.001)**	**0.002**	**0.28 (0.14-0.60)**	**0.008**
C-G IBW	**-0.002 (0.001)**	**0.001**	**0.34 (0.17-0.66)**	**0.002**
C-G ADBW	**-0.002 (0.000)**	**0.001**	**0.33 (0.17-0.65)**	**0.001**
C-G LBW	**-0.002 (0.001)**	**0.003**	**0.35 (0.18-0.70)**	**0.002**
C-G NBW	**-0.002 (0.000)**	**0.0003**	**0.34 (0.18-0.65)**	**0.002**
Salazar-Corcoran	**-0.001 (0.000)**	**0.0008**	**0.33 (0.17-0.70)**	**0.001**
MDRD	**-0.001 (0.000)**	**0.02**	**0.40 (0.21-0.80)**	**0.003**
CKD-EPI	**-0.002 (0.000)**	**0.002**	**0.41 (0.24-0.71)**	**0.001**

Data were analyzed in BMI, Framingham score, ethnicity, deformed joints, CDAI, chloroquine, leflunomide, penicillamine and non-steroidal antiinflammatory agent use adjusted linear or logistic regression models for cIMT and plaque, respectively. Significant relations are shown in bold.
EGFR = estimated glomerular filtration rate, SD = standard deviation, IDMS = isotope dilution mass spectrometry, RA = rheumatoid arthritis, cIMT= carotid intima-media thickness, C-G = Cockroft-Gault, AWB = actual body weight, IBW = ideal body weight, ADBW = adjusted body weight, LBW = lean body weight, NBW = no body weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

S4 Table. EGFR equations without anthropometric measures in black compared to white RA patients after adjustment for metabolic risk.

EGFR equation	Black (n=112)	White (n=121)	p*	p†	p§
Jelliffe	76 (19)	82 (24)	0.2	0.5	0.6
C-G NBW	87 (22)	94 (28)	0.2	0.4	0.5
MDRD	**78 (20)**	**89 (27)**	**0.01**	**0.04**	0.05
CKD-EPI	90 (17)	95 (17)	0.08	0.3	0.3

Significant associations are shown in bold.
EGFR = estimated glomerular filtration rate, C-G = Cockcroft-Gault, NBW = no body weight, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.
*adjusted for body mass index
†additionally adjusted for hypertension
§additionally adjusted for diabetes

Summary and conclusions

This thesis comprises of 6 controlled studies that were aimed at investigating the atherosclerosis burden and its risk factors in black African patients with RA. The control groups included mostly white Africans with RA (papers 1), non-RA black African persons (paper 2) or exclusively white Africans with RA (papers 3 to 6).

Atherosclerotic cardiovascular disease risk remains lower in the sub-Saharan black African population compared to developed populations. However, recent studies have documented an emergence of atherosclerotic risk factor profiles and disease in South African black Africans [1-4]. This is in keeping with the presence of a socioeconomic development induced epidemiological health transition in the respective population [5]. In this regard, South Africa is socioeconomically more developed than other sub-Saharan African countries but vast income and health inequalities persist [6].

It is now well recognized that RA enhances the risk of particularly atherosclerotic cardiovascular disease [7-9]. However, these data originate generally in studies that were performed in RA patients living in developed countries that are further mostly inhabited by white populations. RA occurs as frequently in black as white urbanized Africans [10,11].

These reported evidences triggered the work presented in this thesis. Initially and as given in paper 1, we investigated whether the atherosclerotic cardiovascular risk burden was more favourable in black compared to other Africans with RA. In keeping with the presence of an earlier health transition stage as reported in non RA black Africans, we found disparities in the prevalence of individual traditional cardiovascular risk factors amongst the 2 groups. Indeed, black African RA patients experienced more frequent hypertension and obesity and smoked less often. Strikingly however, the overall traditional atherosclerotic cardiovascular risk burden was as large in black compared other Africans. In addition, the burden of non-traditional atherosclerotic cardiovascular risk factors or RA characteristics did not differ by population origin. This indicates that black African persons that have developed RA may no longer experience the protection against atherosclerosis that is reported in their non-RA counterparts. Cardiovascular risk stratification and management should be performed irrespective of ethnic origin and epidemiological transition stage in RA.

Is the unanticipated large atherosclerotic cardiovascular risk burden in black African patients as found in paper 1, attributable to RA? To address this question, we explored the impact of RA on atherosclerotic cardiovascular risk factor profiles and carotid intima-media thickness in black Africans with and

without established RA. In contrast to the association of RA with adverse traditional risk factor profiles that was reported in patients from developed populations, RA was not independently related to either dyslipidemia, hypertension, diabetes or smoking prevalence. Also, whereas RA associates with excess adiposity in developed populations, overall and abdominal obesity were reduced in black Africans with RA. Joint derived cytokines or high grade inflammation mediated the adverse alterations in metabolic risk factors in previous RA studies [12,13]. In the African black population, we found that circulating C-reactive protein concentrations were unchanged and interleukin-6 levels were reduced among patients with RA. In line with this, systemic inflammation was not related to clinical RA activity parameters in these patients. Finally, no difference in carotid intima-media thickness was observed in RA compared to non-RA black Africans. This study indicates that RA does not enhance atherosclerotic cardiovascular disease risk in black Africans with RA. An absent interleukin-6 release from inflamed joints into the circulation may account for this unaltered cardiovascular disease risk.

Given the unfavourable atherosclerotic cardiovascular risk factor profiles in black Africans with RA (paper 1), is the atherosclerosis burden still smaller in this group compared to white Africans that constitute a developed population? Also, does an earlier epidemiological heath transition stage translate into a

potentially altered influence of cardiovascular risk factors on atherosclerosis in black Africans with RA? These questions were addressed in paper 3. The ultrasound determined carotid atherosclerosis burden and its relations with atherosclerotic risk factors were compared amongst black and white Africans with RA. Disparities in cardiovascular risk factors amongst the two groups were overall similar to those reported in paper 1. In demographic variable adjusted regression models, carotid plaque prevalence and intima-media thickness were as large in black as in white Africans with RA. Systolic blood pressure, total cholesterol-to-high density lipoprotein ratio, extraarticular manifestations and C-reactive protein concentrations were associated with atherosclerosis in white but not black African patients with RA. By contrast, the Arthritis Impact Measurement Scales tension score was related to both plaque and intima-media thickness only in black African RA patients. The Framingham score was strongly related to intima-media thickness in white but not black patients.

This study has several clinical implications. Firstly, it supports the conclusion in paper 1, i.e. that cardiovascular risk should be adequately addressed in patients with RA irrespective of ethnic origin and epidemiological transition stage. Secondly and more challengingly, data on cardiovascular disease risk stratification in RA that originate in developed populations [9]

cannot merely be extrapolated in developing populations. Interestingly and support of this interpretation, we recently documented that the Framingham score and SCORE at markedly low cut-off values are useful in identifying Spanish and South African white but not black RA patients with very high cardiovascular risk as represented by plaque presence [14].

The above reported findings call for the identification of alternative risk factors that are useful in cardiovascular disease risk stratification in black Africans with RA. This was the aim addressed in papers 4, 5 and 6.

Black African women experience a markedly large adiposity burden [15]. We therefore performed a detailed analysis of anthropometric measures in paper 4. Associations between adiposity measures and carotid atherosclerosis were assessed in black and white African women with RA. The generalized and abdominal obesity burden were larger in black compared to white African women with RA. Fat distribution as reflected by waist-to hip ratio was similar in both groups. The impact of excess adiposity on metabolic abnormalities was not influenced by population origin. The atherosclerosis burden was similar in both groups. Despite the excess adiposity in black African patients with RA, associations between anthropometric measures and carotid atherosclerosis were consistently absent in this group. By contrast, body mass index was related to carotid intima-media thickness and waist-to-hip ratio to plaque in

white RA patients. These associations were explained by metabolic abnormalities. Anthropometric measures should be considered in cardiovascular risk stratification among white patients with RA. The excess adiposity experienced by black African RA patients does not translate into atheroma at this stage.

The metabolic syndrome is associated with a 2 fold increased risk of cardiovascular events [13]. In non-diabetic patients, this cluster of interrelated risk factors also increases the risk of type 2 diabetes 2 to 5 fold [13]. The metabolic syndrome comprises excess adiposity and its metabolic complications [13]. In RA patients from developed populations, metabolic risk factors are associated with atherosclerosis [13,16,17]. We evaluated the National Cholesterol Education Program Adult Treatment Panel III Metabolic Syndrome in black and white African women with RA [13]. The metabolic syndrome prevalence (30.8% versus 9.7%) and mean number of criteria (2.1 versus 1.3) were each significantly larger in black compared to white African women with RA. In white African RA women, the metabolic syndrome definition was associated with carotid intima-media thickness whereas the number of criteria and triglyceride criterion were associated with plaque. By contrast, among black African RA women, the blood pressure criterion was related to carotid intima-media thickness, which can represent age and blood

pressure induced hypertrophy of medial cells rather than atherosclerosis. These findings indicate that cardiovascular risk stratification should be performed irrespective of metabolic abnormalities in black African women with RA.

Chronic kidney disease as mostly determined by reduced estimated glomerular filtration rate, is a strong independent cardiovascular risk factor and its prevalence may be much larger in sub-Saharan black Africans compared to persons belonging to developed populations [18,19]. Chronic kidney disease is associated with cardiovascular disease in RA patients from developed populations. In paper 6, we calculated 9 reported estimated glomerular filtration rate equations in black and white African patients with RA. We compared the prevalence of chronic kidney disease (Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate <90 ml/min/1.73 m^2) and the associations of estimated glomerular filtration rate equations with endothelial activation and carotid intima-media thickness and plaque between black and white Africans with RA.

A reduced estimated glomerular filtration rate was observed in 49.1% of black and 30.6% of white African RA patients. The estimated glomerular filtration rate was overall consistently associated with monocyte chemoattractant protein-1 and angiopoietin 2 among white but not black

African RA patients. By contrast, all except the Modification of Diet in Renal Disease equation were associated to a similar extent with both carotid artery intima-media thickness and plaque in Receiver Operating Characteristic curve analysis among black but not white African patients with RA. The area under the curve in Receiver operating characteristic curve analysis ranged from 0.607 for the Chronic Kidney Disease Epidemiology Collaboration equation to 0.670 for the Cockroft-Gault actual body weight equation. The optimal cut-off values ranged from 49 ml/min/m^2 for the Cockroft-Gaultlean body weight equation to 85 ml/min/$m^2$for Cockroft-Gault actual body weight equation. Specificities and sensitivities ranged from 42% to 60% and 70% to 91%, respectively. In European League Against Rheumatism modified Framingham score adjusted regression analysis, a reduced estimated glomerular filtration rate increased the odds ratio for plaque 2.2 to 4.0 fold. A low estimated glomerular filtration rate comprises the first reported and in fact routinely available cardiovascular risk marker that was found to be clinically useful in atherosclerotic cardiovascular disease risk stratification.

Taken together, the 3 main findings in the work presented in this thesis are: (1) whereas black African patients with RA are currently indeed at an earlier epidemiological transition stage compared to their white counterparts, theiroverall cardiovascular risk and atherosclerosis burden arenot reduced; (2)

the modifiable traditional atherosclerotic cardiovascular risk factors of hypertension, dyslipidemia and obesity as well as RA characteristics are not associated with atherosclerosis in black Africans with RA and (3) estimated glomerular filtration rate equations are clinically useful in identifying black African RA patients with very high risk of atherosclerotic cardiovascular events as represented by plaque presence.

Interestingly, RA did not adversely impact on cardiovascular risk factor profiles and carotid intima-media thickness amongst black Africans. A limitation in this study is that carotid artery plaque prevalence was not determined among non-RA subjects, as arterial plaque is a more definite marker of atherosclerosis than intima-media thickness [20-25]. Therefore, the potential impact of RA on atherosclerosisamong black Africans requires further investigation.

Given these findings, can cardiovascular disease risk be reliably performed in black Africans with RA? Although the estimated glomerular filtration rate equations were found to be useful in this context, the area under the curve in Receiver Operating Characteristic curve analysis for their relationships with carotid artery plaque was consistently lower than 0.700. Clearly, other approaches are urgently needed to more adequately identify black African RA patients that are at high cardiovascular risk and therefore need intervention

with cardiovascular drugs and particularly lipid lowering agents. One option would be to systematically perform carotid ultrasound in these patients. However, sub-Saharan black Africans with RA have generally no access to this investigation at present. In this regard, it is of interest that we recently identified population origin independent relationships between novel cardiovascular risk biomarkers and subclinical cardiovascular disease among African patients with RA. This was the case for circulating concentrations of interleukin-6 and several adipokines [26-32].

The studies presented in this thesis have strengths and further limitations. We comprehensively assessed potential traditional and non-traditional cardiovascular risk factors in relatively large groups of black African RA patients and controls. Besides the infrequent and absent use of biological agents in white and black Africans with RA, respectively, non-steroidal anti-inflammatory agents, glucocorticoids and traditional synthetic disease modifying agents were employed to a similar extent in both groups. Confounder adjusted multivariable regression analysis was applied throughout. The most important limitation is that the present studies were each cross-sectionally designed. The reported data require confirmation in longitudinal investigations. Further, the high frequency of hypertension among black African RA patients indicates a need for inclusion of aortic and left ventricular function as outcomes in future

studies.Finally, whether RA increases cardiovascular event rates among black Africans requires further studies. Notably in this regard, we found no increase in the cardiovascular risk factor burden and carotid intima-media thickness among black RA compared to non-RA subjects. However, as the presence of established ischemic heart, cerebrovascular or/and peripheral artery disease or/and heart failure could not be consistently and reliably ascertained in non-RA subjects, the potential impact of RA on cardiovascular events could not be determined. These issues are presently addressed in our setting.

In conclusion, the cardiovascular risk and atherosclerosis burden are currently as large in black compared to white African patients with RA. Modifiable traditional risk factors that are currently recommended for consideration in cardiovascular risk stratification strategies were consistently unrelated to atherosclerosis in black African patients with RA. Further, disease characteristics were also not associated with atherosclerosis in black African RA patients. Impaired kidney function comprised the only routinely available cardiovascular risk factor that was useful in identifying black African RA patients with high risk atherosclerosis. Systematic vascular imaging and possibly the use of novel cardiovascular risk biomarkers may be required for adequate cardiovascular risk stratification among black African patients with RA.

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To whom it may concern,

I hereby confirm that Dr Ahmed Solomon has substantially contributed to the data collection, conception of each of the studies, interpretation of the results and writing of the manuscripts that are included in this PhD thesis.

Yours sincerely,

Professor Patrick H Dessein MD, FCP (SA), FRCP (UK), PhD

11 December 2016

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Solomon et al

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M051121**
PROJECT	Ongoing Adutiting of Hospital Records in Order to Identify Determinants of Disease Outcome and Comorbidities and Treatment....
INVESTIGATORS	Drs A et al Solomon et al
DEPARTMENT	Faculty of Health Sciences
DATE CONSIDERED	05.11.25
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 05.11.28 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr PM Dessein

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Patrick H Dessein *MD, FCP(SA), FRCP (London), PhD*
Specialist Physician/Internist
Cardiovascular Pathophysiology and Genomics Research Unit
School of Physiology, Faculty of Health Sciences
University of Witwatersrand
Rheumatology Unit, Milpark Hospital, Parktown
Johannesburg, South Africa

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Melville 2109
Johannesburg, S Africa

Tel: 27 (0)11 482 8546
Fax: 27 (0)11 726 6835
Email: Dessein@telkomsa.net

12th October 2008

To: Professor PE Cleaton-Jones
Chairperson
Human Research Ethics Committee (Medical)

Dear Professor Cleaton-Jones,

As discussed with you at our last Ethics meeting, I hereby wish to ask you whether the study entitled 'The contribution of the interactions of rheumatoid arthritis disease activity with metabolic syndrome features to endothelial dysfunction, arterial stiffness and atherosclerosis' (Protocol Number M060733; approved on 11.08.06 and amendment approved on 11.10.07) could now be also be performed at the Johannesburg Hospital. The set-up in the rheumatoid arthritis clinics at the latter hospital has improved to the extent that it is now possible to perform this study in the respective clinics whereas so far it has only been initiated in my private practice. This would allow us to adequately assess cardiovascular risk and disease in this rheumatoid arthritis population in which we expect to find a high burden of comorbid cardiovascular disease thereby indicating a need for systematic application of preventative measures.

Yours sincerely,

Patrick Dessein

Ahmed Solomon

Approved 14/10/08

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Patrick H Dessein

CLEARANCE CERTIFICATE	**M120562**
PROJECT	The Contribution of the Interaction of Rheumatoid Arthritis Disease Activity with Metabolic Syndrome Features to Endothelial Dysfunction, Arterial Stiffness and Athero-Sclerosis
INVESTIGATORS	Dr Patrick H Dessein.
DEPARTMENT	Department of Medicine
DATE CONSIDERED	Ad hoc
+DECISION OF THE COMMITTEE*	Renewal Approved

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 31/05/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof B Joffe

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Drs A Solomon/P Dessein

CLEARANCE CERTIFICATE	**M120563**
PROJECT	Ongoing Auditing of Hospital Records in Order to identify Determinants of Disease Outcome and Comorbidities and Treatment.....
	(Previously M051121)
INVESTIGATORS	Drs A Solomon/P Dessein.
DEPARTMENT	Department of Medicine
DATE CONSIDERED	Ad hoc
+DECISION OF THE COMMITTEE*	Renewal Approved

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 31/05/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr P Dessein

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...