NOVEMBER/DECEMBER 2019
VOL 30 NO 6

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ISSN 1995-1892 (print)
ISSN 1680-0745 (online)

CVJ AFRICA

Cardiovascular Journal of Africa | www.cvja.co.za

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INDEXED AT SCISEARCH (SCI), PUBMED, PUBMED CENTRAL AND SABINET

PUBLISHED ONLINE **(Available on www.cvja.co.za and in PubMed)**

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The *Cardiovascular Journal of Africa*, incorporating the *Cardiovascular Journal of South Africa*, is published 10 times a year, the publication date being the third week of the designated month.

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LAYOUT:
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ONLINE PUBLISHING & CODING SERVICES:
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Editorials

The challenges of improving benzathine penicillin usage for prevention of rheumatic fever in Africa

Ana Olga Mocumbi

Rheumatic heart disease (RHD) is arguably the most preventable of all cardiovascular diseases, but remains an important global health challenge. While acute rheumatic fever (ARF) frequently causes death, chronic rheumatic heart disease is an important cause of chronic heart failure[1] and associated premature mortality in low- and middle-income countries (LMIC).[2]

The World Health Organisation (WHO) recommends administration of benzathine penicillin G (BPG) every two to four weeks to prevent recurrent episodes of ARF and/or progression to RHD. The regimens may vary according to the severity of the first ARF attack, the presence of carditis, and the estimated risk of recurrence depending on age and socio-economic environment. It is accepted that for patients who have had ARF, there is a need for long-term prophylaxis but the duration of the prevention takes into account the occurrence of ARF and the severity of the cardiac lesions. It is established that optimal delivery of regular BPG injections is vital to preventing disease morbidity and cardiac sequelae in affected paediatric and young adult populations, and even low adherence rates reduce the recurrence of ARF and the risk of all-cause mortality.[3]

BPG administration has been a challenge in Africa. In their article on page 369, Ali *et al*.[4] describe BPG availability and administration for the prevention of rheumatic fever (RF), as assessed through an online survey targeting 30 health workers from 14 countries on the continent. The study reports concerning levels of unavailability of BPG, lack of guidelines for administration, excessive use of skin testing, unavailability of emergency kits to respond to anaphylactic reactions, and health practitioners not being confident to manage BPG allergy. The authors conclude that shortage of BPG supply is a concern that needs to be urgently addressed by governments, and that clinicians must be trained to use BPG and to deal with its major adverse events.

Despite the obvious limitations of the study methodology, this work from the Working Group on Penicillin from the Taskforce on Rheumatic Heart Disease of the Pan-African Society of Cardiology helps us to understand the barriers and practices regarding usage of BPG in Africa, where RHD is endemic. Among the barriers for implementation of RF/RHD prevention programmes in this region, erratic penicillin supply, deficient service delivery, resistance from health workers to administer injectable BPG, low access to health facilities, and individual issues related to cost and loss of working time are the most commonly discussed. Pain caused by intramuscular injection of BPG contributes to low adherence. With the dissemination of echocardiography for screening, large cohorts of young people with confirmed asymptomatic disease have increased the number of people who need BPG. Therefore, adequate supply of high-quality BPG at an affordable cost and skilled health professionals to administer it are needed.

Unfortunately, the BPG market worldwide has been hampered by insufficient stocks of penicillin, with a dramatic reduction of producers worldwide in the last decades. A study carried out by Health Reproductive Programme, the Special Programme of Research, Development and Research Training in Human Reproduction in the WHO's Department of Reproductive Health and Research and the Clinton Health Access Initiative (CHAI) used a combination of data-collection methods to obtain data on BPG availability globally. The motivation for this study was BPG use to prevent mother-to-child transmission of syphilis.

Of the 114 countries approached, 95 had valuable information; of these, 39 (41%) reported a BPG shortage and 10 indicated the use of alternative treatments, including ceftriaxone, amoxicillin and erythromycin.[5] Because it is an off-patent medication, BPG is currently sold at a very low price, estimated at US$0.11 for a 1.2-million international unit (IU) dose and US$0.20 for a 2.4-million IU dose in LMICs. This is in clear contrast to the significant financial investment in specialised manufacturing infrastructure that is needed to manufacture injectable BPG, therefore reducing the enthusiasm for commercial manufacturers to enter or even continue in the BPG market. Moreover, none of the three current active pharmaceutical ingredient manufacturers of BPG has market authorisation from a global regulatory authority, and two have experienced quality issues in the past few years, further disrupting supply. In addition, issues such as underestimating need, inflexible purchasing cycles, lack of funding, and limited BPG product registrations contribute to low availability of BPG.[5]

Poor uptake of secondary prophylaxis for RF/RHD remains a problem globally, related to patient demographics, clinical, socio-cultural and healthcare service-delivery factors. New knowledge is needed to support the necessary changes within the health systems and delivery platforms. In northern Australia a stepped-wedge, randomised trial of five pairs of indigenous community clinics provided a multicomponent intervention to support activities to improve penicillin delivery, aligned with a chronic-care model and continuous quality-improvement feedback on adherence.[6] Over 30 to 39 months of implementation, there was a modest improvement in adherence among high-adhering

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patients and a decrease in the proportion of days at risk in the whole cohort in the maintenance phase. ARF recurrence rates however did not differ between study sites during the intensive phase and the whole jurisdiction, showing that the strategy did not improve adherence to RHD secondary prophylaxis within the study time frame.[6]

Within the health services, fear of major adverse events related to the drug, including severe anaphylactic reactions also needs to addressed. In Zambia, concern by health workers about allergic events following the administration of BPG was addressed through an educational and access-to-medicine programme, resulting in increased usage of the drug.[7] Understanding the determinants and mechanisms of non-allergic deaths will also help to overcome this fear.

Recently, Marantelli and colleagues[8] assessed adverse reactions to BPG by circulating a questionnaire through professional networks, soliciting retrospective reports of adverse events from treating physicians, and using the Brighton Collaboration case definition to identity potential anaphylaxis. Ten cases with clinical or echocardiogram-obtained evidence of valvular disease were reported from various locations, with patients ranging from early teens to adults; 80% had received BPG prior to the event with no previous adverse reaction. In eight cases, the reaction was fatal, but only three cases met criteria consistent with anaphylaxis. The authors suggest that major allergic reactions are not the main cause of adverse reactions to BPG. Moreover, they proposed sudden death in people with severe RHD as an alternative mechanism, opening up the possibility of risk stratification of patients to help in identifying those who may not be suitable for injectable BPG.

While primary and secondary prophylaxis significantly improves outcomes and is recognised to be the standard of care, with intra-muscular BPG being recommended as the preferred agent by many technical experts, progress in tools to describe BPG pharmacokinetics has been slow and inconvenient in the context of endemic regions, considering the need for repeated venous blood collection, the young age of the patients, the high prevalence of anaemia in the endemic communities, and the scarcity of laboratories with capacity for blood preservation and testing of BPG blood levels. The recent development and validation of point-of-care dried blood spot (DBS) assays would facilitate pharmacokinetic studies in situations where frequent venous blood sampling is logistically difficult or clinically unacceptable. Interestingly, the limit of quantification for penicillin G in DBS, using samples from adult patients receiving penicillin as part of an infection-management plan was 0.005 mg/l, and plasma and DBS penicillin G concentrations for patients receiving BPG and penicillin G given via bolus doses correlated well and had comparable time–concentration profiles.[9] These results open new possibilities for research into novel formulations and delivery systems for BPG.

Owing to the early disease onset in Africa, the current prophylactic treatment should last for 15 to 25 years, representing a high burden to the patient, the family and the health system. Biodegradable polymer matrices have been investigated, trying to reduce the frequency of BPG administration to improve adherence. The results show that some are not suitable for development of sustained-release BPG treatments, while others provide favourable release behaviour, but the total size of the implant still presents a hurdle. Taking into account the mass of polymer tested and the total dose of drug calculated from the literature on pharmacokinetic parameters for penicillin G, an implant size of over 7 g would still be required, precluding clinical deployment of polymer matrix-type delivery system for this indication in children and adolescents.[10]

In conclusion, research using modern tools is needed to address the unmet needs for RF prophylaxis. While awaiting new advances in all components of the complex issue of using BPG for RHD prevention, health system strengthening and innovative strategies to improve delivery platforms for secondary prophylaxis are needed to reach and retain those in need in Africa.

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What is in a number: the impact factor, citation analysis and 30 years of publishing the *Cardiovascular Journal of Africa*

The *Cardiovascular Journal of Africa* (CVJA) has been publishing for 30 years. Improving visibility and accessing milestones along the way have been discussed previously, including citation analysis of the journal.[1-4]

In medicine and in science bibliometrics, citation analysis of journals, specifically, plays a huge role in where researchers aim to publish. The field has been well summarised in a recent article by Roldan-Valadez *et al*.[5] Briefly, it is believed that the status of journals wherein scholars publish, among others, helps to define professional status, is seen as a measure of performance, defines scientific merit, and is used by funders to make decisions.

Citation analyses defining impact range from the granddaddy of all, the original journal impact factor (JIF) from the World of Science (WOS) Journal Citation Reports (JCR), to the Eigenfactor score, CiteScore, SCImago Journal Rank, Source-Normalised Impact per Paper, and others. Furthermore, there is also the H-index, which is used to evaluate the 'impact' of an individual, but it can also be applied to groups such as research groups, departments and faculties. More recently, alternative metrics (altmetrics) has also come to the fore. This involves the use of social media. For example, even tweets or Facebook likes that an article receives are recorded.

As indicated above, there are many approaches to defining a journal's impact. However, put the name of a medical journal in a Google search line and, invariably, besides a clickable list containing the likely journal and some other possibilities, a frame appears on the right side of the screen with three pieces of information, the name of the journal, the JIF and the name of the editor. It may or may not contain other details. So, although this number is not the alpha and omega,[1] it does carry a lot of weight.

I remember distinctly how the editor of the *European Heart Journal* (EHJ), William Wijns, proudly mentioned at the South African Heart Congress in 2017 that the EHJ now had a JIF higher than that of *Circulation*. At the same congress, the editor of the *Journal of Heart and Lung Transplantation* (JHLT) argued that the JIF of JHLT, of around seven at that time, was good, given the highly specialised group it is aimed at, implying that general popularity plays an important role.

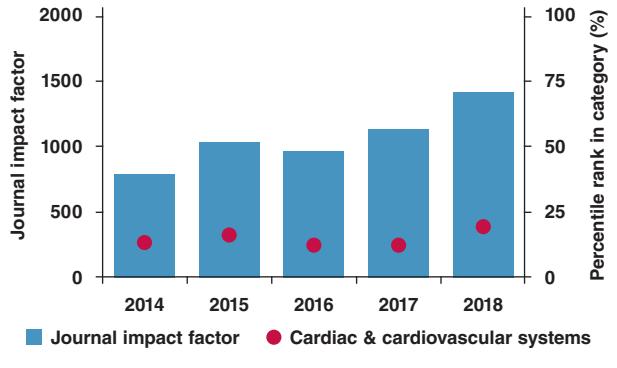

Fig. 1. Five-year trend of the journal impact factor for the *Cardiovascular Journal of Africa*.[6]

In 2013 the CVJA drew attention to the curious case of a lesser-known journal, the *CA: A Cancer Journal for Clinicians* (CA-AC) that had the highest JIF (2018: 223.679) with a massive margin above the world's most well-known general medical journal, the *New England Journal of Medicine* (NJEM) (2018: 70.670).[3,6] To give some perspective, in 2017, CA-AC published 27 articles and the NEJM 327. The CA-AC had 4 089 citations. However a single article, Cancer statistics 2017, is published annually and is responsible for more than 60% of all citations. NEJM had many more citations, namely 22 189 and 327 articles, but the ratio of citations to articles was less. It is an issue of ratios, not popularity.

While listening to the editors at the 2018 Heart Congress, I thought about how in Africa, we compete in a small fishbowl, but there is an ocean out there. With a JIF just above one, rank-wise the CVJA lay third among the 14 medical journals from Africa that are listed on JCR.[7] However, in the cardiovascular field, the CVJA is alone. When a year later a JIF of 1.41 placed the CVJA first among the African medical journals,[6] I felt proud but at the same time, sad.

From Africa, only 68 journals (social sciences included) are listed with the WOS, appear in the JCR and therefore have a JIF. With more than 12 500 journals listed in this index, that is 0.54% of the indexed journals.[6] By contrast, Africa has more than 1.3 billion people, equal to 16.72% of the world's population.[8] Of the 68 journals, CVJA ranks ninth but is top of the 14 medical journals and, furthermore, is the only listed cardiovascular journal. First among the 68 African journals is the *Journal of Advanced Research*, an Egyptian journal, with a JIF of 5.045. Within South Africa, and more specifically the Western Cape, where the office of the CVJA is, the higher ranking accorded the *South African Journal of Enology and Viticulture* (JIF 1.692)[6] may be appropriate. After all the Western Cape is world renowned for its vineyards and wine. However, sitting on a university library committee, I learnt that in certain areas, law for instance, citation analysis is of peripheral interest.

So although CVJA was the number one medical journal in Africa for 2018, with a JIF of 1.410, we must remember that globally, Africa, although very populous, is a small player. Citations to CVJA articles have increased from 370 in 2014 to 899 in 2018, with quite a dramatic increase since 2017. Credit goes to Professor Patrick Commerford, editor of the CVJA. We also thank the authors who publish articles in the CVJA, articles that attract an increasing number of citations. We need to develop globally recognised institutions in Africa.

Paul A Brink
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Cardiovascular Topics

Factors associated with sub-optimal control of anti-coagulation in patients with prosthetic heart valves taking oral anticoagulants in a sub-Saharan African setting

Tigist Chalachew, Dejuma Yadeta, Endale Tefera

Abstract

Background: Replacement of diseased valves reduces the morbidity and mortality rate associated with native valvular disease but comes at the expense of risking complications related to the implanted prosthetic device. Establishing the desired anticoagulation level in a sub-Saharan African setting may be a challenge.

Objectives: This study was conducted to determine the challenges of maintaining a desired level of anticoagulation and factors associated with sub-optimal anticoagulation in patients with prosthetic heart valves on chronic anticoagulation.

Methods: We reviewed 73 patients who had undergone prosthetic valve replacement for chronic rheumatic valvular heart disease and were taking warfarin. The follow up ranged from one to 13 years. We studied international normalised ratio (INR) profiles of the patients for the six months preceding the study and defined optimal control as an INR of 2.5–3.5. We aimed to determine if there were factors associated with sub-optimal control of INR.

Results: Forty-two patients (57.5%) were female. Mean age of the participants was 21.5 ± 3.1 years (range 14–25 years). Warfarin was the anticoagulant in 55 (75.3%) of the patients and 18 (24.7%) were on combined warfarin and aspirin anticoagulation. Thirty-five (47.9%) patients had optimal control of their INR. Educational level of primary school or less, distance from follow-up medical facility of more than 300 km, quarterly or less-frequent check-up visit, and public health institution as a source of free warfarin supply were found to be significantly associated with sub-optimal control of INR.

Conclusion: Educational level, distance from follow-up facility, number of follow-up visits and source of warfarin supply were found to be significantly associated with sub-optimal control of INR.

Keywords: anticoagulation, valve replacement, warfarin, sub-Saharan Africa, rheumatic heart disease

Submitted 20/12/18, accepted 27/4/19
Published online 24/5/19
Cardiovasc J Afr 2019; **30**: 316–320 www.cvja.co.za

DOI: 10.5830/CVJA-2019-024

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Among patients who undergo cardiac valve replacement, approximately 60% receive mechanical valves, and replacement of a diseased heart valve with a prosthetic valve exchanges the native disease for potential prosthesis-related complications.[1,2] Replacement of diseased valves reduces the morbidity and mortality rates associated with native valvular disease but comes at the expense of risking complications related to the implanted prosthetic device.[3] These complications include primary valve failure, prosthetic valve endocarditis and thrombosis, thromboembolism, haemorrhage and mechanical haemolytic anaemia.[4-7] The frequency of serious complications depends upon the valve type and position and other clinical risk factors.[8] Thromboembolic and anticoagulation-related problems are by far the most frequent complications of mechanical valves.[1,2,8]

Chronic rheumatic heart disease is still prevalent and is a major public health problem in sub-Saharan Africa. In recent years, there has been a glimmer of hope for many patients to get surgical intervention in their local environment through locally established facilities,[9] overseas charity referrals or visiting surgical missions. However, determining the optimal strategy to treat such sub-Saharan African patients is a challenge.

Colleagues from Cameroun recently reported their experience with 233 patients who had undergone mechanical valve replacement.[9] Although the surgical results and mid-term event-free survival was good in their report, that may not be the case in other parts of sub-Saharan Africa, primarily due to issues related to anticoagulation. Tissue valves and valve repair strategies tend to be short lived because of the recurrence of

rheumatic fever, as many of these patients fail to comply with penicillin prophylaxis when their cardiac symptoms improve as a result of surgical intervention.

For those who get mechanical valves, the problem starts with regular availability of warfarin itself.[10] Once they are on warfarin, compliance, regular follow up and regular monitoring of their coagulation profile has been a challenge because of lack of facilities in almost all public institutions, and limited access to well-equipped medical facilities. This study aimed at determining factors associated with sub-optimal control of international normalised ratio (INR) in children and young adults who had received mechanical valve replacement for rheumatic valve disease in the last few years.

Methods

This was a cross-sectional study of patients with prosthetic heart valves who are on oral anticoagulation therapy. The study included patients younger than 25 years who were being followed up at the paediatric and adult cardiac clinics of Tikur Anbessa Hospital and the Children's Heart Fund Cardiac Centre, which is also located within the premises of Tikur Anbessa Hospital, Ethiopia.

The study was conducted from December 2014 to September 2015. The principal investigator collected data directly through interviewing patients and attendants and by reviewing medical records during this period. Socio-demographic data, including age, gender, patient's educational level, parental educational level, parental occupation, income, residence, and distance from follow-up health facility were collected on a pre-tested questionnaire.

Clinical data, including current cardiac symptoms, bleeding episodes, strokes, frequency of follow-up visits, frequency of INR determination, source of anticoagulant supply and compliance were collected. For those who missed doses of anticoagulants in the six months preceding the study, possible reasons were inquired.

Patient records were retrieved and reviewed for age at the time of surgery, pre-operative New York Heart Association (NYHA) functional class, indication for valve replacement, prosthetic valve position, type of prosthetic valve implanted, compliance with recommended follow-up visit, INR checks, major bleeding or thrombo-embolic events, and any post-surgical hospital admissions. Where there were discrepancies between patient reports and what had been documented in the medical records, we used the information documented in the records. Definition of adherence to follow-up visit, anticoagulant use and INR determination in this study was based on the doctor's recommendation for each individual patient. The institutional review committee approved the study.

INR determinations during the six-month period ranged from one in the case of some of the patients to multiple values in others. In those with multiple INR recordings, we determined to which side the majority of the readings pointed. There were few patients with mixed optimal and sub-optimal readings in this study.

Our definition of optimal anticoagulation range (2.5–3.5) is in the strict category. We chose the narrower range due to the realities of our setting where frequent follow up, determination of INR and adjustment of extreme boundaries of control is difficult. Although INR values of 2.5–4.9 are considered to be optimal by some,[2] the upper range of this value may have predisposed our patients to bleeding due to lack of frequent determination of their INR and subsequent dose readjustments. The risk of bleeding increases once INR increases above 4.5.[11] Therefore, using a point close to this value would probably have endangered our patients' lives. We did not adjust for valve position, namely mitral or aortic.

Statistical analysis

Data were entered into SPSS version 20 for Windows and analysed. Demographic data were analysed using descriptive statistics. Continuous variables are displayed as mean ± standard deviation (SD). Statistical significance was set at $p < 0.05$. The chi-squared test and binary logistic regression methods were used to test for association of factors to sub-optimal control of anticoagulation.

Results

A total of 73 patients were included in the study and 42 (57.5%) were female. Mean age of the participants was 21.5 ± 3.1 years (range 14–25 years) and mean follow-up period was 5.6 ± 2.5 years (range 1–13 years). Sixty-three of the patients (86.3%) were from urban areas while the rest were from semi-urban or rural areas. Of the 73 patients, 35 (47.9%) had optimal control of their INR. Table 1 shows the socio-demographic data and clinical characteristics of the patients at the time of valve-replacement surgery. With regard to educational status, 24 (32.9%) had primary school education, 29 (39.7%) had secondary education, 19 (26.0%) had higher education and only one patient was illiterate.

Valve brands used included St Jude mechanical valves in 40 (54.8%) patients, Edward's mechanical valves in 12 (16.4%), and other variants in 21 (28.8%) patients. Warfarin was the

Table 1. Baseline socio-demographic and clinical characteristics of patients with prosthetic heart valves on oral anticoagulation therapy

Characteristics	*Frequency*	*Percentage*
Gender		
Female	42	57.5
Male	31	42.5
Age categories at surgery (years)		
11–15	12	16.4
16–20	29	39.7
21–25	32	43.8
Residence		
Urban	63	86.3
Semi-urban	9	12.3
Rural	1	1.4
NYHA functional class (before surgery)		
I	–	–
II	12	16.4
III	29	39.7
IV	32	43.8
Indications for valve replacement (type of valve lesion)		
Severe MR	16	21.9
Severe MS	13	17.8
Severe AR	4	5.5
Multi-valvular lesions	40	54.8

MR: mitral regurgitation; MS: mitral stenosis; AR: aortic regurgitation.

anticoagulant in 55 (75.3%) of the patients and 18 (24.7%) were on combined warfarin and aspirin anticoagulation.

Only 30 (41.1%) patients reported perfect adherence to their medication, while the rest reported that they had missed a few to several doses in the preceding six months. The most common reason for missed doses was forgetfulness, accounting for about 22 (30.1%) of the cases, as reported by the patients themselves. The next most common one was shortage or unavailability of warfarin, accounting for 17 (23.3%) of the cases. Self-perceived side effects and other various reasons accounted for the rest.

Forty-nine (67.1%) patients reported that they had scheduled monthly visits with clinicians, while seven (9.6%) reported that they visited less than once in three months. Thirty-three (45.2%) of the patients reported that they hardly complied with frequency of INR checks as prescribed by their doctors, and the major reason given was cost and availability of the test. Table 2 shows responses and findings in patients with prosthetic heart valves on anticoagulant treatment.

Educational level of primary school or less, more than 300 km distance from follow-up medical facility, quarterly or less-frequent check-up visits, and source of free warfarin supply being from a public institution were found to be significantly associated with sub-optimal control of INR (Table 3). Multiple other factors, including young age, parental level of education, combination of warfarin and aspirin, missed anticoagulant doses and lack of dietary counselling showed a tendency towards an association but did not reach statistically significant levels.

A total of seven patients had major bleeding or stroke in the course of their treatment and four of these patients died as a result (Table 4). One of the fatalities had two episodes of stroke, for which she was admitted. This patient died on the third admission as a result of intracranial bleeding (patient #7).

Table 2. Socio-demographic and clinical characteristics of patients with prosthetic heart valves taking anticoagulants

Characteristics	*Frequency*	*Percentage*
Age at the time of study (years)		
11–15	6	8.7
16–20	16	23.2
21–25	47	68.1
NYHA functional class (at the time of study)		
I	61	88.4
II	7	10.1
III	1	1.5
IV	–	–
Prosthetic valve position		
Mitral	49	67.1
Aortic	9	12.3
Mitral and aortic	14	19.2
Other	1	1.4
INR control		
Optimal	35	47.9
Sub-optimal	38	52.1
Educational status of the patient		
≤ Primary education	25	34.3
Secondary education	29	39.7
Higher education	19	26.0
Parental education (best)		
≤ Primary education	34	46.6
Secondary education	13	17.8
Higher education	26	35.6
Distance from cardiology care clinic (km)		
≤ 150	55	75.3
151–300	4	5.5
> 300	14	19.2
Anticoagulant		
Warfarin alone	55	75.3
Warfarin + aspirin	18	24.7
Drug supply source		
Private	19	26.0
Public for payment	36	49.3
Public for free	18	24.7
Frequency of INR determination		
Every month	54	74.0
Every 2 months	4	5.5
Quarterly or longer	15	20.5
Laboratory facility for INR		
Private	73	100
Public	–	–
Missed doses (approximate)		
Never	30	41.1
1–2 doses per week	34	46.6
> 2 doses per week	9	12.3
Bleeding or thromboembolic complications	7	9.6

Table 3. Factors associated with sub-optimal control of INR in patients with prosthetic heart valves

Factors analysed for association	*Optimal control*	*Sub-optimal control*	p-*value*
Age at surgery (years)			
< 15	7	10	0.588
≥ 15	28	28	
Gender			
Female	21	21	0.813
Male	14	17	
Educational status of the patients			
≤ Primary education	6	19	0.003
≥ Secondary education	29	19	
Parental/caretaker education (best)			
≤ Primary education	14	20	0.350
≥ Secondary education	21	18	
Distance from follow-up facility (km)			
< 300	32	23	0.003
≥ 300	3	15	
Clinic visit frequency			
Once in a month	28	21	0.022
Once in a quarterly or less	7	17	
Approximate monthly income ($US)			
≤ 50	14	12	0.162
> 50	21	16	
Medications			
Warfarin alone	28	27	0.425
Warfarin + aspirin	7	11	
Source of medication supply			
Private or public for fee	30	25	0.047
Public for free	5	13	
Medication adherence counselling (as per patient's report)			
Yes	32	33	0.712
No	3	5	
Dietary counselling (as per patient's report)			
Yes	24	20	0.232
No	11	18	
Anticoagulant doses missed (approximate)			
None or < 1 dose per week	33	31	0.155
≥ 1 dose per week	2	7	

Table 4. Description of patients with prosthetic heart valves and thrombo-embolic events

Age (years)	*Gender*	*Educational status*	*Age at surgery (years)*	*Valve position*	*Duration of follow up*	*Type and number of events*		*Outcome*
						Bleeding	*Thrombo-embolism*	
18	*F*	Secondary education	16	Aortic	2 years	1	2	Alive, no sequelae
14	M	Primary education	14	Aortic and mitral	6 months	3	2	Alive, no sequelae
20	F	Primary education	20	Aortic	8 months	1	1	Alive, neurological sequelae
12	M	Primary education	11	Mitral	1 year	2	1	Deceased
15	F	Primary education	15	Mitral	6 months	1	1	Deceased
20	F	Primary	18	Mitral	2 years	1	1	Deceased
11	F	Primary education	9	Aortic and mitral	2 years	2	1	Deceased

Overall, 16 of the patients had hospital admissions after valve replacement surgery and the reasons included prosthetic valve endocarditis in eight patients, stroke in five and miscellaneous reasons in the rest.

Discussion

Our study showed that educational level of primary school or less, distance from follow-up medical facility of more than 300 km, check-up visit once quarterly or less frequently, and free drug supply from public institutions were significantly associated with sub-optimal control of INR in this group of patients, suggesting the need for interventions directed towards tackling some of these factors.

Review of the existing literature shows a lower level of knowledge consistently affects adherence to prescribed medicines.[12] Multiple other factors including young age, level of parental education, combination of warfarin and aspirin, and missed anticoagulant doses also showed a tendency towards an association, although not statistically significant, probably due to the small sample size of our study. The number of major bleeding/thrombotic events and mortalities in our study is also unacceptably high considering the small number of patients we are reporting on (Table 4).

A lower level of literacy may have influenced the patients' understanding of the nature of the clinical condition they are suffering from, the risks associated with sub-optimal anticoagulation, and the importance of adhering to medications and follow-up clinical visits, even when they do not have clinical symptoms. Longer travel to follow-up clinics and INR test facilities is even more important in sub-Saharan African settings where transportation facilities are not readily available or are too costly for most poor patients to afford, or travel is too difficult. It may be surprising that free drug supply from public facilities was associated with sub-optimal anticoagulation. However, the truth is that warfarin was rarely available in the public institutions, which means it was difficult for the patients to secure a regular and sustainable supply.

Optimisation of anticoagulation in populations with sub-optimal adherence to medication and follow up is a major challenge.[13] Adherence to follow-up care and medication is a challenge once patients are relieved of their cardiac symptoms.[14] Colleagues from Cameroon reported that their cohort of 233 patients with mechanical valves had freedom from neurological events and anticoagulation-related bleeding of 93.1 ± 2.1 and 78.9 ± 3.7%, respectively, at six years.[9] While it is difficult to directly compare our study with theirs due to the small number of patients and differences in methodology, the number of major stroke and bleeding events in our study was disproportionately high.

A study from Rwanda reported that no anticoagulation-related events occurred,[15] but the number of patients with valve replacement in that study was small and the follow up was relatively short. The South African group that compared adjusted-dose warfarin with pre-determined fixed-dose warfarin also reported there were significant numbers of major thrombotic and haemorrhagic events in their study population.[13] However, this study was also significantly different in methodology and cannot be compared with our study.

Our study has important limitations in methodology. We included all patients we could acquire during the study period. We did not know the exact number of patients with prosthetic valves due to lack of records. We did not calculate our sample size therefore our statistical tests should be taken with caution.

Besides the small size of the study population, the study was cross-sectional with only one encounter with each patient participant. We used medical records to determine the six-month INR profile. Some of these patients may have had a single INR determination within that period due to the compliance and logistical problems already mentioned. The ideal study design would have been a cohort study.

We only included patients who came for follow up during the study period. Finally, recall bias may also have been a limitation in our study. This study could prompt the hospital to re-organise record keeping of patients.

It is worth mentioning the inherent drawbacks of warfarin as an anticoagulant. Warfarin has marked individual variation in its metabolism and hence varying dosage requirements and the need for frequent monitoring.[16] However, there are no agreed guidelines on how frequently one should monitor anticoagulation in patients who are on chronic anticoagulation. Besides, warfarin has wide dietary and drug interactions, making it difficult to establish a desired level of anticoagulation. Fixed-dose warfarin has been shown to be better than adjusted-dose warfarin. Future studies may be required to determine the feasibility and safety of this strategy in our patients. It may also be worth considering the feasibility, affordability and effectiveness of novel anticoagulants (NOACs) in our setting.

Finally, it may be better to opt for valve repair surgery whenever possible,[14] although this strategy also has its own drawbacks in this part of the world. Besides the significantly high failure rate in advanced rheumatic heart disease, patients usually fail to comply with their monthly benzathine penicillin prophylaxis, putting themselves at risk of recurrence of acute rheumatic fever. Ideally, development of prosthetic heart valves that do not require anticoagulation may be a future solution to tackle some of these complex problems.

Conclusion

Low educational level, longer distance from medical facility, less frequent follow-up visits, and warfarin from public institutions were found to be significantly associated with sub-optimal control of INR in our study. These findings may help to develop initiatives such as implementing regular outreach clinics, training health workers in remote areas with task shifting, supplying INR self-determination devices, or other innovative ways that may be found to be feasible and effective. It may also be worth considering the feasibility, affordability and effectiveness of NOACs for such patients in our setting.

We thank the staff members of the paediatric and adult cardiac clinics and the children's Heart Fund Cardiac Centre for allowing us to conduct this study and assisting with the data collection. We are also grateful to all those practitioners who care for these patients over the years.

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Associations between body fat distribution and cardiometabolic risk factors in mixed-ancestry South African women and men

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Abstract

Objective: To investigate the relationship between body fat distribution and cardiometabolic risk in mixed-ancestry South African (SA) men and women, and to explore the effect of menopausal status on these relationships in women.

Methods: In a cross-sectional study, 207 mixed-ancestry SA women and 46 men underwent measurement of body composition using dual-energy X-ray absorptiometry, blood pressure, oral glucose tolerance, lipid profile and high-sensitivity C-reactive protein determination. The associations between different body fat compartments and associated cardiometabolic risk factors were explored.

Results: Men had less percentage fat mass (%FM) [26.5% (25–75th percentiles: 19.9–32.5) vs 44.0% (39.8–48.6), $p \leq 0.001$], but more central and less peripheral fat (both $p < 0.001$) than women. Post-menopausal women had greater %FM, waist and visceral adipose tissue (VAT), and less gynoid %FM than pre-menopausal women (all $p \leq 0.004$). After adjusting for age and gender, VAT accounted for the greatest variance in insulin resistance ($R^2 = 0.27$), while trunk %FM and leg %FM accounted for the greatest variance in triglyceride ($R^2 = 0.13$) and high-density lipoprotein cholesterol concentrations ($R^2 = 0.14$). The association between fat mass and regional subcutaneous adipose tissue and cardiometabolic risk factors differed by gender and menopausal status.

Conclusion: Central fat was the most significant correlate of cardiometabolic risk and lower body fat was associated with reduced risk. These relationships were influenced by gender and menopausal status.

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Keywords: DXA, visceral adipose tissue, subcutaneous adipose tissue, menopause, ethnicity, gender, cardiometabolic risk

Submitted 1/3/19, accepted 6/5/19
Published online 12/9/19
Cardiovasc J Afr 2019; **30**: 321–330 www.cvja.co.za

DOI: 10.5830/CVJA-2019-028

Globally, chronic non-communicable diseases (NCDs) are responsible for more deaths than any other cause, with people from the low- and middle-income countries being disproportionately affected.[1] In 2012, cardiovascular diseases (CVDs) and diabetes accounted for 46.2 and 4% of NCDs-related deaths, respectively.[1] The South African (SA) cause-of-death profile for 2012 shows similar trends.[2] An analysis of pooled population-based studies conducted by the NCD Risk Factor Collaboration Africa working group found that estimates of adiposity and diabetes prevalence in SA were higher than the global average.[3] NCD deaths are attributable to the high prevalence of major risk factors, including obesity, which is driven by lifestyle factors such as poor dietary intake and physical inactivity.[4]

Obesity is a well-known risk factor for CVD and metabolic diseases,[5-7] but body fat distribution appears to be a more significant discriminator of risk than generalised adiposity. The association of body fat with CVD risk differs by fat depot. A meta-analysis of 40 observational studies on the associations of different adipose tissue depots with insulin resistance revealed the strongest correlate of insulin resistance to be visceral adipose tissue (VAT).[8] By contrast, the relationship between abdominal subcutaneous adipose tissue (SAT) and cardiometabolic risk is weaker than VAT, as shown in multi-ethnic studies in men and women.[9,10] However, the accumulation of lower body SAT (gluteofemoral obesity) has shown opposing associations with cardiometabolic risk.[11-13]

Body fat distribution is also gender specific, with women having more SAT and less VAT than men.[14,15] The greater central adiposity, in particular VAT, in men translates to higher insulin resistance,[14] type 2 diabetes[16] and an adverse cardiometabolic risk profile in general. The risk of cardiometabolic disease increases with age,[17] and in women, after menopause,[18] when weight gain and increased central adiposity are common.[19]

Differences also exist in body fat distribution among different ethnic groups.[5,20] International studies have shown that Asian Indians have more total and central fat mass than their Caucasian and black counterparts.[21-23] Black Africans on the other hand have less VAT but more abdominal SAT than Caucasians,[24-27] and greater gluteofemoral fat mass compared to Caucasian women.[27]

In addition to differences in body fat distribution, the association with cardiometabolic risk also differs according to gender, age and ethnicity. For example, African American women were shown to have a weaker association between VAT and blood pressure, triglyceride, high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) concentrations than Caucasian women, while African American men displayed a stronger association between VAT, triglyceride and low HDL-C concentrations and the metabolic syndrome (MetS) than their Caucasian counterparts.[28]

While differences in body fat distribution, and associations with cardiometabolic risk between black, Caucasian and Asian women have been described in SA,[24,29,30] no studies have examined the mixed-ancestry population of SA, who present with a high prevalence of the MetS (62%) and type 2 diabetes (28.2%), placing this population at high risk for CVD.[31]

The composition of the mixed-ancestry (collectively referred to as 'Coloured') population of SA is Khoisan (32–43%), Bantu-speaking Africans (20–36%), Europeans (21–28%) and a smaller Asian contribution (9–11%).[32] This population accounts for 8.9% of the South African population and 48.8% of the population of the Western Cape Province. [33] The aims of the study were therefore, for the first time, to investigate the relationship between whole-body fat distribution and cardiometabolic risk factors in mixed-ancestry SA men and women, and to explore the effect of menopausal status on these relationships in women.

Methods

The study sample included all self-described mixed-ancestry volunteers who completed a whole-body dual X-ray absorptiometry (DXA) scan as part of the Cape Town Vascular and Metabolic Health (VMH) study described previously.[34] Inclusion criteria were adults aged 20 years and older. Subjects were excluded if they were pregnant or acutely ill. A total of 46 men and 207 women volunteered for the study.

Ethical approval was obtained from the Ethics Committees of the Cape Peninsula University of Technology and Stellenbosch University (respectively, NHREC: REC-230 408-014, CPUT/HWS-REC 2015/H03 and N14/01/003). All participants signed written informed consent and the study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Anthropometric measurements were taken and included body weight, height and body mass index (BMI), as described in detail previously.[34] Body composition (fat mass and fat-free mass) was acquired by a suitably trained and experienced radiographer using a Hologic Discovery W DXA whole-body scanner configured with software version 13.4.1 (Hologic, Bedford, MA). Participants were positioned as per the NHANES body composition manual, as advocated by Hangartner.[35]

DXA-derived measures of body composition regions included six standard regions of interest (ROI), namely the whole body; the trunk defined by the lower border of the mandible and including the chest, abdomen and pelvic triangle; the arm ROIs (right and left) defined by a line bisecting the shoulder joint of the right and left arm; and the leg ROIs (right and left) defined by a line bisecting the hip joint aligned with the iliac crest and pubis.[27] For the android fat measurement, the ROI is automatically defined with a caudal limit placed on top of the iliac crests and its height is set to 20% of the distance from the top of the iliac crest to the base of the skull as the cephalic limit.[36] The height of the gynoid ROI is double that of the android ROI with the separation between the two regions equating to 1.5 times the height of the android ROI. VAT and SAT were estimated within this android region.

DXA has proved to be as accurate as a clinical computed tomography scan in the quantification of VAT and SAT in adults.[36] Sub-total body fat % and kg, which excluded the head, was used in the analysis. The head was excluded to reduce the possibility of any artefacts in the head region, and total body adipose tissue classification excludes the head. Regional fat distribution (arms, legs, trunk, android and gynoid) are expressed as a percentage relative to sub-total fat mass (%FM).

Blood pressure was measured according to the World Health Organisation (WHO)[37] guidelines using a semi-automatic digital blood pressure monitor (Omron M6 comfort-preformed cuff BP monitor) on the right arm, in a seated position and at rest for 10 minutes. The lowest of three consecutive readings was taken in the analyses.[34]

After an overnight fast (eight to 14 hours), blood samples were taken to measure levels of glycated haemoglobin (HbA_{1c}), glucose, insulin, lipid profile, and biochemical marker for inflammation, high-sensitivity C-reactive protein (hsCRP). After collection of the fasting blood sample, the subjects without previously diagnosed diabetes underwent an oral glucose tolerance test as per the WHO criteria.[38] Participants drank 75 g of anhydrous glucose in 250–300 ml of water over the course of five minutes,[39] following which blood samples were collected after the two-hour test load. Blood samples were transported daily in an icebox for processing using standard pathology practices.

Biochemical parameters were analysed at an ISO 15189 accredited pathology practice (Pathcare, Reference Laboratory, Cape Town, South Africa) as described elsewhere.[34] Plasma glucose level was measured by the enzymatic hexokinase method (Beckman AU, Beckman Coulter, South Africa). HbA_{1c} level was assessed by high-performance liquid chromatography (Biorad Variant Turbo, BioRad, South Africa). Insulin concentration was measured with the paramagnetic particle chemiluminescence assay (Beckman DXI, Beckman Coulter, South Africa). Levels of HDL-C were measured by enzymatic immuno-inhibition, triglycerides by glycerol phosphate oxidase-peroxidase assays, and low-density lipoprotein cholesterol (LDL-C) by enzymatic selective protection (Beckman AU, Beckman Coulter, South Africa). Analysis of hsCRP was performed on the BNA nephelometer (Dade Behring) by particle-enhanced immunonephelometry with a detection limit of 0.18 mg/l and a measuring range of 0.18–1 150 mg/l.

Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin levels.[40] The MetS was quantified using the Joint Interim Statement (JIS) criteria[39] and the WHO glucose tolerance categories were used.

Statistical analysis

Data were analysed using SPSS® version 24 (Armonk, NY: IBM Corp.) and STATA® version 14.2 (STATA corporation, Texas, USA). The participants in the study were a convenient sub-sample of the larger study. The 253 available volunteers who participated in the study provided an 80% power at a 5%

significance level to detect a coefficient of determination (R^2) of 0.042 or greater from the linear regression model comprising three predictors. Categorical variables are presented as frequencies and percentages, while continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables, and median and 25–75th percentiles for skewed variables. Data were tested for normality using the Kolmogorov–Smirnov and Shapiro–Wilk statistic.

The women were also split into two groups based on menopausal age, which was estimated to be 50 years in this population.[41] Group comparisons were made using the Mann–Whitney *U*-test or chi-squared test. Robust regression analyses were used to investigate the associations between body fat distribution and cardiometabolic risk factors (insulin resistance, lipid levels, blood pressure and inflammatory markers), adjusting for age and gender. In addition, we explored the interactions between gender and body composition on cardiometabolic risk factors, adjusting for age, and in women, between menopausal age and body composition.

To investigate whether one body compartment was more closely associated with the risk factor than the other, coefficients of determination were used from robust regressions. We calculated the R^2 for the model with covariates only (age and gender), then the R^2 for models containing covariates and each of the adiposity measures.

Results

In all, 253 participants (18% men and 82% women) were included. The average age of the participants was 55 years, and was similar between men and women ($p = 0.630$). Differences in body composition and body fat distribution between women and men, as well as between pre- and post-menopausal women are presented in Table 1. On average, the women were obese (mean BMI = 32.6 ± 7.2 kg/m^2), whereas the men were overweight (mean BMI = 27.4 ± 6.1 kg/m^2) ($p < 0.001$).

Men had higher fat-free soft tissue mass compared to women, ($p < 0.001$), but body fat mass (kg and %) was significantly higher in the women than men ($p < 0.001$). As a percentage of total fat mass, women had significantly less central fat mass ($p < 0.001$) and greater peripheral fat mass (arm, leg and gynoid fat %, $p \leq 0.003$ for all) than men. VAT area was not different between men and women ($p = 0.474$), but SAT area was higher in women than men ($p < 0.001$).

When examining differences in body composition between the pre- and post-menopausal women, we found that although there were no differences in BMI, more post- than pre-menopausal women were obese (68.9 vs 57.3%), and post-menopausal women had greater fat mass ($p = 0.026$) and %FM ($p < 0.001$) than pre-menopausal women. Although trunk fat mass (%) and android fat mass (%) did not differ between pre- and post-menopausal women (both $p \geq 0.415$), post-menopausal women had greater waist circumference and VAT (both $p \leq 0.004$), and less gynoid %FM ($p = 0.001$) than pre-menopausal women.

Differences in cardiometabolic risk factors between mixed-ancestry men and women and between pre- and post-menopausal women are described in Table 2. While blood pressure, fasting glucose, insulin and lipid levels were not different between men and women (all $p \geq 0.085$), two-hour post-prandial glucose ($p < 0.05$) and HDL-C ($p < 0.001$) concentrations were higher in women than men. The majority of the sample had normal glucose tolerance (NGT) (men 63.1% and women 57.3%). The

Table 1. Comparison of body composition and body fat distribution between mixed-ancestry men and women, and pre- and post-menopausal women

	Men		*Women*		*Men vs women*	*Women*				*Pre- vs post-menopausal women*
Parameters	n	*Total sample*	n	*Total sample*	p-*value*	n	*20–49 years*	n	*≥ 50 years*	p-*value*
Age (years)	46	53.5 (44.8–65.3)	207	55.0 (45.0–63.0)	0.630	75	39.0 (31.0–45.0)	131	61.5 (56.0–67.0)	< 0.001
Anthropometry										
Height (cm)	46	168.0 (163.3–173.6)	206	156.0 (151.5–160.5)	< 0.001	75	157.5 (153.0–160.5)	131	155.0 (151.0–160.5)	0.043
Weight (kg)	46	75.6 (63.6–89.1)	206	78.2 (66.3–90.4)	0.443	75	74.5 (62.1–92.2)	131	79.8 (67.6–90.2)	0.196
BMI (kg/m^2)	46	27.4 ± 6.1	206	32.6 ± 7.2	< 0.001	75	31.4 ± 7.7	131	33.4 ± 6.9	0.083
Waist (cm)	46	96.2 ± 17.5	206	99.3 ± 15.0	0.284	75	95.0 ± 17.1	131	101.9 ± 13.2	0.004
BMI category	46	*%*	207	*% of total sample*	*Pearson chi-squared*	75	*%*	132	*%*	*Pearson chi-squared*
Underweight	2	4.3	3	1.4	< 0.001	2	2.7	1	0.8%	0.010
Normal	14	30.4	29	14.0		18	24	11	8.3	
Overweight	16	34.8	41	19.8		12	16	29	22	
Obese	14	30.5	134	64.7		43	57.3	91	68.9	
DXA-derived body composition and body fat distribution										
Fat-free soft-tissue mass (kg)	46	50.4 (43.8–56.8)	207	38.9 (35.6–44.7)	< 0.001	75	38.9 (34.3–44.7)	132	37.3 (34.2–42.2)	0.243
Body fat (kg)	46	16.4 (12.7–27.8)	207	31.2 (24.4–40.0)	< 0.001	75	30.0 ± 12.5	132	34.1 ± 11.9	0.026
Body fat (%)	46	26.5 (19.9–32.5)	207	44.0 (39.8–48.6)	< 0.001	75	41.5 (35.3–46.8)	132	44.9 (41.4–49.6)	< 0.001
Trunk fat (%FM)	46	57.1 ± 5.2	207	50.7 ± 6.01	< 0.001	75	50.1 ± 6.9	132	51.0 ± 5.4	0.415
Arm fat (%FM)	46	10.7 ± 1.5	207	12.5 ± 1.97	< 0.001	75	12.1 ± 1.8	132	12.7 ± 2.0	0.059
Leg fat (%FM)	46	31.7 (29.0–34.9)	207	36.1 (31.9–40.5)	< 0.001	75	37.5 (32.0–41.5)	132	35.8 (31.5–40.2)	0.180
Android (%FM)	46	10.8 ± 2.0	207	8.9 ± 1.57	< 0.001	75	8.8 ± 1.8	132	9.1 ± 1.4	0.445
Gynoid (%FM)	46	15.6 (14.6–17.2)	207	17.2 (15.4–19.1)	0.003	75	18.1 (16.0–20.7)	132	16.9 (14.9–18.5)	0.001
VAT (cm^2)	46	167.0 (101.2–260.7)	207	180 (135–236)	0.474	75	154.5 (93.2–211.0)	132	197.2 (149.4–244.1)	< 0.001
SAT (cm^2)	46	263.8 ± 143.7	207	451 ± 142	< 0.001	75	432.6 ± 160.6	132	461.0 ± 129.5	0.220

Values presented as means ± standard deviations (SD), median and 25–75th percentiles, or %. BMI (WHO classification), body mass index; WC, waist circumference; FM, fat mass expressed as a percentage relative to sub-total fat mass; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

Table 2. Comparison of cardiometabolic risk factors between mixed-ancestry men and women, and pre- and post-menopausal women

	Men		*Women*		*Men vs women*	*Women*				*Pre- vs post-menopausal women*
Risk factors	n	*Total sample*	n	*Total sample*	p-*value*	n	*20–49 years*	n	*≥ 50 years*	p-*value*
SBP (mmHg)	46	128.5 ± 22.5	207	127.2 ± 20.6	0.894	75	116.6 ± 19.0	132	133.3 ± 19.1	< 0.001
DBP (mmHg)	46	81.9 ± 12.9	207	82.6 ± 11.6	0.472	75	81.3 ± 12.0	132	83.4 ± 11.4	0.228
Fasting glucose (mmol/l)	46	5.1 (4.6–5.8)	205	5.1 (4.7–6.0)	0.550	74	4.8 (4.5–5.5)	131	5.3 (4.8–6.3)	0.001
2-h glucose (mmol/l)	35	5.8 (4.5–7.5)	170	6.6 (5.5–8.0)	0.017	63	6.3 (5.0–7.1)	107	7.1 (5.7–8.2)	0.010
Fasting insulin (mIU/l)	46	6.7 (3.8–13.2)	205	8.4 (5.6–12.6)	0.085	74	8.5 (5.9–14.6)	131	8.4 (5.3–12.1)	0.362
HOMA-IR	46	1.6 (0.9–3.3)	204	2.1 (1.2–3.6)	0.085	73	2.0 (1.3–4.2)	131	2.1 (1.2–3.5)	0.940
TG (mmol/l)	46	1.5 (1.0–1.9)	205	1.4 (0.1–2.0)	0.665	74	1.2 (0.8–1.8)	131	1.5 (1.1–2.1)	0.008
TC (mmol/l)	46	5.1 ± 1.3	205	5.4 ± 1.2	0.208	74	5.2 ± 1.1	131	5.5 ± 1.1	0.017
LDL-C (mmol/l)	42	3.1 (2.3–3.9)	201	3.2 (2.7–4.1)	0.385	72	3.3 (2.6–4.0)	129	3.2 (2.7–4.1)	0.527
HDL-C (mmol/l)	46	1.1 (0.9–1.3)	205	1.3 (1.1–1.5)	< 0.001	74	1.2 (1.0–1.3)	131	1.3 (1.1–1.5)	< 0.001
hsCRP (mg/l)	39	2.8 (1.6–5.5)	152	3.3 (1.7–5.7)	0.467	58	2.8 (1.3–6.6)	94	3.3 (1.8–5.7)	0.508
Glucose tolerance categories										
NGT, *n*/%	29	63.1	118	57.3		50	66.7	68	51.9	
IGT/IFG, *n*/%	3	6.5	33	16.0		9	12.0	24	18.3	
Diabetes, *n*/%	14	30.4	55	26.7	0.249	16	21.3	39	29.8	0.166

Values presented as means ± standard deviations (SD), median and 25–75th percentiles or %. SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model for insulin resistance; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose.

Table 3. Associations between body composition and cardiometabolic risk factors in the whole sample, adjusted for gender and age

Age and gender	*SBP*	*DBP*	*Fasting glucose*	*2-h glucose*	*Fasting insulin*	*HOMA-IR*	*TG*	*TC*	*LDL-C*	*HDL-C*	*hsCRP*
R^2	0.23	0.03	0.07	0.08	0.01	0.02	0.03	0.03	0.01	0.06	0.01
FM (kg)											
β (95% CI)	0.053 (–0.14 to 0.24)	0.142* (0.02 to 0.27)	0.01** (0.00 to 0.01)	0.03**# (0.01 to 0.05)	0.17**# (0.13 to 0.22)	0.04**# (0.03 to 0.05)	0.01** (0.00 to 0.02)	0.01 (–0.00 to 0.02)	0.01 (–0.00 to 0.02)	–0.01** (–0.01to 0.00)	0.09** (0.06 to 0.12)
R^2	0.23	0.04	0.09	0.11	0.20	0.20	0.04	0.04	0.01	0.08	0.13
FM (%)											
β (95% CI)	0.02 (–0.29 to 0.33)	0.26* (0.05 to 0.46)	0.15* (0.00 to 0.02)	0.05** (0.02 to 0.09	0.27** (0.20 to 0.34)	0.06** (0.05 to 0.08)	0.01* (0.00 to 0.03)	0.03** (0.01 to 0.05)	0.02* (0.00 to 0.04)	–0.00 (–0.00 to 0.00	0.16** (0.09 to 0.24)
R^2	0.23	0.05	0.10	0.13	0.21	0.21	0.04	0.05	0.03	0.10	0.13
Trunk fat (%FM)											
β (95% CI)	0.38 (–0.00 to 0.77)	0.54** (0.30 to 0.79)	0.01** (0.00 to 0.03)	0.08** (0.04 to 0.12)	0.26** (0.15 to 0.37)	0.06** (0.03 to 0.08)	0.04**ª (0.30 to 0.06)	0.02 (–0.00 to 0.48)	0.01 (–0.01 to 0.03)	–0.02** (–0.02 to –0.01)	0.11** (0.04 to 0.18)
R^2	0.24	0.10	0.09	0.13	0.10	0.10	0.13	0.04	0.01	0.12	0.06
Arm fat (%FM)											
β (95% CI)	1.19* (0.01 to 2.36)	1.12** (0.34 to 1.90)	0.01 (–0.03 to 0.05)	0.04 (–0.10 to 0.18)	0.40* (0.03 to 0.76)	0.09**# (0.01 to 0.18)	0.04 (–0.10 to 0.09)	–0.00 (–0.08 to 0.08)	0.01 (–0.06 to 0.08)	–0.03** (–0.05 to –0.01)	0.19 (–0.02 to 0.41)
R^2	0.24	0.05	0.07	0.08	0.03	0.03	0.03	0.03	0.01	0.08	0.02
Leg fat (%FM)											
β (95% CI)	–0.43* (–0.79 to –0.08)	–0.56** (–0.79 to –0.34)	–0.01** (–0.03 to –0.00)	–0.06** (–0.10 to –0.03)	–0.25** (–0.36 to –0.15)	–0.06** (–0.08 to –0.03)	–0.04**ª (–0.05 to –0.03)	–0.02 (–0.04 to 0.00)	–0.01 (–0.03 to 0.01)	0.02** (0.01 to 0.02)	–0.11** (–0.17 to –0.05)
R^2	0.24	0.12	0.09	0.13	0.10	0.10	0.13	0.03	0.01	0.14	0.07
Android fat (%FM)											
β (95% CI)	0.46 (–0.91 to 1.82)	1.74** (0.87 to 2.62)	0.08** (0.04 to 0.13)	0.29** (0.14 to 0.42)	1.01** (0.65 to 1.39)	0.24** (0.15 to 0.32)	0.13**ª (0.08 to 0.18)	0.10* (0.01 to 0.19)	0.06 (–0.02 to 1.43)	–0.05** (–0.07 to –0.03)	0.59** (0.35 to 0.82)
R^2	0.23	0.08	0.13	0.14	0.12	0.13	0.10	0.04	0.01	0.11	0.11
Gynoid fat (%FM)											
β (95% CI)	–1.12** (–1.93 to –0.31)	–1.13** (–1.66 to –0.60)	–0.03** (–0.06 to –0.00)	–0.15** (–0.23 to –0.06)	–0.70** (–0.91 to –0.47)	–0.17** (–0.22 to –0.11)	–0.10**ª (–0.13 to –0.07)	–0.04 (–0.09 to 0.02)	–0.01 (–0.06 to 0.04)	0.03** (0.02 to 0.05)	–0.25** (–0.40 to –0.10)
R^2	0.25	0.09	0.09	0.12	0.15	0.15	0.12	0.03	0.01	0.11	0.06
VAT (cm²)											
β (95% CI)	0.02 (–0.01 to 0.05)	0.03** (0.01 to 0.05)	0.00** (0.00 to 0.00)	0.01** (0.00 to 0.01)	0.04** (0.03 to 0.05)	0.01** (0.01 to 0.01)	0.00**ª (0.00 to 0.00)	0.00 (–0.00 to 0.00)	0.00 (–0.00 to 0.00)	–0.00** (–0.00 to –0.00)	0.01** (0.01 to 0.02)
R^2	0.23	0.07	0.12	0.16	0.29	0.27	0.09	0.03	0.01	0.12	0.14
SAT (cm²)											
β (95% CI)	0.01 (–0.01 to 0.02)	0.02** (0.01 to 0.03)	0.00** (0.00 to 0.00)	0.00**# (0.00 to 0.00)	0.01**# (0.01 to 0.02)	0.00**# (0.00 to 0.00)	0.00** (0.00 to 0.00)	0.00* (0.00 to 0.00)	0.00 (–0.00 to 0.00)	–0.00** (–0.00 to –0.00)	0.01** (0.01 to –0.01)
R^2	0.23	0.06	0.11	0.12	0.19	0.20	0.06	0.05	0.02	0.09	0.15

Diabetic participants were excluded from insulin-sensitivity measurements. Beta coefficients, confidence intervals, total R^2 for: %FM, expressed as a percentage of sub-total fat mass (FM). HOMA-IR, homeostasis model for insulin resistance; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.
*$p < 0.05$, **$p < 0.01$, #significant in men, ªsignificant in women

prevalence of diabetes (30.4 and 26.7%) and screen-detected diabetes (8.7 and 9.2%) was similar in men and women, respectively ($p = 0.249$).

Post-menopausal women had higher systolic blood pressure (SBP), fasting glucose ($p < 0.001$), two-hour glucose ($p = 0.01$), triglyceride ($p < 0.01$), TC ($p < 0.05$) and HDL-C ($p < 0.001$) concentrations than pre-menopausal women. The prevalence of impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) and type 2 diabetes was similar in the pre-and post-menopausal women ($p = 0.166$).

Table 3 shows the associations between body fat variables and cardiometabolic risk factors in the whole sample, adjusting for gender and age. In terms of total body fat (kg and %), positive associations were observed for diastolic blood pressure (DBP) ($p < 0.05$), two-hour glucose, fasting insulin, HOMA-IR (all $p < 0.01$) and triglyceride concentrations ($p < 0.05$) as well as hsCRP, and in the case of body fat %, TC ($p < 0.01$) and LDL-C levels ($p < 0.05$).

When examining associations between central fat mass (trunk fat %FM, android %FM, VAT and SAT area) and cardiometabolic risk profile, we found positive associations with DBP, fasting glucose, two-hour glucose, fasting insulin, HOMA-IR, triglyceride and hsCRP concentrations ($p < 0.01$ for all), and negative association with HDL-C levels ($p < 0.01$ for all). When examining the relationships of peripheral fat mass, we found that arm fat mass was positively associated with SBP ($p < 0.05$), DBP ($p < 0.01$), levels of fasting insulin ($p < 0.05$) and HOMA-IR ($p < 0.01$), and negatively associated with HDL-C ($p < 0.01$) levels. By contrast, lower body peripheral fat mass (gynoid %FM and leg %FM) was negatively associated with all CVD risk markers, except for HDL-C, which was positively associated with gynoid and leg %FM ($p < 0.01$).

We then compared the proportion of the variance that age, gender and the different body composition measures explained for each cardiometabolic risk factor. Together with age and gender, VAT area accounted for the greatest variance in fasting insulin (29%) and HOMA-IR (27%) levels, while SAT area accounted for the greatest variance in hs-CRP (15%) concentrations. Trunk %FM and leg %FM contributed equally

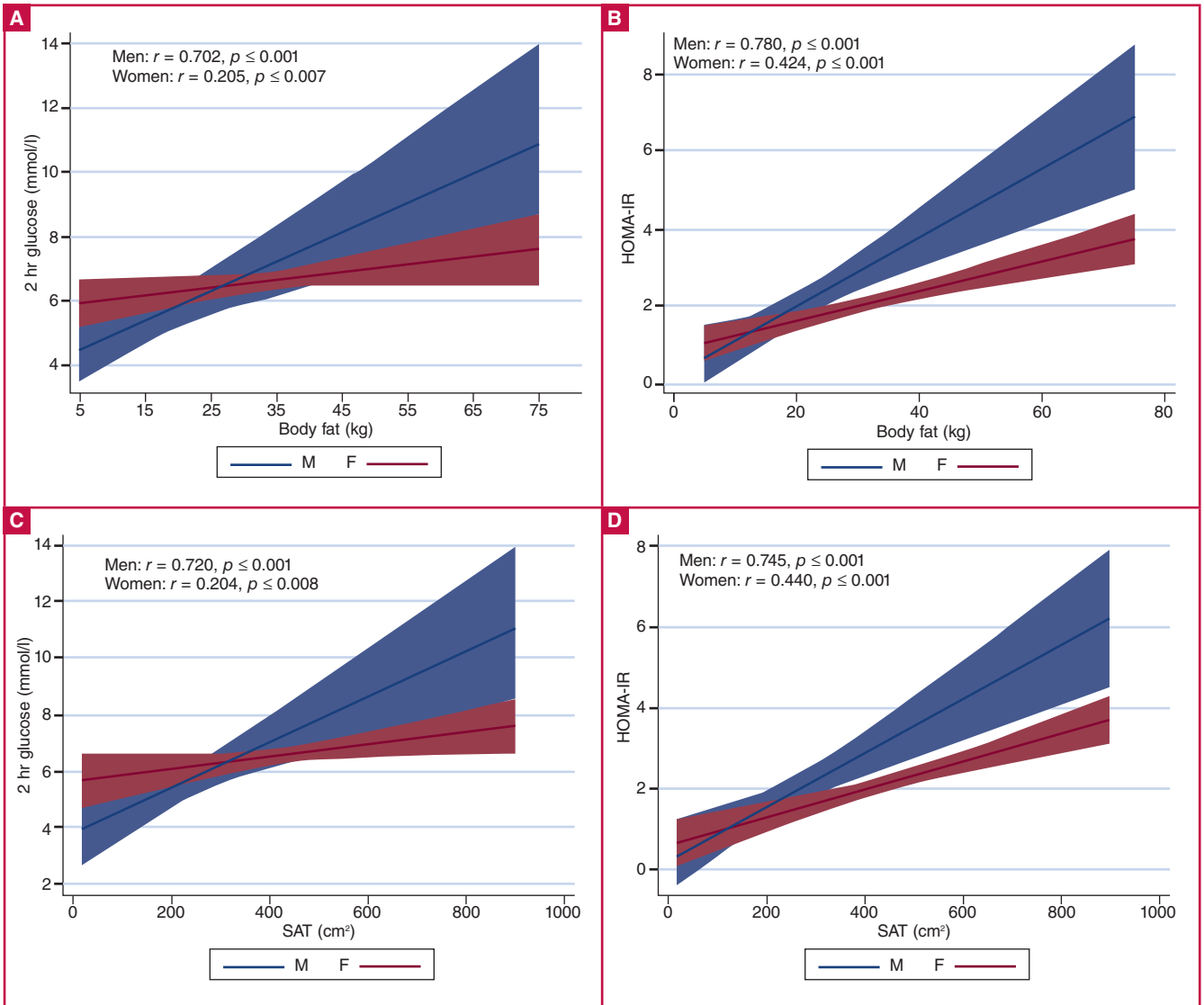

Fig. 1. Gender-specific associations between total body fat and abdominal subcutaneous adipose tissue (SAT) and two-hour glucose (A, C) and insulin resistance, estimated using HOMA-IR (B, D), respectively.

Table 4. Associations between body composition and cardiometabolic risk factors in the pre- and post-menopausal women

Body composition	*SBP*	*DBP*	*Fasting insulin*	*TG*	*TC*	*LDL-C*	*hsCRP*
FM (kg)							
Pre-meno	0.264[a]	0.292[a]	0.629[A]	0.502[A]	0.459[A]	0.394[A]	0.592[A]
Post-meno	–0.092[#]	0.028	0.380[B#]	0.081[#]	–0.120[#]	–0.079[#]	0.198
FM (%)							
Pre-meno	0.198	0.246[a]	0.509[A]	0.357[A]	0.462[A]	0.451[A]	0.528[A]
Post-meno	–0.123[#]	0.006	0.318[B]	0.001	–0.073[#]	–0.053[#]	0.226[b]
Trunk fat (%FM)							
Pre-meno	0.443[A]	0.507[A]	0.562[A]	0.585[A]	0.199	0.128	0.504[A]
Post-meno	–0.002[#]	0.118	0.358[B]	0.525[B]	0.126	0.004	0.067[#]
Arm fat (%FM)							
Pre-meno	0.209	0.283[a]	0.156	0.203	0.190	0.260[a]	0.400[A]
Post-meno	0.131	0.158	0.215[b]	0.076	–0.098	–0.076[#]	–0.023[#]
Gynoid (%FM)							
Pre-meno	–0.449[A]	–0.531[A]	–0.615[A]	–0.591[A]	–0.242[a]	–0.164	–0.679[A]
Post-meno	–0.158	–0.107	–0.388[B]	–0.450[B]	0.023	0.137[#]	0.074[#]
VAT (cm)^2							
Pre-meno	0.415[A]	0.436[A]	0.737[A]	0.635[A]	0.411[A]	0.339[A]	0.597[A]
Post-meno	–0.047[#]	0.037[#]	0.519[B]	0.336[B]	–0.086[#]	–0.098[#]	0.243[b]
SAT (cm)^2							
Pre-meno	0.274[a]	0.334[A]	0.601[A]	0.533[A]	0.430[A]	0.369[A]	0.605[A]
Post-meno	–0.117[#]	0.063	0.387[B]	0.132	–0.059[#]	–0.040[#]	0.231[b]

Values are Spearman's correlation coefficients. %FM, expressed as percentage of sub-total fat mass (FM). SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
[a]$p < 0.05$ and [A]$p < 0.01$ for pre-menopausal women; [b]$p < 0.05$ and [B]$p < 0.01$ for post-menopausal women; [#]$p < 0.05$ for age × body composition interaction.

to the greatest variance in triglyceride concentrations (13%). Additionally, leg %FM also accounted for the greatest variance in HDL-C (14%) levels. Body composition did not add to variance in TC and LDL-C concentrations above that of age and gender.

There were gender-specific differences in the associations between body fat distribution and measures of cardiometabolic risk. While fat mass (kg) and abdominal SAT were associated with two-hour glucose (Fig. 1A, C), HOMA-IR (Fig. 1B, D) and fasting insulin levels in both men and women, the association was stronger in men compared to women (all interactions $p \leq 0.027$). Conversely, the associations between serum triglycerides and the distribution of body fat were significant in women, but not in men. Specifically, central adiposity measures (trunk %FM and android %FM) were positively associated with serum triglyceride concentrations (Fig. 2A, B, all interactions $p \leq 0.014$), and peripheral fat mass (leg %FM and gynoid %FM) were negatively associated with serum triglyceride levels (Fig. 2D, E, both interactions $p \leq 0.022$) in women, but not in men. The association between VAT and triglyceride concentrations was stronger in women than men (Fig. 2C, interaction $p = 0.012$).

The associations between body composition and cardiometabolic risk factors in pre-and post-menopausal women are shown in Table 4. For the most part, the association between body fat distribution and cardiometabolic risk did not differ between the pre- and post-menopausal women. Significant interactions were however seen between fat mass (kg), central fat distribution (%FM, trunk %FM, VAT and SAT area) and SBP (all interactions $p \leq 0.042$) and VAT and DBP (interactions $p = 0.030$), such that these were significant in pre-menopausal women but not in post-menopausal women.

Similarly, fat mass (kg), fat mass (%), VAT and SAT were associated with TC (all interactions $p \leq 0.002$) and LDL-C levels (all interactions $p \leq 0.007$) in pre-menopausal women only. Fat mass (kg) was associated with fasting insulin in both pre- and post-menopausal women, but the association was stronger in pre- than post-menopausal women (interaction $p = 0.019$), while fat mass (kg) was associated with triglyceride concentrations in pre-menopausal women only (interaction $p = 0.016$). Peripheral fat (arm %FM and gluteofemoral %FM) was associated with LDL-C (both interaction $p \leq 0.032$) and hsCRP levels (both interactions $p \leq 0.012$) in pre- but not post-menopausal women.

Discussion

This is the first study to investigate the relationship between body composition and cardiometabolic risk profile in mixed-ancestry South Africans. The main findings of the study are that body fat and, in particular central adiposity, were associated with unfavourable cardiometabolic risk profiles, while lower-body peripheral fat was associated with favourable risk profiles. However, the associations between body fat distribution and cardiovascular risk profile differed by gender and menopausal status, such that the associations were stronger in men and pre-menopausal women.

Although the women in our sample had nearly twice as much body fat mass, and had higher obesity rates than the men, the prevalence of cardiometabolic risk factors was similar between genders (apart from two-hour glucose and HDL-C concentrations being higher in women). This may be explained by the fact that despite marked differences in total body fat, VAT area was similar in men and women. Indeed, VAT was the most consistent and significant correlate of cardiometabolic risk (insulin resistance, glucose tolerance, triglyceride and HDL-C concentrations) in this sample. Furthermore, the association between VAT and cardiometabolic risk did not differ by gender.

Similarly, a recent study among Korean men and women showed that DXA-derived VAT was the best correlate of diabetes and pre-diabetes.[42] Likewise, the meta-analysis by Zhang and co-workers[8] supports VAT as the strongest correlate of insulin resistance, followed by total fat mass. The mechanisms linking VAT accumulation to metabolic complications include a higher production of pro-inflammatory cytokines and higher lipolytic activity compared to SAT, with the consequent increase in cytokine and free fatty acid delivery to the hepatic portal system impacting on insulin sensitivity.[5] VAT is also proposed to be a marker of insulin resistance as a consequence of lipotoxicity, in particular an increase in fat deposition in the liver.[5]

In contrast to VAT, women had more abdominal SAT than men.[14,15] Notably, the relationship between both total adiposity and abdominal SAT and insulin resistance was stronger in men than women. These differences may relate to the fact that oestrogens regulate insulin sensitivity and that female adipocytes are more insulin sensitive compared with male adipocytes.[43] Alternatively, the gender-specific relationship between abdominal SAT and insulin resistance could, in part, be explained by the fact that men have greater deep SAT (dSAT) and less superficial SAT (sSAT) than women.[44]

Nazare *et al.* showed that of the two SAT layers, dSAT had a higher association with inflammation and oxidative stress, suggesting that dSAT is an important determinant of the

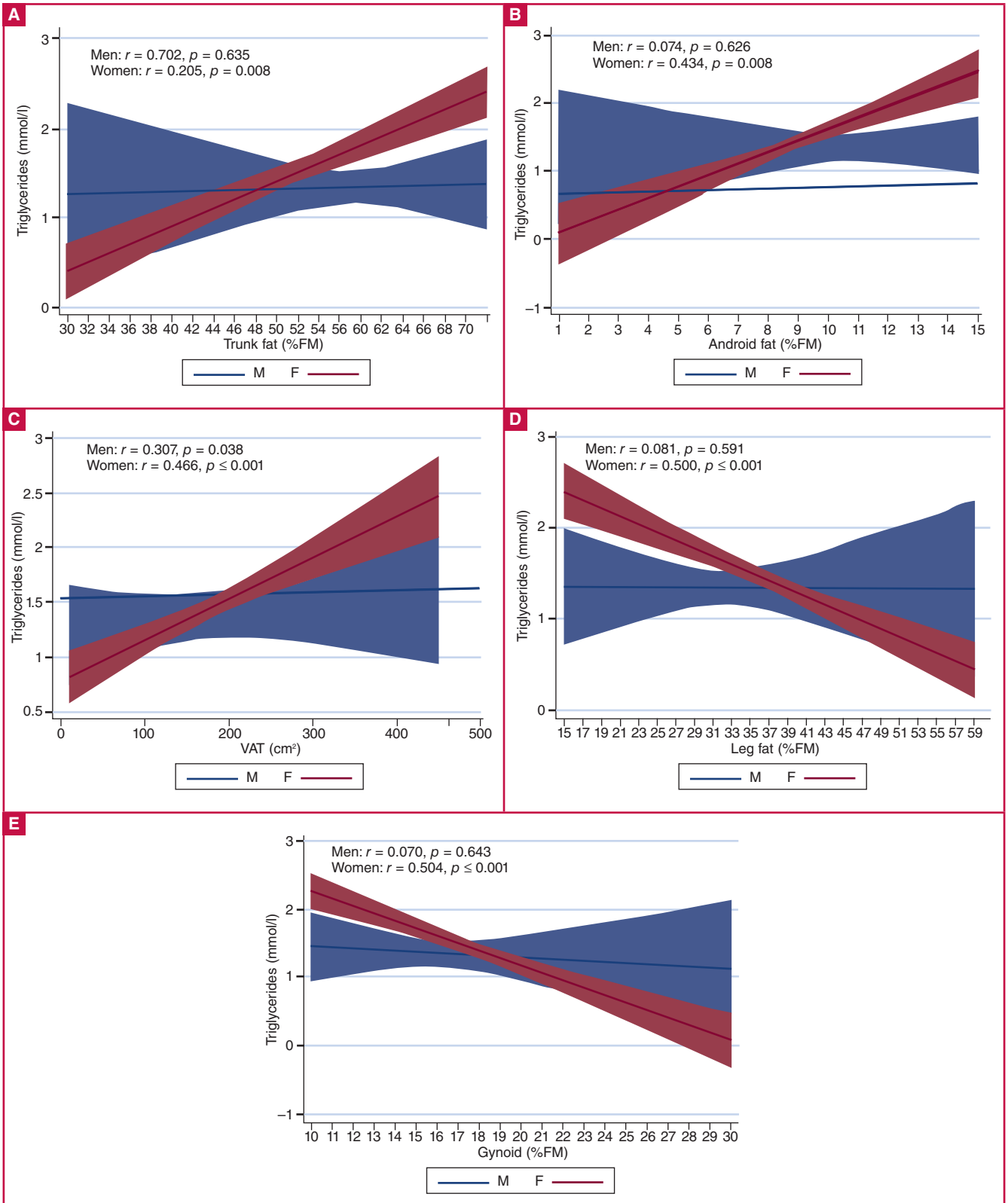

Fig. 2. Gender-specific associations between serum triglyceride concentrations and trunk % fat mass (%FM) (A), android %FM (B), visceral adipose tissue area (VAT) (C), leg %FM (D), and gynoid %FM (E).

MetS.[22] Accordingly, abdominal SAT should be considered as two functionally distinct compartments rather than a single entity.[22] A suggestion for further investigation in this population would be to explore the role of sSAT and dSAT using alternative imaging methods, such as computerised tomography or magnetic resonance imaging, as DXA is unable to differentiate between sSAT and dSAT.

Unlike associations with insulin sensitivity, the associations

between measures of body fat distribution (VAT, android, gynoid and leg %FM) and triglyceride concentrations were more pronounced in women than men. This finding is supported by the results of the Framingham Heart study,[45] where the relationship between VAT in particular and triglyceride concentrations was stronger in women than men, likely explained by the higher rates of lipolysis of VAT in women compared to men.[46]

Greater lower-body peripheral fat mass was associated with a lower cardiometabolic risk, commensurate with findings from previous studies in African American and Caucasian men and women.[47] Similarly, the protective effect of lower-body peripheral fat was observed in a large sample of Asian men and women, showing that those with the MetS had less lower-body peripheral fat that those without the MetS.[13]

Notably, the study by Shorr *et al.*,[48] which examined the differences between gender, body composition and cardiometabolic risk, showed the protective effect of lower-body fat to be stronger in women than men, which supports our study results. The lower-body fat depot is seen as a 'metabolic sink', which traps excess free fatty acids due to the increased lipoprotein lipase activity and lower lipolytic activity in this depot compared to the abdominal fat depot, thus protecting other tissues from lipid overflow and insulin resistance associated with ectopic lipotoxicity.[11,12,44] The protective effect of lower-body peripheral fat on triglyceride concentrations was however not observed in the sample of men, who had significantly less lower-body peripheral fat than women.

We found positive associations between arm fat and cardiometabolic risk, in particular insulin resistance, similar to those found with central adiposity. A possible explanation for this may be that upper-body adiposity is more sensitive to lipolysis and secretes a greater number of inflammatory cytokines.[49] Accordingly, not all peripheral fat may be regarded as protective and these differences should be further investigated.

Contrary to the findings for triglyceride and HDL-C concentrations, TC and LDL-C concentrations were not associated with body fat in either men or women. This is at variance with findings from similar studies in other ethnic groups,[50] but similar to those shown in black SA women.[27] These findings suggest that factors other than body fat and its distribution, including genetics, dietary intake, physical activity and smoking influence HDL-C, TC and LDL-C concentrations.

Commensurate with the decline in oestrogen following menopause, the post-menopausal women had greater VAT and lower gynoid %FM compared to pre-menopausal women, corresponding to their greater cardiometabolic risk, as previously demonstrated.[18,19] However, the association between body fat distribution and cardiometabolic risk was weaker in the post- compared to pre-menopausal women. A possible explanation for this is that as oestrogen levels decline and levels of bioavailable testosterone increase at menopause, this results in a shift in body weight and body fat distribution and disruptions in glucose regulation.[43] Interestingly, studies have shown that aging and lack of physical activity rather than menopause are the main reasons for weight gain and obesity in midlife women.[19]

This study adds to the literature the associations between body composition and cardiometabolic risk factors in the mixed-ancestry population, which previously had not been researched. In particular, the women in our study had higher VAT than the men, which is in contrast to other studies and ethnicities.[48] This is possibly due to the vast difference in total body fat between men and women, which may be unique in this sample. Additionally, post-menopausal women had increased VAT compared to pre-menopausal women, which is commensurate with recent literature.[51] In clinical practice the importance of preventing weight gain and centralisation of body fat prior to menopause should be highlighted. Even though the women in our study had substantially more abdominal SAT, the relationship between abdominal SAT and insulin resistance was stronger in the men, a finding similar to that of the Netherlands Epidemiology of Obesity study.[52]

The strengths of the study include the proven accuracy of DXA to measure body composition, and the use of robust analytical approaches to carefully explore the targeted associations. Although there were multiple comparisons, the relationships were consistent, which suggests that false-positive results were unlikely.

Possible limitations were the cross-sectional nature of the study and the inclusion of a convenient sample of women and only a small sample of men. However, this is typical of a South African population survey in which more women are usually included than men.[31] Furthermore, the gender disparities in obesity prevalence shown in this study are similar to those reported in the national prevalence data.[53]

We did not have an objective measure of menopausal age. These findings could therefore reflect an age effect and warrant further investigation. We lacked information on important potential confounders such as socio-economic status, diet, physical activity and smoking, which are known to affect body fat and cardiometabolic risk. In addition, we did not adjust for medication use, but the participants were instructed not to take any medications prior to testing.

Conclusion

Central fat mass was associated with increased cardiometabolic risk, and lower body peripheral fat mass was associated with reduced risk. However, these associations were influenced by gender and menopausal status. Notably, VAT was the most consistent and significant correlate of insulin resistance. Future studies should focus on the mechanisms underlying the gender-specific associations between SAT (in particular dSAT and sSAT) and cardiometabolic risk. Additionally, the relationship between DXA-derived VAT and SAT and simpler anthropometry measurements to predict cardiometabolic risk should be investigated. Specific VAT cut-off points for cardiometabolic risk in the mixed-ancestry populations should be derived in an effort to identify high-risk individuals.

We thank the Bellville South (Ward 009) community for participating in the study. We are also grateful to the Bellville South Community Health Forum for supporting the engagement with the Bellville South community.

This research project was funded by the South African Medical Research Council (SAMRC) with funds from National Treasury under its Economic Competitiveness and Support Package (MRC-RFA-UFSP-01-2013/ VMH Study) and strategic funds from the SAMRC received from the South African National Department of Health. Any opinion, finding and conclusion or recommendation expressed in this material is that of the author(s) and the SAMRC does not accept any liability in this regard. FED was funded by the Cape Peninsula University of Technology research fund (URF).

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Significant financial stress associated with 13-fold higher odds of having a heart attack

Significant financial stress is associated with a 13-fold higher odds of having a heart attack, according to research presented at the 18th Annual Congress of the South African Heart Association.

'The role of psychosocial factors in causing disease is a neglected area of study in South Africa, perhaps because there are so many other pressing health challenges such as tuberculosis and HIV,' said lead author Dr Denishan Govender, associate lecturer, University of the Witwatersrand, Johannesburg.

'The INTERHEART study showed that psychosocial factors are independently associated with acute myocardial infarction (heart attack) in Africa but as far as we are aware there are no other published local data,' said last author Professor Pravin Manga, professor of cardiology, University of the Witwatersrand.

This study included 106 patients with acute myocardial infarction who presented to a large public hospital in Johannesburg. A control group of 106 patients without cardiac disease was matched for age, gender and race. All participants completed a questionnaire about depression, anxiety, stress, work stress and financial stress in the previous month. The Likert scale was used to grade the experience of each condition.

Regarding financial stress, patients were graded with no financial stress if they were coping financially; mild financial stress if they were coping financially but needed added support; moderate financial stress if they had an income but were in financial distress; and significant financial stress if they had no income and at times struggled to meet basic needs. Levels of psychosocial conditions were compared between groups and used to calculate associations with having a heart attack.

Self-reported stress levels were common, with 96% of heart attack patients reporting any level of stress, and 40% reporting severe stress levels. There was a three-fold increased risk of myocardial infarction if a patient had experienced any level of depression (from mild to extremely severe) in the previous month compared to those with no depression.

Both work stress and financial stress were associated with a higher risk of acute myocardial infarction. The odds of myocardial infarction was 5.6 times higher in patients with moderate or severe work stress compared to those with minimal or no stress. Patients with significant financial stress had a 13-fold higher odds of having a myocardial infarction.

Dr Govender said: 'Our study suggests that psychosocial aspects are important risk factors for acute myocardial infarction. Often patients are counselled about stress after a heart attack but there needs to be more emphasis prior to an event. Few doctors ask about stress, depression or anxiety during a general physical and this should become routine practice, like asking about smoking. Just as we provide advice on how to quit smoking, patients need information on how to fight stress.'

continued on page 335…

Fluorine-18 fluorodeoxyglucose positron emission tomography in assessing myocardial viability in a tertiary academic centre in Johannesburg, South Africa: a pilot study

Dineo Mpanya, Nqoba Tsabedze, Carlos Libhaber, Brenda Kagodora, Mboyo-Di-Tamba Vangu

Abstract

Background: Positron emission tomography detects patients with myocardial contractile dysfunction secondary to ischaemic heart disease who may benefit from coronary revascularisation.
Methods: We reviewed technetium-99m sestamibi single-photon emission computed tomography (SPECT) and fluorine-18 fluorodeoxyglucose (F18-FDG) positron emission tomography (PET) data from 236 patients imaged between January 2009 and June 2015. The patients were grouped into three groups: no evidence of viability, viability 1–10% and viability > 10%.
Results: Viability exceeding 10% was evident in 55% of the patients. On multivariate analysis, aspirin intake [OR: 1.92; 95% CI: 1.08–3.41; $p = 0.026$] and hypertension [OR: 1.89; 95% CI: 1.07–3.33; $p = 0.029$] were clinical factors associated with the presence of myocardial viability.
Conclusion: Our study demonstrated that F18-FDG PET was able to identify 55% of patients with ischaemic heart disease with viability in more than 10% of the total myocardium when using a 17-segment model.

Keywords: positron emission tomography, fluorine-18 fluorodeoxyglucose, myocardial viability, hibernation

Submitted 13/10/18, accepted 8/5/19
Published online 12/6/19
Cardiovasc J Afr 2019; **30**: 331–335 www.cvja.co.za

DOI: 10.5830/CVJA-2019-029

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Positron emission tomography (PET) is a non-invasive molecular imaging modality that may be used to distinguish myocardial infarction from myocardial hibernation in patients with ischaemic heart disease. Regions of the myocardium with hibernating cells demonstrate preserved fluorine-18 fluorodeoxyglucose (F18-FDG) uptake while lack of F18-FDG uptake represents infarcted tissue.[1,2] Much controversy surrounds the clinical utility of PET in directing the management of stable coronary artery disease complicated with cardiomyopathy.

Coronary revascularisation of hibernating myocytes is associated with improved patient survival.[3,4] However, some studies have failed to show a reduction in cardiac death, myocardial infarction or recurrent hospitalisation for a cardiac cause, when comparing PET-guided management versus standard of care.[3,5-7] The clinical benefit of PET in guiding the management of patients with ischaemic cardiomyopathy has never been assessed in Johannesburg, South Africa. In this preliminary work, we aimed to report on our experience with the use of F18-FDG PET for the evaluation of myocardial viability in patients with ischaemic heart disease.

Methods

We conducted a retrospective analysis of hospital medical records for 240 consecutive patients referred for evaluation of myocardial viability in the Department of Nuclear Medicine and Molecular Imaging at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The medical records reviewed were from January 2009 to June 2015. We included all patients who were 18 years of age or older who had had a prior resting perfusion study with technetium-99m sestamibi (Tc-99m sestamibi) gated single-photon emission computed tomography (SPECT), subsequently followed by cardiac imaging with F18-FDG PET.

A total of four patients did not meet the inclusion criteria. One patient had viability imaging assessed with a different radiopharmaceutical agent (thallium-201 chloride), another had a resting perfusion study done outside the CMJAH referral network, and two patients had missing perfusion scan results (Fig. 1).

All patients had ischaemic heart disease as documented by a clinical history of myocardial infarction, resting and stress electrocardiograms (ECG), echocardiography or angiography. Clinical information was collected from in- and out-patient medical records. The referral centres included the CMJAH, Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). These centres are all part of the clinical academic complexes of the University of the Witwatersrand in Johannesburg, South Africa. Ethical clearance was awarded by the University of the Witwatersrand Human Research Ethics Committee.

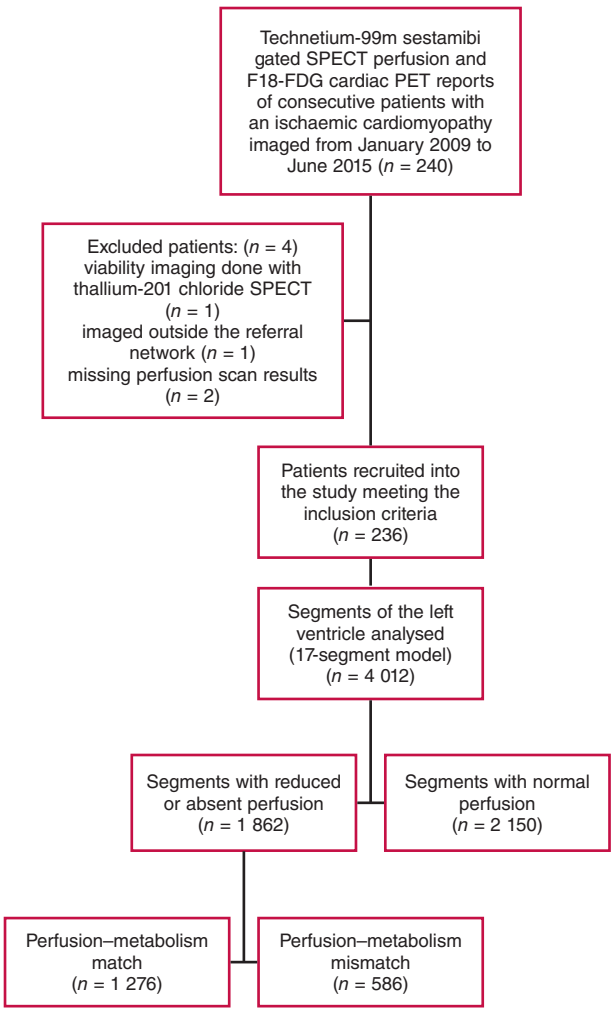

Fig. 1. Flow chart of the study showing patients referred for imaging with technetium-99m sestamibi gated single-photon emission computed tomography (SPECT) and fluorine-18 fluorodeoxyglucose positron emission tomography (F18-FDG PET). Segments demonstrating normal perfusion are considered viable and were not subjected to further analysis on PET imaging.

For resting gated SPECT myocardial perfusion imaging, empirical radioactivity of 555–1 110 MBq of Tc-99m sestamibi was administered intravenously. After a delay of approximately 60 minutes, patients were positioned supine with both arms raised above the head. ECG gated myocardial perfusion data was acquired with a dual-head gamma camera (General Electric Hawkeye, GE) equipped with a low-energy, high-resolution collimator. Twenty-four datasets in frame mode were acquired per cardiac cycle at 30 seconds per step. Data were stored in a 64 × 64 matrix. A 17-segment model was used to analyse the myocardium of the left ventricle.

Perfusion defects were scored between 0 and 4. A Tc-99m sestamibi uptake score of 0 represents normal perfusion; 1 is allocated when there is equivocal or mildly reduced uptake. A score of 2 indicates moderately reduced uptake, 3 represents severely reduced uptake and a score of 4 is assigned when there is absent uptake. Patients demonstrating evidence of transmural perfusion defects (scores 3 and 4) concomitantly with abnormal wall motion were then selected for further imaging with PET. This approach was done to exclude patients with a non-ischaemic dilated cardiomyopathy.

For cardiac PET imaging, fasting blood glucose levels were used to determine the total dose for oral glucose loading. Patients received an oral glucose dose of 25–75 g of dextrose monohydrate glucose (Medicolab) diluted in 200 ml of water. This was then followed by a finger-prick to determine the blood glucose level. F18-FDG radioactivity of 185–370 MBq was then injected intravenously.

After a delay of approximately 45 minutes from the time of the radiopharmaceutical injection, patients were positioned supine with both arms raised above the head and a Siemens Biograph Somaton Sensation 40 PET/CT camera was used for the acquisition of cardiac PET images. These images were acquired in three-dimensional mode for 10 minutes per bed position. A low-dose computed tomography was used for attenuation correction. The images were then segmented in the short-axis, vertical and longitudinal long-axis planes.

Each segment of the myocardium was also scored between 0 and 4, where a score of 0 represents preserved FDG uptake and 4 represents absent FDG uptake. The segments of the myocardium with a Tc-99m sestamibi uptake score that was more severe than the reduction in FDG uptake by one or more points was considered viable (Fig. 2).

The percentage of total viable myocardium was calculated by dividing the number of segments demonstrating a perfusion–metabolism mismatch by 17. We subsequently multiplied the value obtained by 100 to obtain a percentage of viable myocardium. We further classified patients into those with viability exceeding 10% of the total myocardium, less than 10% viability of the total myocardium and those with no viable segments.

Statistical analysis

The statistics were generated with STATA MP version 13.0 (StataCorp, Texas). Normally distributed continuous variables were summarised as mean and standard deviation. The median and interquartile ranges were used for continuous variables with a skewed distribution. The chi-squared test was used to compare categorical variables. Both univariable and multivariable regression analyses were used to find independent predictors of myocardial viability. Confidence intervals were calculated at 95% interval levels and differences were considered statistically significant at a p-value of < 0.05.

Results

The study population consisted of 236 patients. There were 196 (83.1%) males and the mean age was 59.1 ± 11 years. More than half of the patients were Caucasians (53.0%), with only 13.6% classified as black. The median fasting blood glucose level was 5.8 mmol/l (interquartile range: 5.2 – 6.9). The mean systolic and diastolic blood pressure was 127.0 ± 22.3 and 77.5 ± 13 mmHg, respectively. The rest of the demographic and clinical parameters are summarised in Table 1.

Myocardial perfusion and cardiac PET imaging findings: A total of 4 012 segments of the left ventricle were evaluated for the presence of perfusion defects; 1 862 segments had perfusion

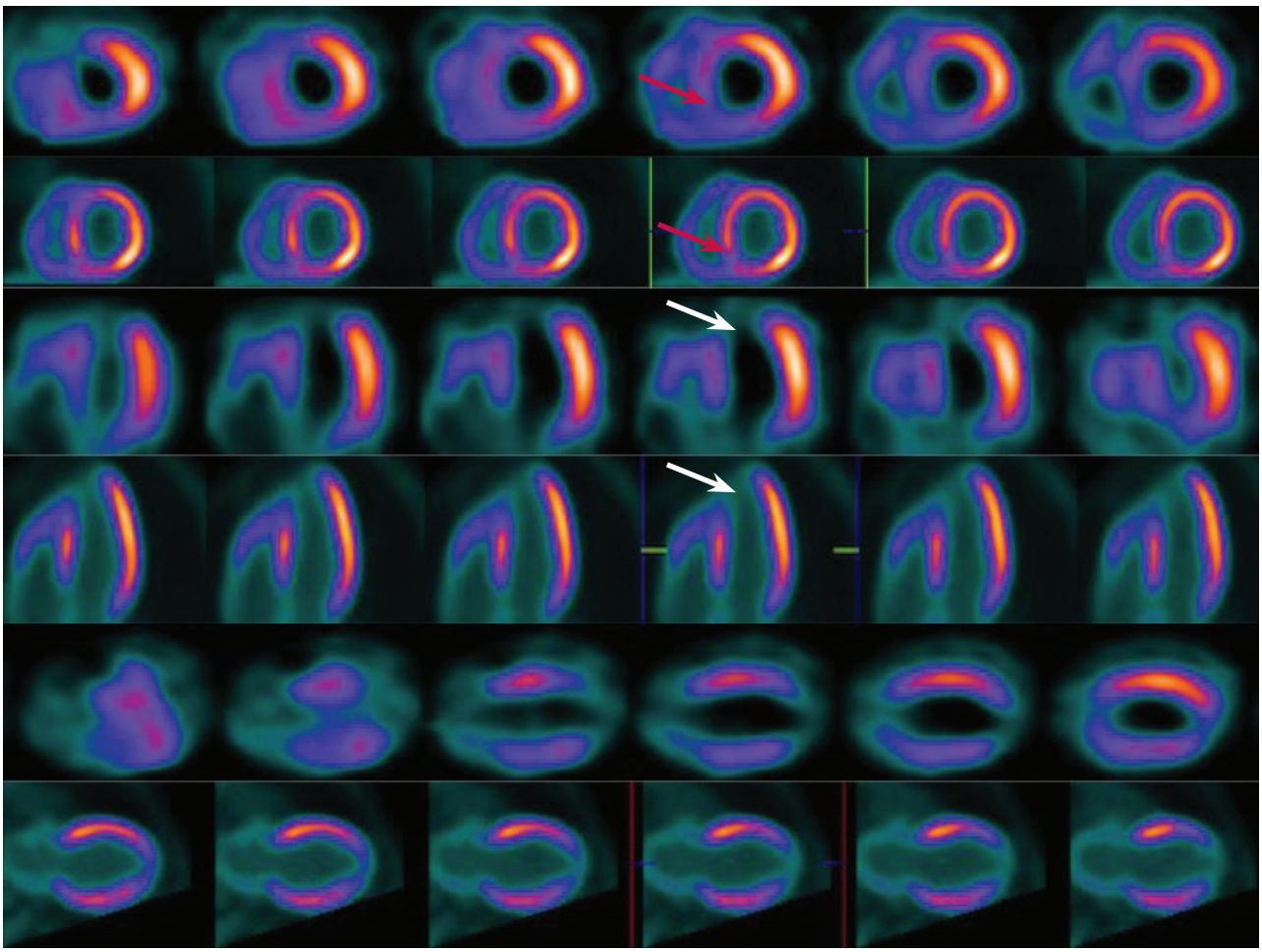

Fig. 2. Resting technetium-99m sestamibi gated single-photon emission computed tomography (SPECT) perfusion images in the first, third and fifth rows. Fluorine-18 fluorodeoxyglucose positron emission tomography (F18-FDG PET) cardiac images (second, fourth and sixth rows). All segments of the myocardium with reduced perfusion demonstrate a perfusion–metabolism mismatch pattern (myocardial viability) (red arrows), except the apex with matched perfusion and metabolism (infarcted tissue) (white arrows).

defects. Global hypokinesia was evident in 52.5% of patients. There were 183 (77.5%) patients with a left ventricular ejection fraction (LVEF) less than 40%. One hundred and thirty-one patients (55.5%) had viable myocardium exceeding 10% of the total myocardium. This translated to a perfusion–metabolism mismatch pattern (hibernating myocardium) seen in 586 of the 1 862 segments with perfusion defects (31.5%).

Predictors of myocardial viability: The univariable analysis showed an association between myocardial viability and hypertension, diabetes mellitus, oral beta-blocker therapy, aspirin, statins and the resting LVEF. Aspirin intake and hypertension were the only independent predictors of viable myocardium in the multivariable regression model (Tables 2, 3).

Discussion

In our pilot study, the prevalence rate of myocardial viability was 55.5%. Auerbach *et al*. previously reported a myocardial viability prevalence rate of 55.0% (using a 19-segment model) in patients with ischaemic heart disease.[8] Schinkel *et al*. also used PET to assess the prevalence of myocardial hibernation in 104 patients with ischaemic heart disease and reported a prevalence of 61%.[9] Unlike our study, Schinkel *et al*. used a 16-segment model and functionally significant myocardial viability was defined as the presence of viability in four or more myocardial segments.

Despite different cut-off values to define functionally significant myocardial viability, our study cohort had similar demographic and clinical characteristics to the two European study populations mentioned above. These similarities included age, gender, ethnicity and the extent of left ventricular systolic dysfunction.[8,9]

PET is a well-established, non-invasive tool for evaluation of myocardial viability in patients with coronary artery disease. Patients with segments of the myocardium demonstrating reduced or absent perfusion and preserved F18-FDG uptake are subsequently selected for coronary revascularisation. Percutaneous coronary intervention or coronary artery bypass grafting have been associated with an improvement in left ventricular function.[10]

Table 1. Baseline characteristics of patients according to myocardial viability

Variable	*Overall population* (n = *236*)	*No viability, 0%* (n = *91*) *(38.6%)*	*Viability, 1–10%* (n = *14*) *(5.9%)*	*Viability, > 10%* (n = *131*) *(55.5%)*	p-*value*
Male, *n* (%)	196 (83.1)	75 (82.4)	11 (78.6)	107 (81.7)	0.613
Ethnicity, *n* (%)					0.156
Caucasian	125 (53.0)	56 (61.5)	7 (50.0)	62 (47.3)	
Indian	71 (30.1)	21 (23.1)	7 (50.0)	43 (32.8)	
Black	32 (13.6)	12 (13.2)	0 (0.0)	20 (15.3)	
CV risk factors, *n* (%)					
Hypertension	115 (48.7)	33 (36.3)	10 (71.4)	72 (55.0)	0.005
Diabetes mellitus	62 (26.3)	17 (18.7)	5 (35.7)	40 (30.5)	0.101
Dyslipidaemia	93 (39.4)	29 (31.9)	11 (78.6)	53 (40.5)	0.004
Smoking	93 (39.4)	35 (38.5)	8 (57.1)	50 (38.2)	0.375
Family history	59 (25.0)	17 (18.7)	6 (42.9)	36 (27.5)	0.093
HIV	4 (1.7)	2 (2.2)	0 (0.0)	2 (1.5)	0.818
Medication, *n* (%)					
Beta-blocker	108 (45.8)	31 (34.1)	6 (42.9)	71 (54.2)	0.012
Aspirin	104 (44.1)	29 (31.9)	8 (57.1)	67 (51.2)	0.010
Statin	100 (42.4)	29 (31.9)	8 (57.1)	63 (48.1)	0.028
ACE inhibitor	81 (34.3)	26 (28.6)	5 (35.7)	50 (38.2)	0.332
Ca^{2+} antagonists	65 (27.5)	20 (22.0)	1 (7.1)	44 (33.6)	0.035
Nitrates	46 (19.5)	14 (15.4)	4 (28.6)	28 (21.4)	0.366
Wall motion, *n* (%)					
Akinesia	65 (27.5)	29 (31.9)	2 (14.3)	34 (26.0)	0.324
Dyskinesia	80 (33.9)	24 (26.4)	5 (35.7)	51 (38.9)	0.149
Global hypokinesia	124 (52.5)	49 (53.9)	9 (64.3)	66 (50.4)	0.582
LVEF (SPECT), *n* (%)					
Preserved (≥ 50%)	15 (6.4)	4 (4.4)	3 (21.4)	8 (6.1)	0.027
Mid-range (40–49%)	32 (13.6)	6 (6.6)	2 (14.3)	24 (18.3)	
Reduced (< 40%)	183 (77.5)	77 (84.6)	9 (64.3)	97 (74.1)	

Data are shown as absolute numbers and (percentage) for categorical variables. CV: cardiovascular; CAD: coronary artery disease; HIV: human immunodeficiency virus; Ca^{2+}: calcium; ACE: angiotensin converting enzyme; SPECT: single-photon emission computed tomography; LVEF: left ventricular ejection fraction. Family history refers to history of any cardiovascular disease.

Table 2. Univariable logistic regression

	Odds ratio	*Std error*	z	p-*value*	*Confidence interval*
LVEF ≤ 39%	2.25	1.98	0.93	0.354	0.40–12.6
LVEF 40–49%	6.00	5.74	1.87	0.061	0.92–39.2
LVEF ≥ 50%	2.29	2.30	0.82	0.413	0.32–16.5
Dyskinesia	1.67	0.47	1.82	0.069	0.96–2.91
Hypertension	1.76	0.47	2.13	0.033	1.04–2.96
Aspirin	1.92	0.52	2.43	0.015	1.13–3.26
Male	0.98	0.33	–0.04	0.964	0.51–1.92
Diabetes	1.68	0.51	1.65	0.098	0.91–3.02
Dyslipidaemia	1.10	0.30	0.37	0.712	0.65–1.87
Smoking	0.89	0.24	–0.43	0.664	0.52–1.50

LVEF: left ventricular ejection fraction; std error: standard error.

Table 3. Multivariable logistic regression

	Odds ratio	*Std error*	z	p-*value*	*Confidence interval*
LVEF ≤ 39%	1.90	1.70	0.71	0.478	0.33–11.0
LVEF 40–49%	4.90	4.91	1.58	0.113	0.68–34.9
LVEF ≥ 50%	3.87	4.13	1.27	0.205	0.48–31.3
Dyskinesia	1.66	0.51	1.64	0.102	0.90–3.04
Hypertension	1.89	0.55	2.19	0.029	1.07–3.33
Aspirin	1.92	0.56	2.23	0.026	1.08–3.41

LVEF: left ventricular ejection fraction; Std error: standard error.

The 2018 European Society of Cardiology (ESC) and the European Association for Cardiothoracic Surgery (EACTS) published guidelines on myocardial revascularisation. They recommended revascularisation in patients with stable angina or silent ischaemia with a large area of ischaemia, defined as ischaemia exceeding 10% of the left ventricular myocardium as detected by functional testing, as a class I recommendation, level of evidence B.[11] In these guidelines, the recommendation to revascularise based on viability imaging is not stated.

In our study, more than half of the patients referred for viability imaging had potentially reversible myocardial contractile dysfunction (viability > 10%). The decision to use 10% as a cut-off point was informed by findings by Ling *et al.*, who found that revascularisation of patients with hibernating myocardium that exceeded 10% of the total myocardium was associated with increased survival, mainly if revascularisation was performed not later than 92 days after PET imaging.[12]

Different study designs and variable interpretation of perfusion–metabolism images have resulted in conflicting study outcomes that have caused controversy surrounding the clinical utility of myocardial viability imaging. For example, the sub-study of the Surgical Treatment for Ischemic Heart Failure (STICH) trial failed to show a survival benefit in patients referred for viability imaging prior to revascularisation. In this trial, participants were referred for viability imaging with SPECT and dobutamine stress echocardiography. These modalities have been reported to have a lower diagnostic accuracy for detecting myocardial viability when compared to F18-FDG PET.[13]

In our study, there were two clinical variables found in the multivariable regression analysis to be significantly associated with myocardial viability. Patients on aspirin therapy were twice as likely to have viable segments. In a meta-analysis evaluating the benefit and risk of low-dose aspirin in patients with stable cardiovascular diseases, aspirin was associated with a 21% reduction in the risk of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death.[14] The anti-platelet effect of aspirin in culprit vessel lesions most likely improves myocardial perfusion and therefore viability.

Hypertension was another clinical variable significantly associated with myocardial viability. In a recent prospective study evaluating the role of F18-FDG PET in the assessment of myocardial viability involving 120 patients with myocardial contractile dysfunction, Srivatsava *et al.* reported a higher number of infarcted segments in hypertensive patients (p = 0.0005).[15] This is in contrast to our study findings, where hypertensive patients were almost twice as likely to have viable segments compared to patients without hypertension. We were unable to find a plausible explanation for this association.

All challenges and limitations associated with retrospective analysis of data apply in this study. Other relevant clinical parameters such as atrial fibrillation, high sensitivity C-reactive protein and a lipid profile were not available. Despite these limitations, our pilot study demonstrates that in the clinical management of patients with ischaemic heart disease referred for PET evaluation, there is a cohort of patients with hibernating or viable myocardium. Whether the clinical utility of PET has a significant impact on cardiovascular outcomes remains to be evaluated.

The next phase of our research study is to identify patients with viability who were subsequently revascularised and to evaluate the clinical impact of viability testing on functional cardiovascular outcomes and mortality rate. Gated SPECT and cardiac PET image analysis and interpretation using convolutional neural networks promise to be some of the future directions of nuclear medicine.

Conclusions

Our study demonstrated that F18-FDG PET was able to identify 55% of patients with ischaemic heart disease who had viability in more than 10% of the total myocardium when using a 17-segment model.

The authors thank Mr Desmond Maleeme and Mr Pitso Mokemane at the CMJAH Nuclear Medicine and Molecular Imaging for technical support, and Professor Jonathan Levin, Division of Epidemiology and Biostatistics in the School of Public Health at the University of the Witwatersrand for statistical support. We acknowledge the role of our colleagues at the CMJAH and the CHBAH, and thank the Division of Cardiology at the CMJAH and the HJH for their administrative support.

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… continued from page 330

Professor Manga said: 'There is growing recognition that many developing countries are experiencing an increasing prevalence of chronic diseases of lifestyle such as myocardial infarction, and South Africa is no exception. Our study shows that psychosocial aspects are an area of cardiovascular prevention that deserves more attention.'

Dr David Jankelow, chairman of the SA Heart 2017 congress, commented: 'We know that the depressed cardiac patient is at greater risk. We as clinicians need to identify them much earlier, so that they can be referred for appropriate intervention. Cardiac rehabilitation together with counselling and reassurance will play an important role as well.'

Professor Fausto Pinto, ESC immediate past president and course director of the ESC programme in South Africa, said: 'Psychosocial factors including stress at work, depression and anxiety contribute to the risk of developing cardiovascular disease and having a worse prognosis. European prevention guidelines say that psychosocial risk-factor assessment should be considered in people with, or at high risk of, cardiovascular disease to identify possible barriers to lifestyle change or adherence to medication.'

Source: European Society of Cardiology Press Office

Effects of cardiopulmonary bypass on pulmonary function in COPD patients undergoing beating heart coronary artery bypass surgery

Erdem Çetin, Levent Altınay

Abstract

Background: The aim of this study was to compare the effects of cardiopulmonary bypass (CPB) on the postoperative course of patients with chronic obstructive pulmonary disease (COPD) following coronary artery bypass graft (CABG) surgery.

Methods: This retrospective study included 375 COPD patients who underwent isolated CABG surgery with either on-pump (group 1) or off-pump beating heart techniques (group 2) between April 2014 and August 2018.

Results: Group 1 included 42 (11.2%) and group 2 included 333 (88.8%) patients. The mean mechanical ventilatory support times of groups 1 and 2 were 10.6 ± 36.2 and 5.1 ± 2.61 hours, respectively ($p = 0.561$). The mortality rates of groups 1 and 2 were 4.76% (two patients) and 1.50% (five patients), respectively ($p = 0.142$).

Conclusion: The on-pump beating heart CABG surgery did not affect the postoperative mechanical ventilatory support times in patients with COPD.

Keywords: chronic respiratory disease, coronary artery bypass surgery, beating heart coronary artery bypass, off-pump coronary artery bypass, mechanical ventilation

Submitted 11/2/19, accepted 8/5/19
Published online 24/5/19
Cardiovasc J Afr 2019; **30**: 336–340 www.cvja.co.za

DOI: 10.5830/CVJA-2019-030

Off-pump (OPCAB) and on-pump beating heart (ONBHCAB) coronary artery bypass graft (CABG) surgery have frequently been utilised in the last decades in order to eliminate the untoward effects of cardioplegia and ischaemia on the myocardium, such as impaired contractility or myocardial stunning.[1] On the other hand, cardiopulmonary bypass (CPB) has some detrimental pulmonary and systemic effects because of the inflammatory mediator activity triggered by the CPB itself.[2]

Although the presence of chronic obstructive pulmonary disease (COPD) is considered to be a high-risk factor for CABG surgery and it is related to poorer early postoperative outcomes,[3,4] some studies do not support this observation.[5,6] Patients are generally weaned from mechanical ventilatory support (MVS) as soon as they are able to continue breathing on their own, along with some other conditions such as stable haemodynamic status, total consciousness and fully recovered motor functions. The definition of prolonged mechanical ventilation (PMV) varies according to the time threshold selected and it is related to a postoperative mortality rate of up to 42%.[7] The incidence of PMV has been reported to be between 2.9 and 8.6% and the presence of a pre-operative respiratory disease has been found to be a risk factor for PMV.[8,9]

The aim of this study was to evaluate the effects of CPB on postoperative pulmonary function in a subgroup of CABG patients who all had COPD and were being operated on with beating heart techniques for surgical coronary artery revascularisation.

Methods

This study included 375 COPD patients who underwent isolated beating heart CABG surgery between April 2014 and August 2018 in a single cardiac surgery centre. Group 1 included 42 (11.2%) ONBHCAB patients and group 2 included 333 (88.8%) OPCAB patients. All operations were performed by the same surgical team with either OPCAB or ONBHCAB techniques. Patients who underwent emergency operations were excluded as spirometry data could not be obtained.

A diagnosis of COPD was confirmed with both medical history and spirometric analysis. Patients with dyspnoea, chronic cough and sputum production, history of exposure to tobacco smoke and with a post-bronchodilator ratio of forced expiratory volume in the first second and forced vital capacity (FEV_1/FVC) less than 0.70 were classified as having COPD. The severity of COPD airflow limitation was determined with regard to the FEV_1 value, as suggested by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) study[10] (Table 1).

All spirometric evaluations were performed pre-operatively and according to the criteria presented in the guidelines published by the American Thoracic Society (ATS)/European Respiratory Society (ERS).[11] Bronchodilator therapy was ceased before the test, as suggested in the guidelines (short-acting β-agonists or anticholinergic agents four hours, and long-acting β-agonists or oral therapy with aminophylline 12 hours before analysis).

Each patient was asked to perform a minimum of three blows. If eight manoeuvres had not produced a satisfactory set of results, the test was terminated since the results would be problematic.[12] In such cases, the test was repeated the following day. Patients who could not participate in the spirometry tests were excluded. Maximum FVC and FEV_1 values obtained from

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Table 1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) study classification

GOLD class	*Severity of airflow limitation*	*FEV_1 value (%)*
I	Mild	≥ 80
II	Moderate	50 ≤ FEV_1 < 80
III	Severe	30 ≤ FEV_1 < 50
IV	Very severe	< 30

three acceptable measurements were noted for the calculation. Recommendations in the ATS/ERS guidelines were followed for bronchodilator reversibility testing. The measurements were performed before (baseline measurement) and 15 to 20 minutes after the bronchodilator administration.

Patients were asked to inhale a dose of 100 µg salbutamol in one breath to total lung capacity after an incomplete expiration, to hold his/her breath for five to 10 seconds and then exhale. A total dose of 400 µg salbutamol was administered in four separate breaths via a metered-dose inhaler using a spacer. If the FEV_1 and/or FVC value changes were > 12% and 200 ml compared with baseline, it was identified as a significant bronchodilatation.[13] In such a case, the patient was accepted as asthmatic and excluded.[14]

The MVS time was defined as the time elapsed from the beginning of the postoperative period to the time of extubation. Patients were followed with 8–10 ml/kg tidal volume and 2–3 cm H_2O-positive end-expiratory pressure. Weaning from MVS was planned according to the following standard extubation criteria: the patient was expected to maintain stable gas exchange (checked by blood gas analysis, no hypercapnia, no hypoxia, no acidosis or alkalosis, partial pressure of oxygen > 150 mmHg when inspiratory oxygen fraction ≤ 0.5), have stable neurological and motor functions, and be in a stable haemodynamic status (effective urine output, arterial blood pressure and heart rate within expected values). If the patient could not be weaned from MVS after 48 hours, it was accepted as PMV.

Patients who had a history of one pack or more of tobacco product smoking in a day or tobacco smoke exposure were accepted as smokers and were grouped into active and passive smokers, respectively. Active smokers were patients who were tobacco product smokers at the time of the operation, and passive smokers were patients who had no history of tobacco product consumption but were exposed to tobacco smoke.[15,16] Patients who quitted smoking within a year before the CABG surgery were identified as ex-smokers and included in the passive-smoker group, as the benefits of smoking cessation have been most evident in the first year in COPD patients.[17]

Surgery

All patients were sedated with intravenous midazolam 2 mg prior to transport to the operating room. Invasive arterial blood pressure monitoring via a radial artery catheter, and 12-lead ECG, urinary output, pulse oximetry and capnography were established. General anaesthesia was induced with fentanyl 10 µg/kg, midazolam 0.1 mg/kg and rocuronium 1 mg/kg. Also, methylprednisolone 1 mg/kg and intravenous pheniramine were administered in order to prevent possible reactions after protamine administration.

In OPCAB surgery, after a median sternotomy, left internal mammary artery and saphenous vein grafts were harvested according to the number of target vessels. The bilateral internal mammary arteries were not used in any cases. As a standard protocol, 10 ml 15% magnesium sulfate and lidocaine 1 mg/kg were administered as intravenous infusion while the left internal mammary artery graft was being harvested to benefit the anti-arrhythmic effects of magnesium and lidocaine. The level of activated clotting time was maintained above 300 seconds with heparin (100–200 IU/kg) administration.

Two pericardial stay sutures with atraumatic needles were used to stabilise and elevate the heart. The heart was allowed to lean into the right hemithorax by creating an opening in the right pleura, and the patient's position was set at 20 degrees Trendelenburg if a circumflex artery bypass was necessary. The tidal volume was maintained in the range of 350 to 400 ml with high-frequency respiration to keep the heart stabilised. The patient's body temperature was kept between 34 and 36°C, mean arterial blood pressure was kept in the range of 60 to 90 mmHg and the heart rate was kept between 60 and 80 beats/min with esmolol infusion if necessary. The protocol of esmolol administration was 1 mg/kg initial bolus dose intravenous infusion over 30 seconds, followed by 0.15–0.3 mg/kg/min intravenous infusion, adjusted according to the heart rate.

After completion of all anastomoses, the heparin was neutralised with 50–100 IU/kg protamine administration. Low-molecular-weight heparin 1 × 0.6 cm^3 was administered to all patients four to six hours after admission to the intensive care unit (ICU), except for those who underwent a revision for postoperative haemorrhage. On the first postoperative day, 100 mg acetylsalicylic acid and 75 mg clopidogrel were ordered in the ICU.

In ONBHCAB surgery, the activated clotting time was maintained above 450 seconds. CPB was established after an ascending aortic and two-stage right atrial venous cannulas were placed. The patient's body temperature was kept between 34 and 36°C and mean arterial blood pressure between 60 and 90 mmHg. The heart rate was kept in the range of 60 to 80 beats/min with an esmolol infusion that was identical to the protocol followed in OPCAB patients. The tidal volume was maintained in the range of 350 to 400 ml with high-frequency respiration.

The first arterial blood gas measurement was performed while the patient was breathing operating room air. The following intra-operative arterial blood gas analyses were performed just after the initiation of general anaesthesia and every 30 minutes until the end of the operation. In the ICU, the first arterial blood gas measurement was performed just after the patient was admitted to the unit, and the following measurements were done every hour until the patient was weaned from MVS, and every six hours until the patient was transferred back to the ward. The threshold levels of pH and partial pressure of carbon dioxide were in the ranges of 7.35 to 7.45 and 38 to 42 mmHg, respectively. The criteria for re-intubation were partial oxygen pressure below 75 mmHg and oxygen saturation below 80% in arterial blood, accompanied by haemodynamic instability.

Statistical analysis

Statistical analysis of the data was performed with the Statistical Package for the Social Sciences (SPSS 16.0 Inc, Chicago, IL, USA) software. Categorical data are reported as numbers and percentages. Continuous data are reported as mean ± standard

deviation (SD). Data were tested with the Kolmogorov–Smirnov test for normal distribution. Non-parametric data of the groups were tested with the chi-squared test and parametric data were tested with the independent samples *t*-test; *p*-values < 0.05 were considered statistically significant.

Results

The main characteristics of the patients are presented in Table 2. Two groups were matched for all the demographic data except pre-operative left ventricular ejection fraction (LVEF) (significantly lower in group 1). Table 3 presents the postoperative data of the two groups. The mean ± SD of MVS, pH, stay in ICU, time in hospital and drainage amount were similar between the two groups. The groups included similar percentages of patients with PMV, number of grafts, postoperative revision, postoperative atrial fibrillation and mortality rate.

Two patients in group 1 and two in group 2 were re-intubated because of hypercapnia and hypoxia in arterial blood gas analysis. The two patients in group 2 could not be weaned from MVS because extubation criteria could not be achieved. One patient (2.4%) in group 1 could not be weaned from MVS for 240 hours and a tracheostomy cannula was placed. The patient died in the ICU due to cardiac failure. Another patient (0.3%) in group 2 needed MVS for 52 hours but he survived.

All patients with postoperative atrial fibrillation were administered amiodarone at a dose of 150 mg intravenous infusion over 10 minutes, then 0.5 to 1 mg/min infusion for 24 hours. The cardiac rhythm was converted to normal sinus rhythm in three (7.1%) patients in group 1 and four (1.2%) in group 2. Atrial fibrillation persisted in three (0.9%) patients despite the amiodarone therapy in group 2. These patients received oral amiodarone 2 × 200 mg tablets daily after three days of intravenous infusion and were discharged with oral anticoagulation.

Table 2. Demographic data of the patients

Variables	*Group 1 (n = 42)*	*Group 2 (n = 333)*	p-*value**
Age, years (mean ± SD)	60.98 ± 9.98	61.50 ± 9.13	0.390[α]
Male, *n* (%)	40 (95.2)	293 (88.0)	0.161
Pre-operative EF, % (mean ± SD)	32 ± 5	52 ± 7	< 0.001
COPD GOLD class			
I, *n* (%)	15 (35.7)	96 (28.8)	0.068
II, *n* (%)	22 (52.3)	207 (62.1)	0.359
III, *n* (%)	5 (12.0)	30 (9.1)	0.092
Diabetes mellitus, *n* (%)	26 (61.9)	168 (50.5)	0.162
Tobacco smoking			
Active, *n* (%)	5 (13.1)	59 (22.3)	0.432[µ]
Passive, *n* (%)	26 (83.9)	206 (77.7)	
Hypertension, *n* (%)	19 (45.2)	162 (48.6)	0.677
Hyperlipidaemia, *n* (%)	3 (7.1)	13 (3.9)	0.328
Thyroid gland dysfunction, *n* (%)	1 (2.4)	11 (3.3)	0.749
Chronic kidney disease, *n* (%)	3 (7.1)	12 (3.6)	0.271
Peripheral artery disease, *n* (%)	0 (0.0)	3 (0.9)	0.537

EF: ejection fraction; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease study.
*Mann–Whitney *U*-test was used to calculate the *p*-values as the data were non-normally distributed.
[α]The *t*-test was used to calculate the *p*-value [*t* (50.051 = –0.344, *p* = 0.731, 95% CI: –3.492, 2.453)].
[µ]Chi-squared test was used to calculate the *p*-value [$\chi^2(1) = 0.616$, *p* = 0.432].

All patients undergoing postoperative revision for bleeding were not extubated until the surgical intervention and the mean MVS time for these patients was 154 ± 256.35 hours (range from four to 450 hours). Postoperative properties of the patients are presented in Table 3.

Discussion

The results of this study suggest that pulmonary function in COPD patients undergoing CABG surgery with ONBHCAB was not significantly affected by CPB. The incidence of COPD in patients undergoing CABG surgery has been reported to be as high as 26.1% and the risk of postoperative and long-term morbidity and mortality increases with increasing age.[18-20] Adabag *et al*.[21] evaluated the results of 1 169 COPD patients undergoing CABG surgery and reported that the mortality risk was significantly higher in patients with moderate or severe COPD. However, Rosenthal *et al*.[22] reported no significant difference among in-hospital mortality rates of patients with or without co-morbidities, including COPD. Manganas *et al*.[6] reported that the mortality rate after CABG surgery was not affected by the presence or severity of COPD. In our study, the mortality rates were 4.76% in group 1 and 1.50% in group 2, but the difference was not statistically significant (*p* = 0.081).

The mean LVEF of group 1 was significantly lower than that of group 2 (32 ± 5 vs 52 ± 7%, *p* < 0.001). This was to be expected

Table 3. Postoperative data

Variables	*Group 1 (n = 42)*	*Group 2 (n = 333)*	p-*value*[α]
MVS time, hours (mean ± SD)	13.52 ± 39.97	7.81 ± 30.17	0.434
PMV*, *n* (%)	2 (4.76)	4 (1.20)	0.083
Arterial pH (mean ± SD)	7.41 ± 2.08	7.43 ± 3.11	0.287
ICU stay time, hours (mean ± SD)	19.26 ± 19.39	18.19 ± 31.67	0.464
HOS time, days (mean ± SD)	4.93 ± 2.09	4.71 ± 1.62	0.559
Drainage amount, ml (mean ± SD)	698.81 ± 162.48	682.28 ± 159.21	0.560
LIMA graft, *n* (%)	36 (85.72)	297 (89.24)	0.987
SVG number			
One SVG, *n* (%)	19 (45.24)	139 (41.74)	
Two SVGs, *n* (%)	16 (38.10)	127 (38.14)	
Three SVGs, *n* (%)	5 (11.90)	31 (9.31)	0.449[µ]
Four SVGs, *n* (%)	1 (2.38)	4 (1.20)	
Inotropic support			
One intoropic agent, *n* (%)	4 (9.52)	55 (16.52)	0.005[β]
More than one intoropic agent, *n* (%)	7 (16.67)	15 (4.50)	
IABP, *n* (%)	6 (14.29)	11 (3.30)	< 0.001
Postoperative revision, *n* (%)	0 (.00)	3 (0.90)	0.537
Postoperative atrial fibrillation, *n* (%)	3 (7.12)	7 (2.14)	0.056
Exitus**, *n* (%)	2 (4.76)	5 (1.50)	0.142

MVS: Mechanical ventilatory support; ICU: intensive care unit; HOS: hospital stay; LIMA: left internal mammary artery; SVG: saphenous vein graft; IABP: intra-aortic balloon pump; PMV: prolonged mechanical ventilation.
*Mean PMV times of groups 1 and 2 were 180 ± 84.85 h (range 120–240 h) and 241 ± 164 h (range 48–450) respectively (*p* = 0.643).
**The mortality rates of the groups were as follows: 4.8% (two patients) in group 1 and 1.5% (five patients) in group 2 (*p* = 0.142).
[α]Mann–Whitney *U*-test was used to calculate the *p*-values as the data were non-normally distributed.
[µ]Chi-squared test was used to calculate the *p*-value [$\chi^2(4) = 3.694$, *p* = 0.449].
[β]Chi-squared test was used to calculate the *p*-value [$\chi^2(2) = 10.690$, *p* = 0.005, Cramer's *V* = 0.169].

since the ONBHCAB technique was particularly chosen in patients with impaired left ventricular function. The OPCAB technique is speculated to be safe and had similar clinical results when compared with conventional CABG.[23-25] The in-hospital mortality rate of group 2 was consistent with other results reported in the literature.[26]

Another type of haemodynamic mechanical support for poor left ventricular function is the intra-aortic balloon pump counter-pulsation. The rate of intra-aortic balloon pump counter-pulsation in group 1 was significantly higher than in group 2 (14.29 vs 3.30%, respectively, $p < 0.001$). As the mean pre-operative LVEF was significantly lower in group 1, this result was predicted.

PMV is another problem in these patients. Saleh *et al*. reported the rate of PMV at 3.5 and 5.3% in moderate and severe COPD patients, respectively, and they found a significant difference when compared to normal patients.[9] Manganas *et al*.[6] defined PMV as mechanical ventilation over 48 hours and reported a non-significant difference between the rates of PMV, which they documented at 2.6 and 3.0% in patient groups with mild–moderate and severe COPD, respectively ($p = 0.37$). Two patients needed PMV in the study population, one patient (2.4%) in group 1 and one (0.3%) in group 2. This result was not statistically significant ($p = 0.081$).

In this study, the difference in the mean MVS times of the groups was not statistically significant but it was slightly longer in group 1. There were three postoperative revisions in group 2 and none in group 1. It seems that it did not significantly affect the mean MVS time of group 2 patients. The patients were followed with a mechanical ventilator setting similar to the traditional method, which was high tidal volume and low positive end-expiratory pressure, until weaning from MVS.[27]

Zupancich *et al*. suggested that mechanical ventilation itself may be a co-factor that influences inflammatory reactions after cardiac surgery.[28] They found higher inflammatory cytokine levels in patients followed with high tidal volume/low positive end-expiratory pressure than levels in patients followed with low tidal volume/high positive end-expiratory pressure. They also reported significantly higher partial pressure of carbon dioxide levels in arterial blood, causing respiratory acidosis in patients followed with low tidal volume/high positive end-expiratory pressure, compared to levels in patients followed with high tidal volume/low positive end-expiratory pressure. No respiratory acidosis occurred in this group of patients, however, the inflammatory cytokine levels could not be evaluated because of lack of data.

A serious limitation of this study is the retrospective design. Salivary cotinine levels or exhaled carbon monoxide levels could not be measured so objective data on the smoking status of the patients could not be acquired. Most of the patients could not clearly list their medications for COPD. The patients were followed up by lung disease specialists for COPD in other health centres after being discharged from hospital so follow-up data on their pulmonary function could not be retrieved.

Conclusion

OPCAB and ONBHCAB techniques can be safely utilised in CABG surgery instead of conventional techniques in selected patients. The ONBHCAB technique prevents the negative effects of cardioplegia on the heart while it provides the haemodynamic support of the CPB system. COPD has negative effects on postoperative outcomes of CABG surgery. No difference was found in MVS times of COPD patients operated with either the OPCAB or ONBHCAB technique, so it can be stated without hesitation that the ONBHCAB technique can be safely used in COPD patients with impaired left ventricular function.

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More aggressive statin therapy sometimes needed to fight 'bad' cholesterol

A study shows more aggressive treatment may be needed for a large number of patients taking statin medications, and that treatment could help reduce cases of cardiovascular disease, the leading cause of death in the US.

High levels of low-density lipoprotein cholesterol (LDL-C), sometimes called 'bad' cholesterol, are associated with cardiovascular disease. The new research finds a third of people in Indiana are not reaching a safe level of LDL-C while taking statin medications.

The collaboration by researchers at Merck, known as MSD outside the US and Canada, Regenstrief Institute, Indiana University School of Medicine and the University of North Carolina at Chapel Hill looked at electronic health records in the state of Indiana and found that about a third of people taking statins did not reach a therapeutic level of LDL-C. The researchers say these patients seem to be at an increased risk for cardiovascular disease events such as heart attack and stroke, and may represent an important and potentially preventable burden on healthcare costs.

Principal investigator and cardiologist from the University of North Carolina, Dr Ross Simpson, Jr, says this study adds to the body of evidence that many people are not getting adequate treatment for high cholesterol levels. 'This provides an opportunity for improving care, whether it's with higher doses, more aggressive treatments or new therapies.'

The study set out to determine how many patients on statins achieved the therapeutic threshold of LDL-C, estimate the number of potentially avoidable cardiovascular disease events if that threshold were reached, and forecast potential healthcare cost savings.

The team examined electronic health records from the Indiana Network for Patient Care for 86 000 patients who started taking statins. They found 33.7% of those people did not reach therapeutic levels of LDL-C (< 100 mg/dl = 2.59 mmol/l) after six to 18 months on therapy. In a high-risk subgroup, 58% did not reach a more stringent LDL-C standard (< 70 mg/dl = 1.81 mmol/l) commonly applied to them. Among patients who regularly took their statin therapy as directed, 24% of the full population and 51% of the high-risk subgroup did not meet their respective thresholds.

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The walking estimated limitation stated by history (WELSH): a visual tool to self-reported walking impairment in a predominantly illiterate population

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Abstract

Background: The prevalence of cardiovascular diseases is increasing in low-income countries. Various questionnaires to estimate walking capacity in patients are available in multiple languages but they are not suitable for illiterate patients.

Objective: The walking estimated limitation stated by history (WELSH) tool aims at rating individual walking disability using only drawings and four items.

Methods: A six-month prospective study was performed on new patients referred to the Department of Cardiology at the Centre Hospitalier Universitaire Sourô Sanou in Bobo-Dioulasso, Burkina Faso. We administered the WELSH tool after a short oral presentation in the patient's language or dialect. Thereafter, patients performed a six-minute walking test in the hospital corridor under the supervision of a nurse who was blinded to the results of the WELSH score. We performed a step-by-step multilinear regression analysis to determine the factors predicting maximal walking distance (MWD).

Results: There were 40 female and 10 male patients in this study. Their ages ranged from 54.8 ± 10.7 years. Only 32% of the patients had attended primary school. Most patients were classified as stage I to III of the New York Heart Association (NYHA) classification. The objective measurement of MWD during a six-minute walking test showed no association with the subjects' educational level, body mass index, NYHA stage or gender, but a significant correlation with the WELSH scores. The Spearman *r*-value for the WELSH score-to-MWD relationship was 0.605 ($p < 0.001$).

Conclusions: The WELSH tool is feasible and correlated with measured MWD in a population of predominantly illiterate patients.

Keywords: questionnaire, illiteracy, exercise, walking impairment, quality of life

Submitted 1/2/19, accepted 20/5/19
Published online 30/8/19
Cardiovasc J Afr 2019; **30**: 341–346 www.cvja.co.za

DOI: 10.5830/CVJA-2019-032

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The prevalence of diabetes, hypertension and their cardiovascular complications is increasing in Africa.[1-3] Coronary artery disease is projected to be the leading cause of disability-adjusted life years lost in low-income countries by 2030.[4] Estimation of walking disability in routine medical practice is of major interest, specifically in cardiovascular diseases. Among other available questionnaires, the walking estimated limitation calculated by history (WELCH) tool and the walking impairment questionnaire (WIQ) have been validated in different languages.[5-10] The WELCH tool compares favourably with the WIQ in terms of ease of use and scoring.[5,11,12] Unfortunately, all available questionnaires require the patient and/or healthcare provider to be able to read. Therefore they are unsatisfactory in countries with a high prevalence of illiterate people.

To the best of our knowledge, to date no standard questionnaire to estimate walking impairment has ever been developed that could be used by healthcare providers (nurses or technicians) and/or proposed for patients (children or adults) who are uncomfortable with reading or unable to read. Since illiteracy is still high in Burkina Faso, as in many sub-Saharan African countries,[13] we aimed to test an empirical new tool: the walking estimated limitation stated by history (WELSH). The WELSH tool is derived from the WELCH but is based on drawing (text-free). Furthermore, we wanted the WELSH score to be simple and calculable without the need for a computer.

The aim of this study was to estimate the applicability of the WELSH tool in a population of predominantly illiterate or low-literacy patients in Burkina Faso. The WELSH tool aims at evaluating walking impairment quickly by history. Although walking tests remain of interest, they are time consuming and do not necessarily reflect self-perceived impairment. Correlation of the New York Heart Association (NYHA) classification with walking capacity is very poor.[14] The WELSH tool would not replace the NYHA classification but, once validated as an applicable tool, it could be proposed as an easy method to analyse outcome under treatment in future studies.

Methods

A six-month prospective study was performed on new patients referred to the Department of Cardiology in the Centre Hospitalier Universitaire Sourô Sanou in Bobo-Dioulasso, Burkina Faso. The patients were referred for follow up of a confirmed cardiovascular disease.

Eligibility was age over 18 years, ability to read time on a clock/watch dial, ability to walk without physical assistance, and ability to understand the study goal and potential instructions. We did not include patients classified as NYHA stage IV[14] who had a recent history of unstable coronary syndrome or recent myocardial infarction.

In the context of the Burkina Faso healthcare system and due to the very low accessibility of investigative tools, most diagnoses remain unconfirmed. For this study we retrieved the diagnosis at referral and provided results for the few available functional investigations.

All investigators participating in the study were trained by the principal investigator on how to perform the investigations, complete the files and score the questionnaires. The questionnaire was first explained to the two technicians, who filled a minimum of 10 files and calculated the score with the principal investigator, before doing the tests alone.

For each included patient, we recorded general social and anthropometric characteristics. We used the NYHA classification as a descriptive tool of self-reported limitation.[15] This tool is commonly used as a method for functional classification in patients with heart disease.[14]

We used the concept of the WELCH questionnaire to build a new form based on only simple drawings. The original WELCH included four items. The first three items proposed various durations that patients felt they were able to perform at different walking speeds without stopping, and the fourth item questioned the usual walking speed. We designed the WELSH tool on the same concept.

The WELSH tool requires the patients to estimate their walking time on an empty watch dial from zero to 59 minutes

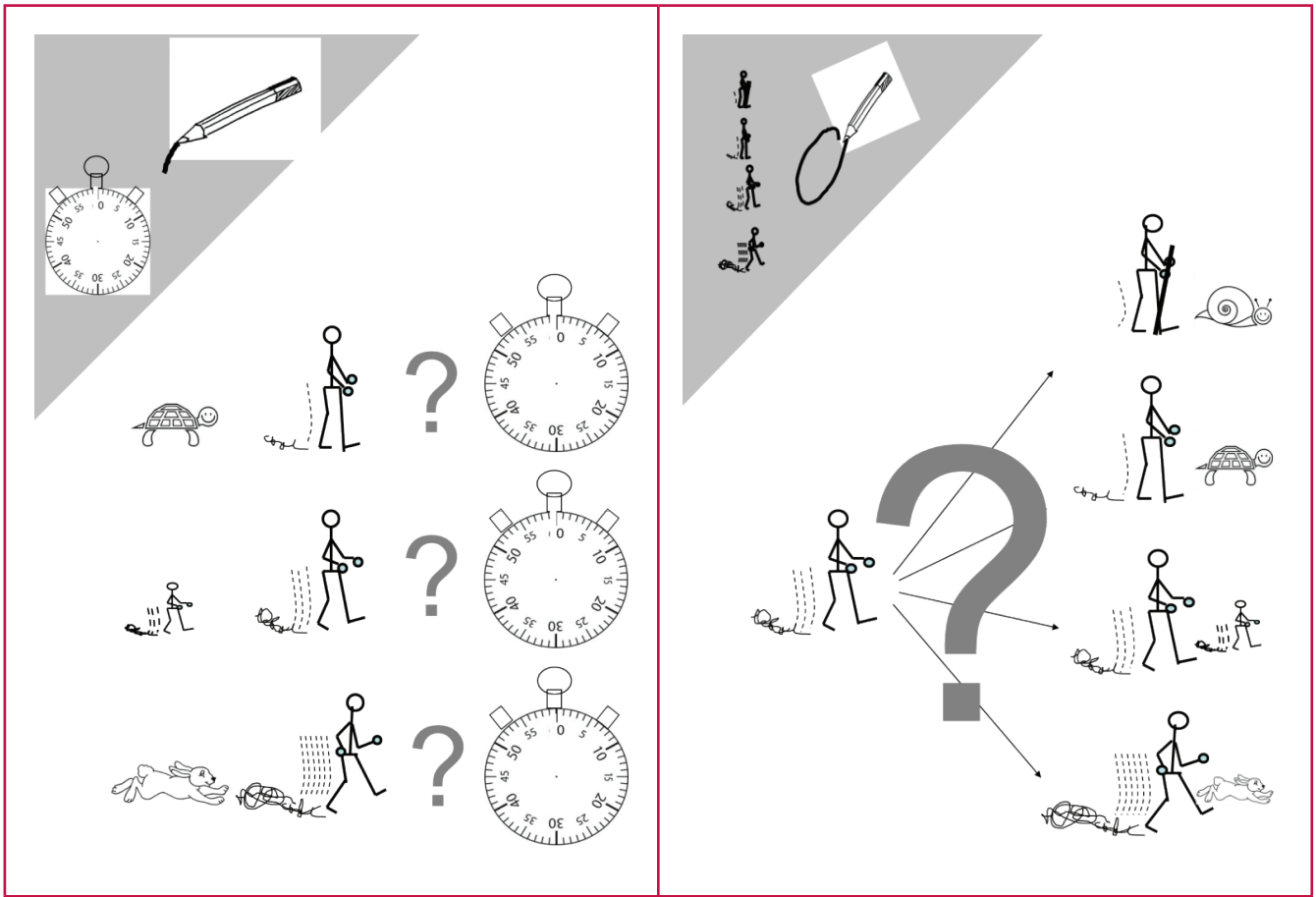

Fig. 1. The WELSH tool. On the first page the patient is asked to draw a line on the number of minutes corresponding to the duration sustainable without stopping for different tasks (see text for explanation). The second page requires the patient to estimate his/her usual walking pace.

for three different walking speeds: slow (illustrated by the turtle), normal (illustrated by a human) and fast (illustrated by a rabbit). If unable to do the task (e.g. walk fast), they were instructed to put a cross on the watch screen. A fourth and last item requires the patient to estimate his/her usual pace: very slow (illustrated by a snail), slow (illustrated by a turtle), normal (illustrated by a human) or fast (illustrated by a rabbit). Illustrations of the WELSH tool are presented in Fig. 1.

Patients were provided a blue or black pen and reading glasses if needed, and received oral explanation of the protocol and on how to fill in the WELSH questionnaire in their native language or dialect. Patients were asked to self-complete each of the three watch dials and define whether they felt they walked at their usual pace. The two series of drawings (first three items about maximal duration at different paces and fourth item on usual pace) were printed on each side of the same sheet and were thereby submitted in a random order.

Once self-completed, the technician, nurse or physician checked the questionnaire and completed any incomplete questionnaires. For the WELSH tool, an error was defined as a missing answer, multiple answers to the same item or a reported increase in the duration of a task that was more difficult than the task of lower intensity (e.g. reported higher ability to walk fast than to walk at a normal speed). Errors were discussed with the patient and corrections or additions were made and written in red.

We empirically defined a method for scoring of the questionnaire that could easily be memorised and done by mental calculation and would result in a maximal score of 100. The number of points attributed to the possible durations ranged from zero points if the task was impossible, to eight points for 51 to 60 minutes. The number of points increased by one point for each interval of five minutes up to 20 minutes, and for each interval of 10 minutes from 20 minutes to one hour. Estimated usual walking speeds were attributed coefficients ranging from one for 'much slower – snail' to four for 'faster – rabbit'. The final score was the sum of the number of points obtained at each pace plus one, multiplied by the coefficient resulting from the estimation of walking speed. Therefore the minimum possible WELSH score is $1 = [(0 + 0 + 0) +1] \times 1$, and the maximal score is $100 = [(8 + 8 + 8) +1] \times 4$.

All patients had a six-minute walking test to objectively quantify their walking ability. This test was performed by a different physician, technician or nurse from the one who supervised the WELSH completion and blinded to the results of the WELSH score. The test was performed between two plastic cones positioned 30 m from each other in a corridor. Oral instruction in the patient's language or dialect was to: (1) walk (never run) back and forth as many times as possible, turning around the plastic cones; (2) cover as much distance as possible over six minutes; (3) slow down or stop if needed, and restart walking when possible. For all tests, we recorded the maximal walking distance performed at minute six (MWD).

The study was approved by the Institutional Review Board of the Ministry of Health of Burkina Faso in August 2017, and registered on ClinicalTrials.gov Identifier: NCT03482869. It was performed according to the international ethics standards and conforms to the Helsinki Declaration. A signature confirming informed consent to participate in the study was obtained from all patients after oral (and written when possible) explanation of the study.

Statistical analyses

We analysed the number of incomplete questionnaires to estimate the questionnaire feasibility. The correlations of the WELSH scores with MWD were performed with step-by-step linear regression analysis to determine the factors associated with MWD. Then the Pearson *r*-coefficient of correlation between the WELSH score and MWD was calculated. Results are presented as mean ± standard deviation or number and percentages.

From previous studies, we estimated the *r*-coefficients of correlation between the objective measure of walking distance and the questionnaire to range from 0.35 to 0.66.[6,16-18] Assuming a coefficient of correlation between WELSH and MWD of at least 0.40, the minimum number of subjects to reach a power of 80% for two-tailed alpha equal to 0.05 was 47 subjects.

For organisational reasons, the protocol was scheduled over a series of periods starting in March 2018, in order to recruit 50 patients. Correlation from 0.40 to 0.59 was considered fair, from 0.60 to 0.75 was considered good, and above 0.75 was considered very good. Statistical analyses were performed with SPSS V15.0. For all tests, a two-tailed $p < 0.05$ was used to indicate statistical significance.

Results

Of the 50 patients, 29 (58.0%) were referred for the follow up of treatment for chronic hypertension, 10 (20.0%) were referred for apparent non-ischaemic cardiomyopathy, three (6.0%) had a clinical history of infarction and four patients (8.0%) were assumed to suffer from chronic valvular disease. Among all these patients, only four had an echocardiography and two had chest X-ray imaging to estimate the cardiothoracic index.

The characteristics of the 50 included patients are presented in Table 1. Notably, two-thirds of the patients stopped their education at elementary school. Among the 50 patients, one was unable to complete the WELSH questionnaire even under supervision. Among the other 49 patients, 33 patients completed

Table 1. Characteristics of study patients

Characteristics	*Number (%)*
Age (years)	54.8 ± 10.7
Females	40 (80.0)
Residential area	
Urban	47 (94)
Suburban	1 (2)
Rural	2 (4)
School level	
Never been to school	19 (38.0)
Elementary	15 (30.0)
Primary	13 (26.0)
Secondary	3 (6.0)
Weight (kg)	74.9 ± 15.2
Height (cm)	163 ± 10
Body mass index (kg/m²)	28.6 ± 9.2
Waist circumference (cm)	92.5 ±11.8
Self-reported walking limitation	33 (66.0%)
Heart failure	34 (68.0%)
New York Heart Association classification	
No dyspnoea	18 (36)
I	13 (23)
II	15 (30)
III	4 (8)

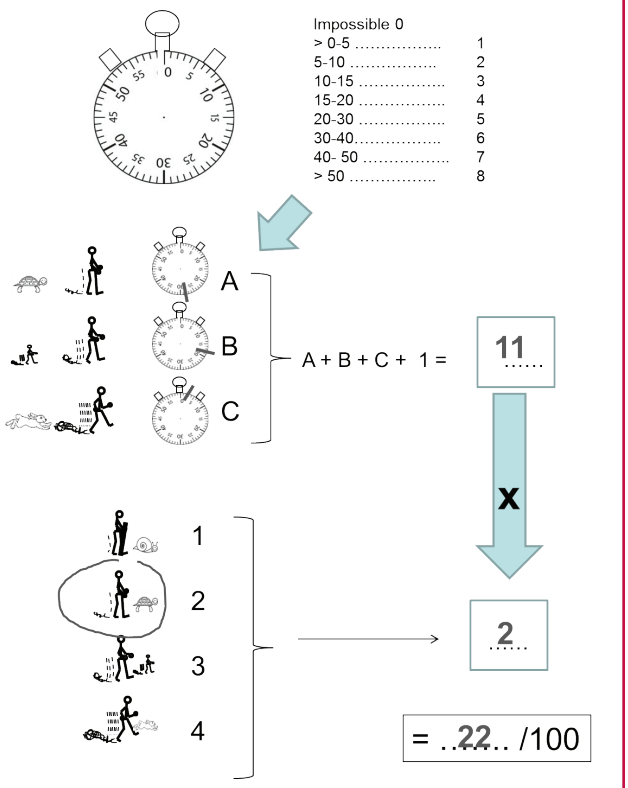

Fig. 2. Example of scoring sheet for the WELSH tool.

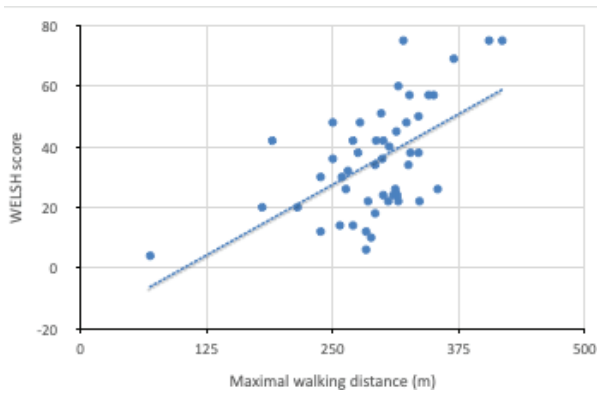

Fig. 3. Scatterplot of WELSH score and maximal walking distance.

the WELSH tool without errors and the other 16 patients (32.6%) made errors on one or more of the four items, with a median number of errors of two items, mainly in the first three items dealing with the duration of each task. Most of these errors related to a paradoxical increase in the duration that could be sustained for a walking speed with an increase in task difficulty, and were corrected after discussion with the patients.

The WELSH scores were calculated for all patients and the mean was 35 ± 17. An example of scoring is presented in Fig. 2. In this example, the subject reported he/she was able to walk for a maximum of approximately 23 minutes at a 'slow' speed (five points), approximately 17 minutes at a 'normal' speed (four points) and approximately three minutes at a 'fast' speed (one point) and reported he/she walked slower (turtle) than other people (coefficient = 2). The final score was 22 = [(5 + 4 + 1) +1] × 2 (Fig. 2).

No adverse event occurred during the six-minute walk test. The mean maximal walking distance was 292 ± 57 m.

The step-by-step multilinear regression analysis stopped at step one with the WELSH score being the sole predictor of MWD (r = 0.68, p < 0.001) and the model being MWD = 1.99 × score + 224 m. None of the other variables introduced in the model (gender, age, school level, body mass index, waist circumference, NYHA class) reached statistical significance for the association with MWD, as shown in Fig. 3.

Discussion

This is the first ever reported standard tool developed to facilitate and standardise the estimation of walking disability in illiterate patients. The feasibility of the WELSH tool is relatively high, keeping in mind that half of the self-completed walking impairment questionnaires (the most widely used tool to estimate walking impairment) need correction.[19] The WELSH tool is easily scored and its correlation with objectively measured maximal symptom-limited walking distance and the six-minute maximal walking distance was good.

Beyond the obvious interest in a tool for non-literate children or illiterate adults, developing a tool to score walking disability based on only drawing could also be valuable to eliminate language differences in questionnaire translations. What is of particular interest is that the proportion of our patients attending primary and secondary school was in the range of literacy estimated for the Burkinabe population.[20] Indeed, using a questionnaire in a language that is different from the language in which it was initially developed is a complex process, requiring cross translation and validation in the new language.[9,10,21-23] Whether or not the WELSH tool can be used in a context other than the African population remains to be studied.

We underscore here that the drawings were chosen on purpose with animals that are present worldwide. Specifically, when developing the WELSH tool, the fast speed was initially suggested to be an antelope but these animals are not present in all countries (e.g. America or Australia).

Another issue to be solved was the representation and estimation of time. With digital watches, classic watch screens may gradually disappear, and the selection of patients able to read a classic clock/watch screen may have biased our results.[24] In fact very few patients, except those with cognitive disorders, were excluded because of their inability to read a watch. This might partly be due to the use of watches and clocks for religious purposes because of a high proportion of Islamic patients in Burkina Faso.[20] A second question was whether or not numbers should be added on the clock. Adding Western type (Arabic) numbers may have facilitated the completion of the questionnaire, and these can easily be converted to other types (e.g. Roman or Chinese) with no ambiguity.

The WELSH tool can provide additional information to the six-minute walking test about the self-reported impairment in the community, keeping in mind that the six-minute test is performed at a forced pace,[25] and not at the usual pace of the patient. Furthermore, the WELSH tool should not replace the

NYHA scoring by the physician but provide information on self-perceived impairment, which the NYHA does not do.[14]

Walking disability is observed in a wide variety of diseases. The WELCH tool (from which the WELSH was inspired) was validated in only patients with suspected peripheral artery disease (PAD). The WELSH tool was tested on a population of patients referred to the cardiology department for various conditions that unfortunately could not be confirmed.

In Burkina Faso, the prevalence of hypertension is estimated at 46%, with 27.4% of patients having a medical history of dilated cardiomyopathy.[26] From a thesis completed in 2014 in Bobo Dioulasso on 127 diabetic patients, the most represented cardiovascular pathologies were hypertension (60.3%), ischaemic heart disease (26.6%) and cardiomyopathy (3%).[27] It can be assumed that our population was similar. Testing the WELSH tool in more selected patients is necessary but we assume that the WELSH tool is not PAD-specific.

Limitations

There are limitations to this study and to the use of the WELSH tool. First, it is important to note that in the context of Burkina Faso medicine, information on and confirmation of the cardiovascular disease underlying the patient's symptoms is rarely possible. The university hospital in Bobo Dioulasso has only occasional access to ultrasound and radiology and diagnoses are based on clinical evidence in most cases. Besides, as no centralised data files and archives are available, patients are responsible for their own files and rarely bring them for repeat visits. This could appear to be a major limitation but the WELSH tool is not disease-specific and the fact that the population is likely to be heterogeneous and poorly defined on the basis of para-clinical confirmation is not, in our opinion, a major limitation.

Second, the WELSH tool cannot be considered a tool that can be self-completed because initial explanations are needed to understand how the drawings must be completed. However it allows for both a standardisation of the estimation of walking impairment and a simple scoring system.

Third, no validation against treadmill testing could be performed because no treadmill was available for routine use in the hospital of Bobo Dioulasso. The six-minute walking test is probably not the ideal reference tool because of the ceiling effect of the technique. Other methods of validation not requiring a treadmill could be used, such as the global positioning system (GPS).

Fourth, we arbitrarily predefined the WELSH scoring, which is possibly not optimal. It may be changed to improve the correlation between the WELSH score and objective measurement of walking impairment, such as the MWD, but the correlation was already quite high. Future studies are needed to confirm these results.

Conclusion

The WELSH tool is feasible for use in predominantly illiterate or low-literacy cardiac patients in Burkina Faso. There was a good correlation between the WELSH score and the six-minute walking test. Its applicability in other populations of patients remains to be tested. Test–retest reproducibility as well as its sensitivity to therapeutic interventions remain to be assessed in futures studies.

The study is presented on behalf of the SOCOS group. We thank Abaz Ouedraogo and Ben Souleyman Wilfred Adjaba for technical help and Ms Albertine Lucas for grammar and style reviewing.

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'Statins are first-line therapy in patients with hyperlipidaemia because they clearly prevent cardiovascular events,' said Dr Robert Boggs, director of outcomes research, Centre for Observational and Real-world Evidence (CORE) at Merck. 'This study demonstrates not only the value of helping patients adhere to their statin therapy but, in some cases, the need for additional treatments to get their LDL-C down to reasonable thresholds.'

Researchers estimated that reducing the LDL-C levels of the subgroup who were above the threshold could avoid 1 173 cardiovascular disease events. If those patients were given the necessary treatments to lower their bad cholesterol levels to the recommended threshold, the reduced risk would save about $1 455 per person.

This study is fairly unique because researchers were able to analyse the records of patients from the entire state of Indiana. Therefore, the results are more representative of the state's population and may have greater public health implications than studies conducted with, for instance, patients of a single health system.

'The presence of the health information exchange in Indiana was a crucial factor in being able to do this study,' said Dr Titus Schleyer, the first author on the article and a research scientist at Regenstrief Institute. 'The Indiana Network for Patient Care allows us to gather health data from large numbers of people on an ongoing basis. While that information is a by-product of going to the doctor, it is tremendously useful for research.'

This study provides evidence to health insurance agencies and physicians that there are opportunities to improve care and reduce the cost of treating cardiovascular events with more aggressive therapy for bad cholesterol. Schleyer hopes information from studies like these could eventually be used to identify populations at risk and help prevent negative outcomes.

In addition to his appointment as a Regenstrief Institute investigator, Schleyer is a faculty member of Indiana University School of Medicine. The study team also included Dr Siu Hui, Dr Jane Wang, Dr Zuoyi Zhang and Dr Jarod Baker from Regenstrief Institute.

Source: Medical Brief 2019

Ellisras Longitudinal Study 2017: body frame variation and adiposity among Polokwane private school children (ELS 9)

RB Sebati, MS Monyeki, KD Monyeki

Abstract

Objective: Obesity affects both developed and developing countries and it affects children worldwide. The aim of this study was to investigate the relationship between body frame size and adiposity among Polokwane private school children.

Methods: A total of 2 162 children (1 126 boys and 1 036 girls) aged five to 15 years attending three private schools in Polokwane, a city in the Limpopo Province of South Africa, participated in the study. Most of the participants were black children (99.77%), whereas 0.2% were white, 0.01% were coloureds and 0.02% were Indians. Subjects underwent anthropometric measurements including weight and height, skinfolds including triceps and subscapular, and body frame including bi-iliocristal and transverse chest.

Results: There was a negative significant correlation between body mass index (BMI) (reflects adiposity) and height only (reflects body frame) ($r^2 = –0.268$ and $r^2 = –0.303$, respectively) among children in age group five to seven years. BMI was also significantly and positively correlated with skinfolds and vice versa (both reflect adiposity) ($r = 0.345–0.571$).

Conclusion: There was a positive significant correlation between adiposity (reflected by skinfolds and BMI) and several measures of body frame size among Polokwane private school children. Moreover, body frame size can be used in the detection of risk for obesity.

Keywords: obesity, adiposity, body frame, skinfolds

Submitted 11/4/18, accepted 24/5/19
Cardiovasc J Afr 2019; **30**: 347–351 www.cvja.co.za

DOI: 10.5830/CVJA-2019-033

Obesity is a health epidemic affecting children worldwide.[1] The rapidly growing prevalence of obesity could be due to changes in behavioural patterns such as reduced physical activity as well as over-consumption of high-fat and energy-rich foods.[2] Moreover, individual differences in energy consumption and food metabolism could be responsible for the adiposity existing among individuals.[3] Lifestyle influences that regularly impact on patterns of nutritional intake, and physical activity, along with other environmental factors that affect the development of the body frame, seem to be more evident during adolescence.[4,5]

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Body frame size can be defined as the structure that supports the skeleton and is used in the adjustment of skeletal mass and size in measures of body weight and composition.[6] A study assessing the relationship between body frame size and adiposity in American urban school children found that body frame size was related to the amount of fat in different adipose tissue depots but not adipose tissue distribution.[7] Furthermore, in urban and rural coloured South African school children, skeletal frame width and the amount of adiposity were correlated.[7] It was further elaborated that the correlation between skeletal frame and adiposity persists longitudinally throughout childhood and adolescence among individuals residing in very poor and in good environmental conditions.[3]

Since body mass index (BMI) has been validated as a measure of adiposity among children and adolescents,[8] several studies have been conducted across South Africa using BMI to determine the adiposity status.[1,9] Some researchers took race and school type into consideration,[10] while others considered socio-economic status.[11] Another study conducted among children in Limpopo assessed adiposity using two adiposity measures, namely BMI and skinfold thickness.[12]

Although a study relating adiposity with body frame size has been conducted among children and adolescents in the Western Cape Province of South Africa,[3] similar studies have never been reported in the Limpopo Province or among Polokwane school children. Therefore, the aim of this study was to investigate the relationship between body frame size and adiposity among Polokwane private school children aged five to 15 years.

Methods

A total of 2 162 children (1 126 boys and 1 036 girls) aged five to 15 years attending three private schools in Polokwane, a city in the Limpopo Province of South Africa, participated in the study. Most of the participants were black children (99.77%) and 0.2% were white; 0.01% were coloureds and 0.02% were Indians, which resulted in their exclusion from the analysis. South African children attending private schools are mostly within the middle and upper socio-economic groups of the population. Children who were available at the schools during the days of the survey participated in the study.

The ethics committee of the University of Limpopo granted ethical approval prior to the study. Written informed consent was attained from parents and guardians of the children.

All anthropometric measurements were done according to the International Society for the Advancement of Kinanthropometry (ISAK).[13] Height was measured using a Martin anthropometer to the nearest 0.1 cm. An electronic scale was used to measure weight to the nearest 0.1 kg. BMI was calculated as weight (kg)/height (cm) squared. Skinfold thickness (subscapular, abdominal

and triceps) was measured three times with the use of a Slim Guide skinfold calliper, and the values were rounded to the nearest 0.1 mm.[14]

Bi-acromial width was measured while the subject was in a relaxed standing position with the arms hanging at the sides, using the branches of the large sliding calliper. They were placed on the most lateral points of the acromion processes at an angle of 90 degrees pointing upwards. Pressure was applied to compress the overlying tissue without moving the shoulders. Bi-iliocristal width was measured using the branches of the anthropometer held at 45 degrees pointing upwards on the most lateral points on the iliac crests, with firm pressure applied to reduce the effect of the overlying tissue.

Transverse chest width was measured using the superior aspect of the calliper scale at the level of the front mesosternale and the blades were positioned at an angle of 30 degrees downwards. The calliper was positioned at the lateral borders of the ribs. Anterior–posterior chest depth was measured using the branches of the calliper placed on the level of the mesosternale. The rounded tips of the calliper were held between the thumb and digits two and three over the right shoulder while the subject breathed normally. The rear branch of the calliper was positioned on the spinous process of the vertebra at the horizontal level of the mesosternale and measurement was taken at end-tidal expiration.

Chest girth was measured around the thorax using a measuring tape at the level of the mesosternale. During the measurement the subjects lowered the abducted arms to a relaxed position but still abducted horizontally. Waist girth was measured at the level of the narrowest point between the lower costal border (rib) and the iliac crest using a measuring tape with the arms slightly abducted to a relaxed position. Gluteal girth was measured 1 cm below the level of the gluteal fold, perpendicularly to the long axis of the thigh, using a measuring tape while the subject's feet were together and the gluteal muscles relaxed.

It was customary in the Polokwane private school project to aggregate numbers so that individual identity was obscured. A standard data-collection form designed by investigators was used in the study. After the information had been captured electronically, the data forms were kept safe under lock and key to safeguard the identity of the subjects. The principal investigator discarded personal identity information when consolidating data for the purpose of statistical analysis.

Statistical analysis

Descriptive statistics were expressed for weight, height, BMI, triceps, subscapular and abdominal skinfolds, sum of skinfolds, bi-acromial width, anterior–posterior chest depth, transverse chest depth, bi-iliocristal width, and waist, gluteal and chest girth by age group of critical periods in childhood for the development of obesity [adipose rebound (five to seven years), adolescence (eight to 10 years and 11–15 years)][15] and gender. Pearson correlation coefficients was performed to determine the relationship between adiposity (BMI, waist girth, gluteal girth, abdominal, triceps and subscapular skinfolds, sum of skinfolds) and body frame variables (bi-acromial width, anterior–posterior chest depth, transverse chest depth, bi-iliocristal width and chest girth) by age group. All the data were analysed with a statistical package for social sciences (SPSS) version 23. A statistically significant difference was assumed at $p < 0.05$.

Results

Table 1 shows the descriptive statistics for adiposity and body frame variables among Polokwane private school children. Boys in the age group 11 to 15 years had a higher mean height (132.4 cm) than boys in age group five to seven years (103.7 cm). Adiposity status based on sum of skinfolds for girls in age group five to seven years had a slightly lower mean (19.2) than girls in age group 11 to 15 years (19.7). The highest prevalence of obesity was among girls in age group eight to 10 years (5.5%) while boys in age group 11 to 15 years had the highest prevalence of mild undernutrition (23.8%).

Table 2 shows Pearson correlation coefficients for body frame and adiposity variables among Polokwane private school children for age group five to seven years. There was a negative significant correlation between BMI (reflects adiposity) with height only (reflects body frame) (r^2 = –0.303). There was

Table 1. Descriptive statistics for body frame and adiposity variables among Polokwane private school children by gender and age group

	Age group					
	5–7 years		*8–10 years*		*11–15 years*	
	Boys	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*
Variables	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
Number	88	74	361	348	677	614
Age	7.2 (0.54)	7.1 (0.53)	9.5 (0.91)	9.5 (0.88)	12.3 (0.92)	12.1 (0.73)
Weight	14.6 (1.74)	14.4 (2.34)	19.0 (3.24)	18.8 (3.13)	24.3 (3.60)	24.2 (4.25)
Height	103.7 (5.74)	102.9 (6.75)	118.5 (7.96)	118.5 (7.59)	132.4 (6.67)	132.0 (6.82)
Body mass index	13.5 (1.15)	13.6 (2.30)	13.5 (1.16)	13.3 (1.40)	13.8 (1.26)	13.8 (1.55)
Triceps skinfold	7.0 (1.76)	7.2 (1.88)	5.9 (1.38)	6.7 (1.62)	5.9 (1.53)	7.3 (2.28)
Subscapular skinfold	5.2 (1.15)	5.5 (1.31)	4.8 (0.78)	5.2 (1.05)	5.0 (0.91)	5.85 (1.58)
Abdominal skinfold	5.5 (1.35)	6.4 (1.85)	5.0 (1.08)	5.7 (1.51)	5.2 (1.41)	6.5 (3.55)
Sum skinfolds	17.7 (3.40)	19.2 (4.28)	15.7 (2.68)	17.5 (3.52)	16.0 (3.18)	19.7 (6.24)
Bi-acromial width	21.4 (1.64)	21.2 (1.87)	24.7 (1.91)	24.5 (1.94)	27.0 (1.91)	26.6 (2.11)
A-P chest	11.8 (1.12)	11.3 (0.95)	12.5 (1.12)	12.1 (0.99)	13.2 (1.02)	12.9 (1.30)
Transverse chest	16.1 (1.29)	15.7 (1.35)	17.6 (1.32)	17.2 (1.23)	19.0 (1.33)	18.7 (1.52)
Bi-iliocristal width	15.0 (1.05)	14.8 (1.25)	16.5 (1.35)	16.4 (1.17)	17.8 (1.20)	17.8 (1.45)
Waist girth	48.9 (2.81)	47.6 (2.80)	50.7 (2.98)	49.8 (3.20)	53.2 (3.25)	52.1 (3.41)
Gluteal girth	51.3 (2.66)	51.9 (3.38)	55.5 (4.00)	56.8 (4.13)	60.9 (4.07)	62.4 (4.99)
Chest girth	50.5 (2.18)	49.6 (2.88)	54.3 (2.72)	53.1 (2.80)	58.0 (3.10)	56.8 (3.21)
The prevalence of overweight, obesity and undernutrition % (*n*)						
Overweight	8.9 (17)	7.9 (17)	10.3 (35)	9.8 (32)	6.3 (20)	13.8 (38)
Obesity	1.0 (2)	0 (0)	2.4 (8)	5.5 (18)	2.5 (8)	2.2 (6)
Mild undernutrition	14.1 (27)	19.4 (42)	13.0 (44)	15.6 (51)	23.8 (75)	11.6 (32)
Moderate undernutrition	8.3 (16)	4.6 (10)	3.5 (12)	2.4 (8)	3.8 (12)	4.0 (11)
Severe undernutrition	8.3 (16)	10.2 (22)	2.1 (7)	2.4 (8)	0.6 (2)	1.8 (5)

*$p < 0.05$; **$p < 0.01$.

Table 2. Pearson correlation coefficients for body frame and adiposity variables among Polokwane private school children for age group five to seven years

	Height	*BMI*	*Triceps skinfold*	*Subscapular skinfold*	*Abdominal skinfold*	*Sum skinfolds*	*Biacromial width*	*A-P chest*	*Transverse chest*	*Biiliocristal width*	*Waist girth*	*Gluteal girth*	*Chest girth*
Height	1	–0.303**	–0.211*	–0.094	–0.081	–0.173	0.499**	0.161**	0.362**	0.551**	0.200	0.328**	0.468**
BMI	–0.340**	1	0.273**	0.292**	0.249*	0.339**	0.094	0.039	–0.070	–0.070	0.179	0.295**	0.271**
Triceps skinfold	0.25	0.339**	1	0.475**	0.423**	0.847**	–0.046	–0.125	–0.109	–0.086	0.269*	0.223*	0.079
Subscapular skinfold	–0.042	0.340**	0.709**	1	0.437**	0.758**	0.106	–0.051	0.018	–0.065	0.161	0.184	0.282**
Abdominal skinfold	0.193	0.237*	0.496**	0.555**	1	0.765**	–0.021	–0.116	–0.015	–0.087	0.137	0.196	0.146
Sum skinfolds	0.081	0.355**	0.871**	0.858**	820**	1	0.003	–0.128	–0.056	–0.101	0.248*	0.256*	0.194
Bi-acromial width	0.755**	–0.009	0.152	0.123	0.280*	0.225	1	0.187	0.475**	0.453**	0.210*	0.280**	0.530**
A-P chest depth	0.169	0.151	0.126	0.250*	0.328**	0.274*	0.434**	1	0.502**	0.446**	0.135	0.020	0.351**
Transverse chest	0.476**	–0.049	–0.12	0.089	–0.003	0.021	0.528**	0.392**	1	0.651**	0.214*	0.133	0.471**
Bi-iliocristal width	0.363**	–0.173	0.013	0.021	0.072	0.043	0.325**	0.434**	0.528**	1	0.307**	0.304**	0.433**
Waist girth	0.235*	0.356**	0.248*	0.409**	0.367**	0.393**	0.340**	0.430**	0.291*	0.247*	1	0.219*	0.480**
Gluteal girth	0.361**	0.438**	0.320**	0.475**	0.494**	0.499**	0.461**	0.445**	0.314**	0.244*	0.630**	1	0.387**
Chest girth	0.436**	0.446**	0.294*	0.397**	0.459**	0.449**	0.544**	0.426**	0.306**	0.288*	0.691**	0.695**	1

*$p < 0.05$; **$p < 0.01$.

a positive significant correlation between BMI and triceps, subscapular and abdominal skinfolds and the sum of skinfolds (all reflect adiposity) ($r = 0.237–0.446$).

Table 3 shows Pearson correlation coefficients for body frame and adiposity variables among Polokwane private school children for age group eight to 10 years. There was a positive significant correlation between sum of skinfolds (reflects adiposity) and BMI (reflects adiposity), bi-acromial width, transverse chest, anterior–posterior chest, bi-iliocristal width, and waist, chest and gluteal girth, all of which reflect body frame ($r = 0.155–0.453$)

Table 4 shows Pearson correlation coefficients for body frame and adiposity variables among Polokwane private school children for age group 11 to 15 years. There were positive significant correlations between BMI (reflects adiposity) and all body frame measurements (height, bi-acromial width, transverse chest, anterior–posterior chest, bi-iliocristal width, and waist, chest and gluteal girth) ($r = 0.172–0.703$). There were also positive significant correlations between the sum of skinfolds (reflects adiposity) and all the above-mentioned body frame measures ($r = 0.114–0.603$). BMI was also significantly and positively correlated with the skinfolds and vice versa (both reflect adiposity) ($r = 0.345–0.571$).

Discussion

The aim of this study was to investigate the relationship between body frame size and adiposity among Polokwane private school children. There was a positive significant correlation between the sum of skinfolds (reflects adiposity) and transverse chest, bi-iliocristal and bi-acromial width and anterior–posterior chest (reflect body frame) among Polokwane private school children in age group 11 to 15 years. A study by Teghan *et al.*[3] among urban and rural coloured South African school children aged six to 20 years in the Western Cape Province also reported a significant correlation between skeletal frame width and the amount of adiposity. Both studies found significant correlations between adiposity and certain variables of body frame, although the significant body frame variables were not the same in the two studies.

The current study found strong significant correlations of the sum of skinfold thickness with chest girth and gluteal/hip girth ($r = 0.283–0.449$) among children in all three age groups (age groups five to seven, eight to 10 and 11 to 15 years). Similar results ($r = 0.42–0.66$) were reported by Henneberg and Ulijaszek[16] among middle-class adult Australian women. The findings from a study by Argnani *et al.*[17] suggested that chest girth is gender dependent,

Table 3. Pearson correlation coefficients for body frame and adiposity variables among Polokwane private school children for age group eight to 10 years

	Height	*BMI*	*Triceps skinfold*	*Subscapular skinfold*	*Abdominal skinfold*	*Sum skinfolds*	*Biacromial width*	*A-P chest*	*Transverse chest*	*Biiliocristal width*	*Waist girth*	*Gluteal girth*	*Chest girth*
Height	1	–0.340**	0.025	–0.042	0.193	0.081	0.755**	0.169	0.476**	0.363**	0.235*	0.361**	0.436**
BMI	0.004	1	0.339**	0.340**	0.237*	0.355**	–0.009	0.151	–0.049	–0.173	0.356**	0.438**	0.446**
Triceps skinfold	0.045	0.415**	1	0.709**	0.496**	0.871**	0.152	0.126	–0.012	0.013	0.248*	0.320**	0.294*
Subscapular skinfold	0.090	0.394**	0.546**	1	0.555**	0.858**	0.123	0.250*	0.089	0.021	0.409**	0.475**	0.397**
Abdominal skinfold	0.101	0.401**	0.568**	0.552*	1	0.820**	0.280*	0.328**	-0.003	0.072	0.367**	0.494**	0.459**
Sum skinfolds	0.091	0.480**	0.867**	0.787**	0.855**	1	0.225	0.274	0.021	0.043	0.393**	0.499**	0.449**
Bi-acromial width	0.741**	0.149**	0.035	0.054	0.084	0.068	1	0.077	0.529**	0.0325**	0.340**	0.461**	0.544**
A-P chest	0.371**	0.181**	0.117*	0.057	0.195**	0.155**	0.267**	1	0.392**	0.434**	0.430**	0.445**	0.426**
Transverse chest	0.597**	0.192**	0.128*	0.176**	0.107*	0.157**	0.609**	0.316**	1	0.528**	0.291*	0.314**	0.306**
Bi-iliocristal width	0.630**	0.215**	0.115*	0.144**	0.141**	0.156**	0.556**	0.302**	0.549**	1	0.247*	0.244*	0.288*
Waist girth	0.432**	0.338**	0.282**	0.304**	0.280**	0.340**	0.403**	0.322**	0.477**	0.439**	1	0.630**	0.691**
Gluteal girth	0.654**	0.398**	0.387**	0.373**	0.382**	0.453**	0.539**	0.385**	0.522**	0.559**	0.561**	1	0.695**
Chest girth	0.616**	0.304**	0.204**	0.228**	0.282**	0.283**	0.608**	0.480**	0.605**	0.527**	0.647**	0.713**	1

Table 4. Pearson correlation coefficients for body frame and adiposity variables among Polokwane private school children for age group 11 to 15 years

	Height	*BMI*	*Triceps skinfold*	*Sub-scapular skinfold*	*Abdominal skinfold*	*Sum skinfolds*	*Bi-acromial width*	*A-P chest*	*Transverse chest*	*Bi-iliocristal width*	*Waist girth*	*Gluteal girth*	*Chest girth*
Height	1	0.172**	0.104**	0.223**	0.264**	0.231**	0.609**	0.343**	0.552**	0.454**	0.442**	0.650**	0.564**
BMI	0.289**	1	0.320**	0.263**	0.282**	0.345**	0.279**	0.346**	0.331**	0.237**	0.465**	0.531**	0.515**
Triceps skinfold	0.257**	0.561**	1	0.505**	0.23**	0.855**	0.136**	0.066	0.132**	0.075	0.263**	0.345**	0.178**
Subscapular skinfold	0.293**	0.571**	0.705**	1	0.526**	0.760**	0.179**	0.060	0.195**	0.109**	0.274**	0.396**	0.250**
Abdominal skinfold	0.200**	0.358**	0.470**	0.526**	1	0.844**	0.207**	0.097*	0.221**	0.114**	0.289**	0.424**	0.224**
Sum skinfolds	0.282**	0.554**	0.812**	0.811**	0.874**	1	0.208**	0.091*	0.216**	0.117**	0.332**	0.466**	0.256**
Bi-acromial width	0.532**	0.322**	0.304**	0.296**	0.198**	0.299**	1	0.251**	0.557**	0.349**	0.428**	0.530**	0.520**
A-P chest	0.317**	0.347**	0.209**	0.189**	0.161**	0.215**	0.480**	1	0.329**	0.307**	0.320**	0.357**	0.465**
Transverse chest	0.412**	0.383**	0.277**	0.282**	0.181**	0.276**	0.584**	0.591**	1	0.424**	0.463**	0.524**	0.596**
Bi-iliocristal width	0.384**	0.217**	0.142**	0.126**	0.053	0.114**	0.475**	0.552**	0.584**	1	0.319**	0.383**	0.390**
Waist girth	0.398**	0.643**	0.501**	0.510**	0.340**	0.506**	0.403**	0.292**	0.358**	0.221**	1	0.598**	0.644**
Gluteal girth	0.629**	0.703**	0.598**	0.602**	0.407**	0.603**	0.484**	0.343**	0.429**	0.342**	0.669**	1	0.631**
Chest girth	0.509**	0.595**	0.424**	0.462**	0.292**	0.438**	0.450**	0.361**	0.460**	0.216**	0.660**	0.650**	1

while Ibeabuchi *et al*.[18] reported that chest size increases with age. Chest girth has been shown to be a valuable indicator of frame size and lean body mass and an estimate of relative weight, and to be more associated with body mass than with stature.[19] This could have contributed to the similarity of findings from the current study and that of Henneberg and Ulijaszek.[16]

Teghan *et al*.[3] found significant correlation coefficients (r = 0.087–0.511) in both males and females aged six to 20 years from the Western Cape Province between bi-acromial and bi-iliocristal indices with three skinfold thicknesses (triceps, subscapular and abdominal), but not between trunk and limb lengths and skinfolds. In the current study, similar results were reported (r = 0.075–0.207) among the age group 11 to 15 years only. Guzmán-de la Garza *et al*.[7] further reported that body frame size in school children was associated with the amount of adipose tissue in various depots but not adipose tissue distribution. Body frame size evaluations have been shown to be valuable proxy estimates of fatness and musculoskeletal strength, according to the Heath–Carter somatotype method.[20,21]

Chest breadth was found to increase with age in the current study (based on the mean) while a study by Ibeabuchi *et al*.[18] also reported age-related increments with chest breadth among adolescent females aged 10 to 17 years. Moreover, similar observations were made in a study conducted among school children aged six to 13 years in Mexico.[22] Chest breadth measure has been shown to be a valuable indicator of frame size and lean body mass. Moreover, it has been shown to be an estimate of relative weight, and is more correlated with body mass than with stature.[19,23]

Research on body frame could be used as an indicator for obesity or cardiovascular risk. The current study could be useful for comparison with similar studies[16] in adults, although it was carried out in children. Ultimately it will assist in determining whether evaluation criteria for children should utilise the same components as that for adults, especially since some body frame measures increase with age.[18]

The girls in age group 11 to 15 years of the current study had the highest prevalence of overweight (13.8%) while the boys in the same age group had an overweight prevalence of 6.3%. The girls in age group eight to 10 years had the highest level of obesity (5.5%) while the boys in the same age group had a prevalence of 2.4%. Most of the boys in the age group 11 to 15 years had mild undernutrition (23.8) while 10.2% of girls in age group five to seven years had severe undernutrition. Moreover, 19% of children from the villages in the central region of Limpopo Province were reported to be underweight.[24]

In a study conducted among rural South African children from Ellisras in Limpopo Province, it was reported that the prevalence of overweight manifested at age 10 years or older, from 1.1 to 2.9% and 0.6 to 4.6% for boys and girls, respectively. It was further reported that the 12-year-old boys and 13-year-old girls (2.9 and 4.6%, respectively) had the highest prevalence of overweight.[25] The prevalence of overweight in the current study was higher than that of Monyeki *et al*.[25] This could be because of differences in the environment and its associated factors that the children are exposed to, such as food, physical activities and socio-economic status, as some children resided in rural settings while others resided in urban areas.

Limitations

Comparison was not made between these urban private school children and their rural public school counterparts. Hence it is unknown whether the environment and socio-economic status of subjects had an impact on the findings. The association between body frame and adiposity was not assessed over time, to eliminate the possibility of temporary factors that may have affected the results. Body weight, fat distribution and adiposity are used and compared for the prediction of bone mineral status,[6] and such an inclusion could have strengthened the study.

Conclusion

There was a positive significant correlation between adiposity (reflected by skinfolds and BMI) and several measures of body frame size among Polokwane private school children. Furthermore, the correlation was the strongest in age group 11 to 15 years. Obesity prevalence was higher in female than male children. Body frame size can be used in the detection of risk for obesity. The results of this study can be used in clinical settings to estimate the optimal body weight of patients for a given height, since body frame size is an essential factor in determining the optimal body weight.[26] Since body frame size is associated with adiposity, this association can be incorporated as part of

an evaluation for cardiovascular risk factors. Furthermore, the adiposity status of individuals can be confirmed by BMI and skinfolds in addition to body frame size.

Future studies on the associations between body frame size and adiposity in Polokwane or Limpopo Province should compare rural and urban children, and private and public school children on a longitudinal basis. They should also use more than one adiposity variable.

The authors thank the Ellisras Longitudinal Study administrators, Mr TT Makata, Ms SP Seleka and Mr W Makata for coding the data. We acknowledge Sandra Duncan, our language editor.

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A 10-year follow-up study of demographic and cardiometabolic factors in HIV-infected South Africans

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Abstract

Objectives: Understanding of the interplay between human immunodeficiency virus (HIV) and cardiovascular disease, especially in Africa, is limited to evidence from longitudinal studies. Therefore the demographic profile and cardiometabolic, renal and liver function of an HIV-infected South African population were profiled from 2005 to 2015.

Methods: The study included 117 HIV-infected and 131 uninfected controls that were examined at baseline, five and 10 years.

Results: Mortality rate declined from 24% (2005–2010) to 0% (2010–2015) after the introduction of ART. Longitudinal increases in C-reactive protein ($p = 0.002$), alanine transaminase ($p = 0.006$) and gamma-glutamyl transferase ($p = 0.046$) levels and estimated glomerular filtration rate ($p < 0.001$) were seen only in the HIV-infected group. This group also showed increased high-density lipoprotein cholesterol (HDL-C) ($p < 0.001$) and total cholesterol ($p < 0.001$) levels and decreased triglyceride:HDL-C ($p = 0.011$) levels. Low-density lipoprotein cholesterol decreased in both groups ($p < 0.001$).

Conclusion: Despite trajectories of deranged lipid and inflammatory profiles, the cardiometabolic disease risk seems stable in HIV-infected South Africans. Inflammation and renal and liver function warrant regular monitoring.

Keywords: human immunodeficiency virus, antiretroviral therapy, cardiometabolic factors, renal function, liver enzymes, South Africa

Submitted 13/11/18, accepted 24/5/19
Published online 2/8/19
Cardiovasc J Afr 2019; **30**: 352–360 www.cvja.co.za

DOI: 10.5830/CVJA-2019-034

Since the discovery of the human immunodeficiency virus (HIV) in the 1980s,[1] the global prevalence of HIV infection has increased from 7.6 million patients in 1990 to 36.7 million in 2017.[2] Of global infections, eastern and southern Africa contributed 53% of new infections and include 19.6 million people living with HIV in these regions.[2]

The HIV epidemic in South Africa received significant attention during the 1990s, due to the growing incidence of HIV infection and deaths related to acquired immunodeficiency syndrome (AIDS).[3] In order to address the growing burden of HIV/AIDS, the South African government implemented the antiretroviral therapy (ART) roll-out programme for HIV-infected patients in April 2004,[4] which is now the world's largest ART roll-out programme.[5] The use of ART has improved the life expectancy of people infected with HIV in a country that has seen a dramatic increase in the number of HIV-infected patients, namely 11.5% (5.35 million) in 2005 to 12.5% (6.19 million) in 2015 (Fig. 1) and 12.6% (7.1 million) in 2017.[6] Despite various campaigns to reduce HIV infection rates, South Africa continues to bear a disproportionate share of the global burden of HIV, as the highest rates of new HIV infection are still reported in South Africa.[2]

The era of ART has exposed new challenges, including cardiometabolic changes such as elevated blood pressure,[7] dyslipidaemia,[7] lipodystrophy[8] and chronic inflammation,[9] which are all associated with increased development of cardiovascular disease (CVD). The use of ART is associated with hepatotoxicity, which often manifests as liver disease in HIV-infected patients.[10] In addition, renal disease, characterised by higher urinary protein excretion and elevated serum creatinine, was observed in HIV-infected individuals.[11] With 56% of the HIV-infected patients on ART in South Africa,[5] the prevalence of cardiometabolic and renal diseases in HIV-infected patients has increased.[12]

The HIV-infected population is at a higher risk of developing CVD due to the complex interlinkage between HIV, ART and cardiometabolic disease.[13] Furthermore, sub-Saharan Africa is faced with co-epidemics of HIV infection and CVD.[14] Further research is required to understand the nexus between these conditions, and limited evidence is available from longitudinal studies in Africa.

In a cross-sectional analysis of 300 newly diagnosed HIV-infected, ART-naïve individuals individually matched with uninfected controls by age, gender, body mass index (BMI) and locality, we previously reported dyslipidaemia and inflammation in the HIV-infected group, which suggested increased risk for the development of CVD.[15] In this study, HIV-infected black Africans and controls were followed over 10 years to profile the demographic factors and to investigate the impact of long-term HIV infection and ART use on cardiometabolic factors, as well as liver and renal function.

Methods

This study is embedded within the Prospective Urban and Rural Epidemiology (PURE) study, which is a multinational

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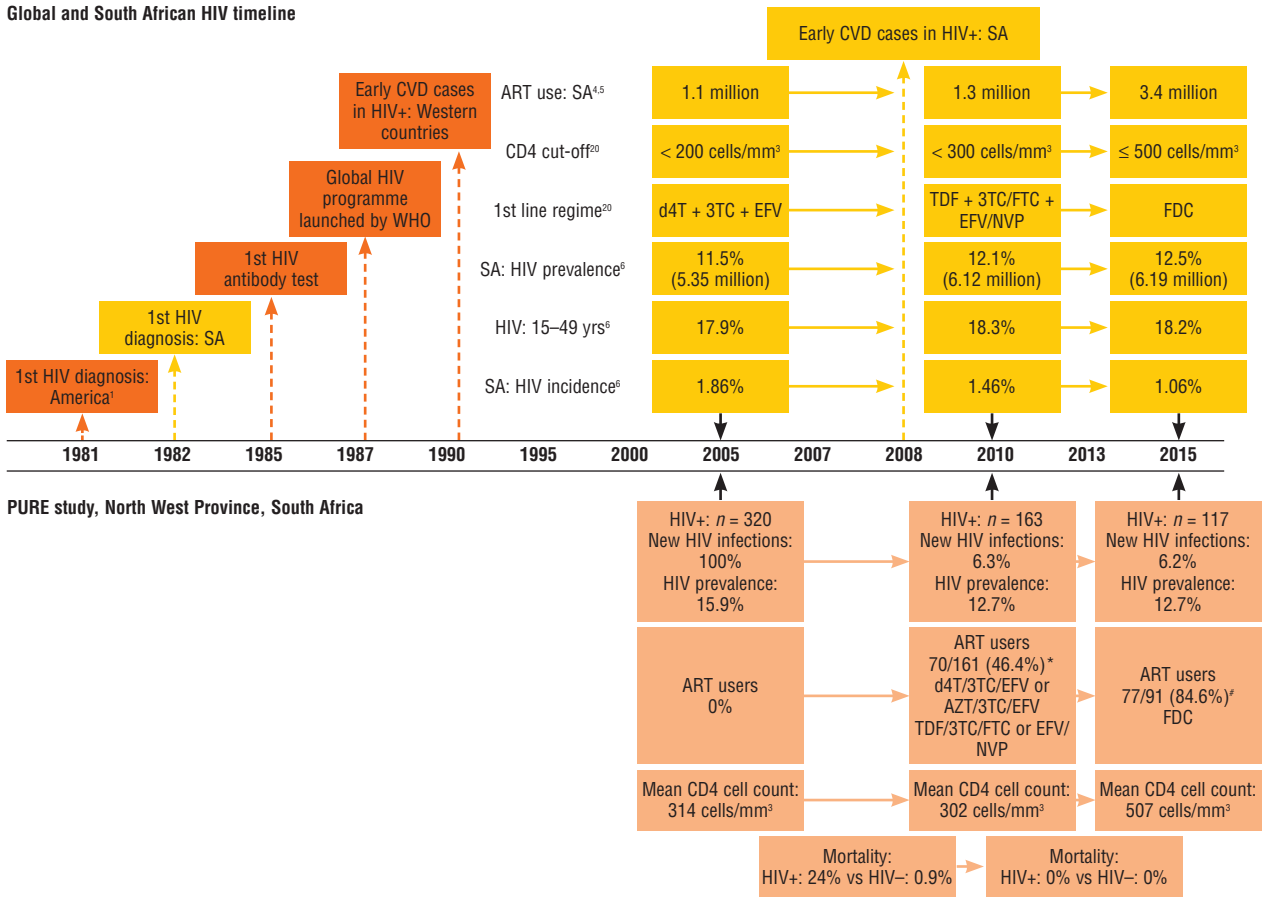

Fig. 1. Selected events in tracking HIV, ART and CVD. HIV, human immunodeficiency virus; ART, antiretroviral therapy; FDC, fixed-dose combination; d4T, stavudine; TDF, tenofovir; 3TC, emtricitabine; EFV, efivarenz; FTC, lamivudine; NVP, nevirapine; AZT, zidovudine; SA, South Africa; WHO, World Health Organisation; CVD, cardiovascular disease; PURE, Prospective Urban and Rural Epidemiology study; HIV+, HIV infected; HIV–, HIV uninfected; vs, versus. *Out of the 163 HIV-infected individuals who were followed in 2010, information on the use of ART was available for 151 participants. #Out of the 117 HIV-infected individuals who were followed in 2015, information on ART use was available for 91 participants.

longitudinal study examining changes in lifestyle and focusing on low-, middle- and high-income countries.[16] In the South African leg of the PURE study, performed in the North West Province, 2 010 participants were randomly recruited from Potchefstroom (urban $n = 1\,004$) and Ganyesa (rural $n = 1\,006$). Data were collected on three occasions, at baseline in 2005, and follow up in 2010 and 2015. Black individuals older than 35 years were invited to take part in the study and were fully informed, procedures were explained and they gave written informed consent. Pregnant and lactating women were excluded

During the 2010 follow up, 1 288 subjects participated in the study, while 221 died and 501 were lost to follow up. In the second follow up in 2015, 926 returned for follow up and 127 deaths were recorded, while 307 did not return for follow up. The attrition level of participants from baseline (2005: $n = 2\,005$) to follow up (2015: $n = 926$) is similar to previous longitudinal studies as a result of refusal to take part, relocation to other locations of the country, ill health of older individuals and death.

In the current study, at baseline in 2005, 320 of the total study population of 2 010 were newly identified with HIV, and at the 10-year follow up, 117 were retained. The 320 newly identified HIV-infected participants were matched with uninfected controls according to age, gender, BMI and locality at baseline. For this longitudinal study, we followed 117 HIV-infected and 131 uninfected participants who participated in the 10-year follow-up data collection. The study population is outlined in Fig. 2.

In 2005, the participants who were newly diagnosed with HIV and were ART-naïve were referred for follow up and CD4 cell count determination to initiate ART according to the guidelines of the South African Department of Health. Five years later (2010), 70 were on ART, which increased to 77 in 2015. ART comprised two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (Fig. 1).

In South Africa, the ART guidelines changed over the 10 years of follow up. In 2004, when ART was introduced, stavudine was the backbone of the ART regimen. However, it was phased out due to its association with lipodystrophy and was replaced with tenofovir in 2010.[17] Fixed-dose combination was introduced in 2012,[17] and a 'test-and-treat' programme was implemented in September 2016.[5]

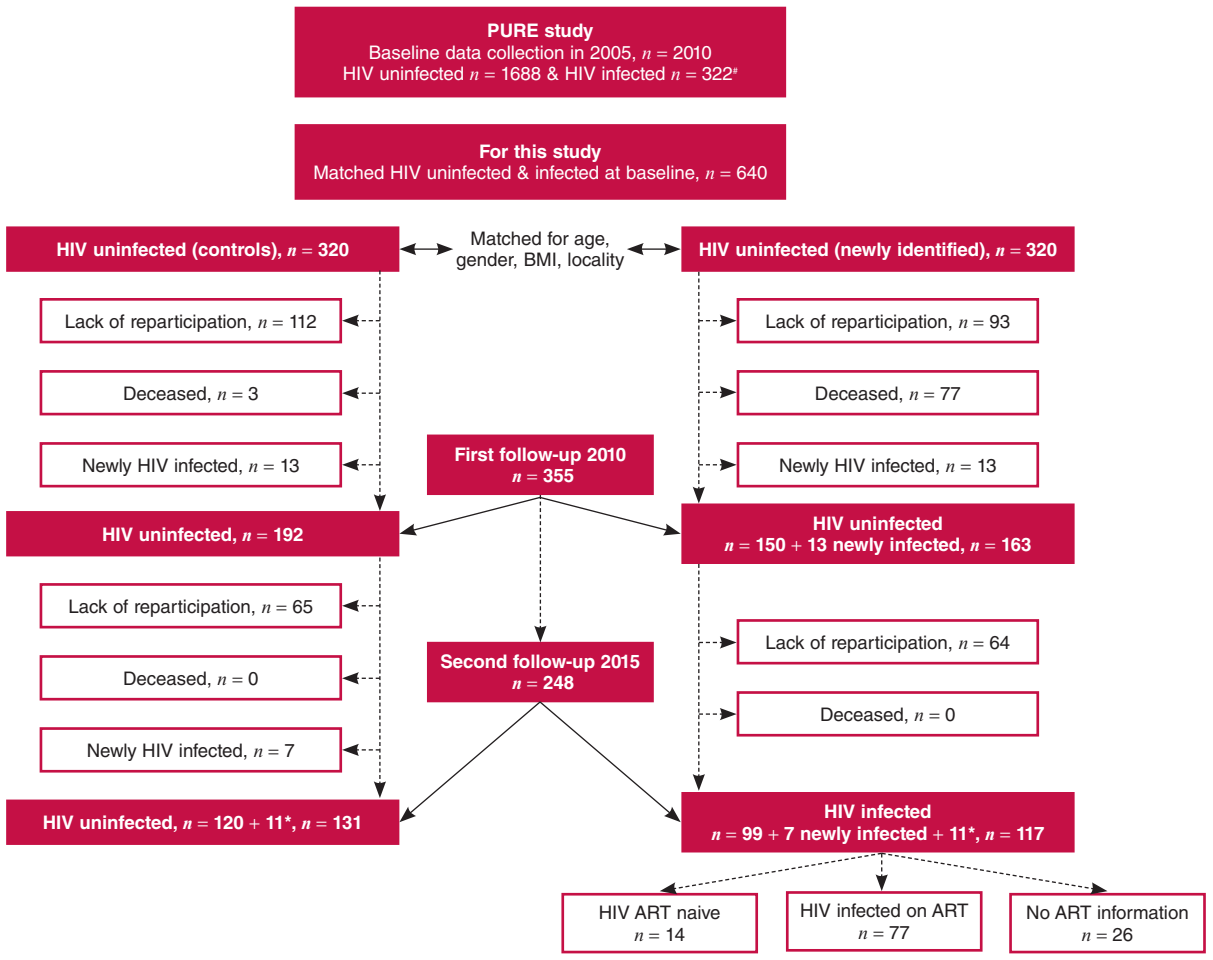

Fig. 2. Outline of the study population. ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; *n*, number of participants; PURE, Prospective Urban and Rural Epidemiology study. #Two of the participants were excluded due to incomplete data. *Participants who were not followed up in 2010 but in 2015: 11 HIV-infected and 11 uninfected participants.

The PURE study was approved by the Health Research Ethics Committee of the North-West University, South Africa. The study protocol and procedures were explained to the participants in their home language (Setswana) and they gave written informed consent.

Questionnaires were used to collect data on demographic information, current health status, medical and family history, medication as well as tobacco and alcohol use. Standardised procedures were used for anthropometric measurements, including height, weight and waist and hip circumferences.[18]

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were taken, in duplicate at an interval of five minutes on the right arm while in a sitting position. The validated OMRON HEM-757 device was used at baseline and at the 2010 follow up while the OMRON M6 device (Omron Healthcare, Kyoto, Japan) was used during the 2015 follow up.

Venous blood samples were collected from the participants after fasting for at least eight hours. Serum and plasma were prepared and along with spot urine samples, stored at –80°C.

Glucose levels from fluoride plasma samples were determined using the Vitros DT6011 chemistry analyser (Ortho-Clinical Diagnostics, Rochester, New York, USA) in 2005 and the Cobas Integra 400 plus (Roche, Indianapolis, IN) at follow up. Glycated haemoglobin (HbA_{1c}) was determined using the D-10 haemoglobin testing system from Bio-Rad (Hercules, California, USA).

Serum samples were used to analyse levels of high-sensitivity C-reactive protein (hsCRP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), γ-glutamyltransferase (GGT), aspartate transaminase (AST), alanine transaminase (ALT) and creatinine using a Konelab20iTM auto-analyser (Thermo Fisher Scientific Oy, Vantaa, Finland) in 2005 and a Cobas Integra 400 plus auto-analyser (Roche, Indianapolis, IN) in 2010 and 2015. Low-density lipoprotein cholesterol (LDL-C) levels were calculated.[19]

Estimated glomerular filtration rate (eGFR) was determined using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation in ml/min/1.73 m^2.[20] Urinary creatinine and albumin levels were analysed using the Cobas Integra 400 plus (Roche, Basel, Switzerland) in 2005 and 2015, and the urinary albumin-to-creatinine ratio (uACR) was calculated.

The HIV status of all participants was determined from whole blood finger-prick using the first response rapid HIV card test (Premier Medical Corporation Limited, Daman, India).

In the case of a positive result, the test was confirmed with the Pareeshak card test (BHAT Bio-tech, India), SD BIOLINE HIV 1/2 3.0 card test (Standard Diagnostics, INC, Korea) and Abon (Biopharm Corporation Ltd, Hanyzhou, China) rapid card test in 2005, 2010 and 2015, respectively.

The CD4 cell counts were determined by the National Health Laboratory Services (Beckman Coulter[a] EPICS[a] XL™, Fullerton, USA) in 2005 and 2010. In 2015 the CD4 cell count was measured on site using finger-prick blood and a point-of-care device, PIMA™ CD4 (Alere, Jena, Germany).

Statistical analysis

Statistical analyses were performed using Statistica version 13.3 (TIBCO Software Inc, Palo Alto, USA, 2017). Normally distributed variables are presented as means with standard deviation, while the logarithmically transformed variables are presented as geometric means with 5th and 95th percentiles. The variables that remained skew after log-transformation are presented as median with 25th and 75th percentiles.

Independent *t*-tests were used to compare the means of continuous variables, and chi-squared tests to compare frequencies in these groups. Percentage change was calculated, and comparison was done using the independent *t*-test between the HIV-infected and uninfected groups. The Mann–Whitney *U*-test was used to compare percentage change of skewed variables between these groups. Repeated measures analysis of variance was used to determine the change in continuous variables in these groups over time.

Results

The baseline and follow-up characteristics of the HIV-infected and uninfected groups were compared over 10 years (Table 1). The HIV-infected participants included fewer men (24 vs 38%) who were younger than the uninfected subjects (baseline mean ages 43 vs 45 years). The measurements of body composition and blood pressure did not differ between the two groups. The HIV-infected participants presented with lower TC ($p < 0.001$) and HDL-C ($p < 0.001$) levels and higher TC:HDL-C ($p = 0.003$) and TG:HDL-C ($p < 0.001$) at baseline compared to the uninfected group. At follow up the HIV-infected participants displayed higher LDL-C ($p = 0.038$) levels and TC:HDL-C ($p = 0.016$).

Lower concentrations of HbA_{1c} ($p = 0.013$) were noted after 10 years (2015) in the HIV-infected than the uninfected participants. At follow up (2015), higher levels of CRP ($p = 0.022$) and liver enzymes, ALT ($p < 0.001$), AST ($p = 0.011$) and GTT ($p = 0.006$) were seen in the HIV-infected group compared to their counterparts, despite comparable levels at baseline. At baseline the HIV-infected patients showed higher serum creatinine ($p = 0.003$) and uACR ($p = 0.003$) levels and lower eGFR ($p = 0.001$) compared to the uninfected subjects. The mortality rate in the HIV-infected group (Table 1) declined from 24% (2005–2010) to 0% (2010–2015).

To establish whether certain attributes could be ascribed to lost or deceased participants during the 10-year follow up, baseline characteristics were compared of the HIV-infected group followed, and those lost to follow up and deceased (Table 2). The deceased HIV-infected participants were older ($p = 0.002$) and showed higher heart rates ($p = 0.001$), lower HDL-C ($p = 0.024$) levels, higher lipid ratios (all $p = 0.033$), and HbA_{1c} ($p = 0.044$), CRP ($p < 0.001$) and GGT ($p = 0.046$) levels compared to those followed and lost to follow up.

In Table 3 the 10-year percentage change between the HIV-infected and uninfected groups was compared. No differences were seen in the percentage change in blood pressure and body composition between the groups, however TC and HDL-C levels increased in the HIV-infected group, opposed to a decrease in the uninfected (all $p < 0.001$) group. Although LDL-C (–1.9 vs –16%, $p < 0.001$) level decreased in both groups, a lesser decrease was noted in the HIV-infected group. The change in TG:HDL-C differed between the HIV-infected and uninfected groups (–8.1 vs 21%, $p = 0.011$).

Glucose level increased more (8.5 vs 4.7%, $p = 0.046$) while HbA_{1c} level remained the same in the HIV-infected group compared to an increase in the uninfected group (0 vs 2.1%, $p = 0.009$). The HIV-infected group displayed a greater increase in CRP (76 vs 0.1%, $p = 0.047$), ALT (25 vs –19%, $p < 0.001$) and GGT (12 vs –34%, $p < 0.001$) levels compared to the uninfected group. The HIV-infected group showed an increase in eGFR (4.8 vs –2.1%, $p = 0.010$) while in the uninfected group, eGFR declined.

The change in cardiometabolic characteristics of the HIV-infected and uninfected participants was determined over the three data-collection time points (Table 4). For this analysis, fewer participants were available due to missing data for 2010 for some variables. In the HIV-infected group, TC, LDL-C and TG:HDL-C (all $p \leq 0.88$) remained the same, but HDL-C level increased ($p = 0.017$), whereas in the uninfected group, all the above lipids decreased over time (all $p \geq 0.023$). The HIV-infected group showed no changes for AST ($p = 0.11$) and an increase in ALT ($p = 0.006$) and GGT ($p = 0.046$) levels, while these markers all decreased (all $p \leq 0.002$) in the uninfected participants. In the HIV-infected group, CRP level increased ($p = 0.002$) while in the uninfected group it did not change ($p = 0.45$). An increase in uACR was noted in the HIV-infected ($p < 0.001$) and uninfected participants ($p < 0.001$), and eGFR ($p < 0.001$) increased over time in the HIV-infected group, whereas in the uninfected counterparts, no change was seen ($p = 0.53$).

Table 5 shows the proportion and percentage of cardiometabolic risk factors of the HIV-infected and uninfected individuals over 10 years. A smaller proportion of the HIV-infected participants had elevated blood pressure than the uninfected controls at both baseline ($p = 0.011$) and five years later ($p = 0.043$). At baseline, more of the HIV-infected men had elevated HDL-C levels compared to the uninfected men ($p = 0.016$). Five years later, the HIV-infected men and women presented with a smaller proportion of individuals with elevated HDL-C levels compared to the uninfected men ($p = 0.046$) and women ($p = 0.002$). A larger proportion of the uninfected women showed central obesity at the 2010 ($p = 0.003$) and 2015 follow up ($p = 0.022$) compared to the HIV-infected women.

Discussion

With 12.7% of the PURE study participants living with HIV after 10 years, the frequency of HIV is aligned with the national South African prevalence (12.5%).[6] One of the aims of the Joint United Nations Programme on HIV/AIDS (UNAIDS) is to increase the number of HIV-infected patients on ART,[21] and

Table 1. Characteristics of the HIV-infected and uninfected individuals successfully followed over 10 years: baseline (2005) and follow-up (2015) data

	Followed up in 2015 using baseline data (2005)			*10-year follow up (2015)*		
	HIV infected n = *117*	*HIV uninfected* n = *131*	p-*value*	*HIV infected* n = *117*	*HIV uninfected* n = *131*	p-*value*
Sociodemographic factors						
Male, *n* (%)	28 (23.9)	50 (38.2)	0.016	28 (23.9)	50 (38.2)	0.016
Urban, *n* (%)	51 (43.6)	52 (36.7)	0.53	51 (43.6)	52 (36.7)	0.53
Age, years	42.9 ± 5.64	44.7 ± 7.63	0.037	52.4 ± 5.66	54.2 ± 7.59	0.036
Anthropometry						
WC, cm	74.2 (61.5; 98.0)	75.8 (62.8; 100)	0.22	81.8 (64.1; 114)	82.8 (65.3; 105)	0.57
BMI, kg/m^2	22.5 (16.4; 35.6)	22.4 (16.9; 32.9)	0.85	23.2 (16.1; 37.5)	23.4 (16.1; 35.7)	0.79
Cardiovascular measurements						
SBP, mmHg	122 (97.0; 155)	126 (95.0; 172)	0.11	123 (94.0; 177)	128 (99.0; 177)	0.13
DBP, mmHg	84.7 ± 13.2	85.6 ± 14.4	0.59	82.3 ± 14.3	85.4 ± 13.8	0.22
PP, mmHg	37.1 (25.0; 59.0)	40.3 (25.0; 67.0)	0.029	40.2 (24.0; 75.0)	42.6 (28.0; 73.0)	0.15
MAP, mmHg	97.5 ± 14.5	99.6 ± 16.4	0.29	97.4 ± 17.1	100 ± 16.4	0.18
HR, beats/min	76.2 ± 13.1	73.5 ± 15.5	0.14	75.3 ± 15.0	73.1 ± 13.9	0.23
Biochemical variables						
TC, mmol/l	4.46 ± 1.27	5.05 ± 1.26	< 0.001	4.54 ± 1.01	4.32 ± 1.12	0.13
HDL-C, mmol/l	1.19 (0.56; 2.43)	1.58 (0.72; 3.19)	< 0.001	1.29 (0.76; 2.48)	1.32 (0.77; 2.53)	0.74
LDL-C, mmol/l	2.56 ± 1.04	2.80 ± 1.12	0.085	2.56 ± 0.23	2.25 ± 1.31	0.038
TG, mmol/l	1.11 (0.52; 2.42)	1.01 (0.57; 2.46)	0.11	1.14 (0.51; 2.79)	1.01 (0.55; 2.52)	0.099
TC:HDL-C ratio	3.59 (1.84; 7.21)	3.10 (1.71; 5.88)	0.003	3.43 (1.86; 16.0)	3.01 (1.56; 6.18)	0.016
TG:HDL-C ratio	0.93 (0.30; 3.17)	0.64 (0.22; 1.79)	< 0.001	0.89 (0.35; 2.39)	0.76 (0.26; 2.53)	0.11
Glucose, mmol/l	4.59 (3.30; 5.70)	4.79 (3.50; 6.30)	0.078	5.13 (4.14; 6.48)	5.09 (3.85; 7.22)	0.74
HbA_{1c}, %	5.46 (4.80; 6.20)	5.49 (4.90; 6.20)	0.52	5.46 (4.80; 6.30)	5.70 (4.90; 6.70)	0.013
CD4 count, cells/mm^3	314 (126; 702)	–	–	429 (145; 1035)	–	–
CRP, mg/l	2.31 (0.25; 40.9)	2.25 (0.23; 28.8)	0.88	4.06 (0.38; 56.9)	2.61 (0.91; 16.1)	0.022
ALT, U/l	17.5 (7.81; 46.4)	18.8 (8.00; 59.0)	0.34	20.7 (10.1; 49.3)	15.0 (8.00; 36.8)	< 0.001
AST, U/l	31.5 (14.2; 96.5)	29.5 (13.4; 108)	0.41	28.2 (15.3; 88.5)	23.5 (13.5; 62.1)	0.011
GGT, U/l	48.2 (17.2; 2228)	57.5 (18.8; 442)	0.128	53.3 (13.9; 342)	36.9 (10.2; 226)	0.006
Renal function						
Serum creatinine, µmol/l	69.2 (47.8; 101)	63.5 (47.0; 88.8)	0.003	55.7 (37.7; 79.8)	57.8 (37.6; 78.4)	0.42
uACR, mg/mmol	0.92 (0.15; 16.3)	0.57 (0.12; 2.63)	0.003	1.89 (0.48; 10.3)	1.48 (0.38; 9.41)	0.095
eGFR, ml/min/1.73 m^2	107 (67.8; 144)	118 (85.1; 149)	0.001	118 (95.6; 139)	116 (97.9; 140)	0.64
Lifestyle factors						
Tobacco use, *n* (%)	71 (60.7)	82 (62.6)	0.76	44/114 (38.6)	61/129 (47.3)	0.17
Alcohol use, *n* (%)	53 (45.3)	58 (44.3)	0.87	38/114 (33.3)	49/129 (37.9)	0.45
Medication use						
ART, *n* (%)	0 (0)	–	–	77/91 (84.6)#	–	–
< 5 years on ART, *n* (%)	0 (0)	–	–	24/77 (31.2)	–	–
≥ 5 years on ART, *n* (%)	0 (0.0)	–	–	53/77 (68.8)	–	–
Antihypertensive, *n* (%)	12 (10.3)	14 (10.7)	0.91	25/112 (22.3)	39/129 (30.2)	0.17
Controlled hypertension, *n* (%)	2 (16.7)	1 (7.14)	0.91	11 (44.0)	15 (38.5)	0.71
Statins, *n* (%)	0 (0.00)	0 (0.00)	1.00	2/112 (1.79)	1/129 (0.78)	0.48
Anti-inflammatory, *n* (%)	15 (12.8)	22 (16.8)	0.38	7/112 (6.25)	11/129 (8.53)	0.50
Antidiabetic, *n* (%)	0 (0.00)	1 (0.76)	0.34	0 (0.00)	3/129 (2.33)	0.10
Mortality, *n* (%)	77/320 (24)	3/320 (0.09)	–	0 (0.00)	0 (0.00)	–

Data are arithmetic mean ± SD or geometric mean (5th and 95th percentile intervals) for logarithmically transformed variables.
Out of the 117 HIV-infected individuals, information on ART use was available for 91 participants.
SD, standard deviation; HIV, human immunodeficiency virus; *n*, number of participants; WC, waist circumference; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; PP, pulse pressure, MAP, mean arterial pressure; HR, heart rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, glycated haemoglobin, GGT, γ-glutamyltransferase; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; uACR, urinary albumin creatinine ratio; eGFR, estimated glomerular filtration rate.

this is in agreement with our data, indicating an almost two-fold increase in ART, from 46% in 2010 to 85% in 2015 in our study cohort. However, in the total South African population, this is not reflected, since the use of ART is estimated at 56%.[22] Even though only 46% of the HIV-infected cohort was on ART in 2010, a marked decline in mortality rate was observed, corresponding well with the global decline in mortality rate with ART use.[2] The HIV-infected participants were younger compared to their counterparts, and showed no difference in chronic medication use. These factors together with the beneficial effect of ART may have contributed to the observed decline in mortality rate.

When tracking the HIV-infected participants and their controls over 10 years, similar changes in blood pressure and body composition were noted, but notable differences were seen for lipid profile and trajectory of elevated CRP, liver enzymes and eGFR in the HIV-infected group. Contrary to expectations of eGFR declining with age,[23] the HIV-infected participants displayed an increase in eGFR, which may suggest improved

Table 2. Baseline characteristics of HIV-infected individuals followed, lost to follow up and deceased

	Followed n = *117*	*Lost to follow* n = *144*	*Deceased* n = *77*	p-*value for trend*
Sociodemographic factors				
Male, *n* (%)	28 (23.9)	64 (44.4)	29 (37.7)	0.003
Urban, *n* (%)	51 (43.6)	75 (54.2)	33 (42.9)	0.14
Age, years	42.9 ± 5.64[a]	43.5 ± 7.86[b]	46.9 ± 10.3[ab]	0.002
Anthropometry				
WC, cm	74.2 (16.5; 98.0)	75.7 (64.2; 98.0)	74.6 (59.5; 99.8)	0.47
BMI, kg/m^2	22.5 (16.4; 35.6)	22.6 (17.3; 34.8)	21.0 (15.1; 32.5)	0.052
Cardiovascular measurements				
SBP, mmHg	122 (97.0; 155)	125 (98.0; 167)	119 (85.0; 166)	0.090
DBP, mmHg	84.6 ± 13.2	84.7 ± 15.3	81.8 ±16.0	0.34
PP, mmHg	37.1 (25.0; 59.0)[a]	40.6 (27.0; 62.0)[a]	37.3 (25.0; 66.0)	0.015
MAP, mmHg	97.5 ± 14.5	98.7 ± 17.1	97.8 ± 18.3	0.25
HR, beats/min	76.2 ± 13.1[a]	74.2 ± 15.0[b]	82.4 ± 18.9[ab]	0.001
Biochemical variables				
TC, mmol/l	4.46 ± 1.27	4.46 ± 1.25	4.30 ± 1.31	0.62
HDL-C, mmol/l	1.19 (0.56; 2.43)[a]	1.12 (0.56; 2.26)	0.97 (0.26; 2.61)[a]	0.024
LDL-C, mmol/l	2.56 ± 1.04	2.65 ± 1.02	2.52 ± 10.4	0.63
TG, mmol/l	1.11 (0.52; 2.42)	1.13 (0.56; 3.03)	1.22 (0.51; 3.10)	0.45
TC/HDL-C ratio	3.59 (1.84; 7.21)[a]	3.85 (2.21; 6.51)	4.22 (1.97; 13.4)[a]	0.033
TG/HDL-C ratio	0.93 (0.30; 3.17)[a]	0.99 (0.38; 4.23)	1.25 (0.51; 3.10)[a]	0.033
Glucose, mmol/l	4.59 (3.30; 5.70)	4.67 (3.40; 5.90)	4.51 (3.50; 5.70)	0.38
HbA_{1c}, %	5.46 (4.80; 6.20)	5.47 (4.70; 6.10)	5.62 (4.80; 6.40)	0.044
CD4 count, cells/mm^3	314 (243; 407)	306 (240; 389)	260 (178; 379)	0.70
CRP, mg/l	2.31 (0.25; 40.9)[a]	2.79 (0.31; 35.98)[b]	6.48 (0.46; 53.8)[ab]	< 0.001
ALT, U/l	17.5 (15.7; 19.6)	18.1 (16.3; 19.9)	18.9 (16.5; 21.8)	0.68
AST, U/l	31.5 (28.0; 35.4)	32.3 (29.1; 35.9)	36.6 (31.7; 42.2)	0.23
GGT, U/l	48.2 (17.2; 228)[a]	54.6 (18.3; 320)	67.0 (20.3; 489)[a]	0.046
Renal function				
Serum creatinine, µmol/l	69.2 (47.8; 101)	63.5 (44.7; 94.4)	67.9 (45.5; 114)	0.17
uACR, mg/mmol	0.92 (0.15; 16.3)	0.67 (0.14; 6.83)[a]	1.19 (0.20; 32.7)[a]	0.012
eGFR, ml/min/ 1.73 m^2	107 (67.8; 144)[a]	118 (79.8; 156)[a]	108 (58.5; 143)	0.008
Lifestyle factors				
Tobacco use, *n* (%)	71 (60.7)	86 (59.7)	43 (55.8)	0.79
Alcohol use, *n* (%)	53 (45.3)	69 (47.9)	40 (60.0)	0.66
Medication use				
ART, *n* (%)	–	–	–	–
Antihypertensive, *n* (%)	12 (10.3)	11 (7.64)	9 (11.7)	0.58
Anti-inflammatory, *n* (%)	15 (12.8)	11 (7.64)	12 (15.6)	0.16

Data are presented as mean and standard deviation for normally distributed variables and logarithmically transformed variables are presented as geographic mean and 5th and 95th percentile. Means with same superscript differ significantly ($p < 0.05$). HIV, human immunodeficiency virus; *n*, number of participants; WC, waist circumference; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; PP, pulse pressure, MAP, mean arterial pressure; HR, heart rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, glycated haemoglobin, GGT, γ-glutamyltransferase; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; uACR, urinary albumin creatinine ratio; eGFR, estimated glomerular filtration rate.

Table 3. Percentage change in cardiometabolic characteristics of HIV-infected and uninfected individuals (2005–2015)

	Percentage change between groups		
	HIV infected n = *117*	*HIV uninfected* n = *131*	p-*value*
Age, %	22.4 ± 3.04	21.7 ± 3.75	0.15
Anthropometry			
WC, %	9.12 (1.09; 18.7)	8.62 (1.73; 16.5)	0.80
BMI, %	3.70 ± 17.2	4.87 ± 11.2	0.53
Cardiovascular measurements			
SBP, %	0.00 (–8.01; 12.2)	0.83 (–9.82; 14.6)	0.84
DBP, %	–0.17 ± 19.1	1.54 ± 18.5	0.48
PP, %	4.82 (–12.5; 33.3)	4.76 (–13.9; 30.8)	0.65
MAP, %	0.84 ± 18.0	2.17 ± 18.0	0.56
HR, %	–1.30 (–13.9; 11.0)	0.00 (–12.6; 13.1)	0.60
Biochemical variables			
TC, %	6.48 (–12.2; 24.3)	–14.5 (–28.8; 2.90)	< 0.001
HDL-C, %	12.7 (–20.0; 46.0)	–15.1 (–31.8; 10.9)	< 0.001
LDL-C, %	–1.92 (–21.5; 33.3)	–16.4 (–38.8; 2.22)	< 0.001
TG, %	2.13 (–28.6; 46.3)	–1.86 (–22.0; 37.5)	0.83
TC:HDL-C ratio, %	–1.63 (–25.5; 22.1)	0.53 (–17.0; 23.1)	0.48
TG:HDL-C ratio, %	–8.10 (–40.5; 54.3)	21.4 (–17.1; 86.6)	0.011
Glucose, %	8.46 (–5.85; 21.6)	4.72 (–9.56; 16.3)	0.046
HbA_{1c}, %	0.01 (–5.71; 5.31)	2.12 (–1.77; 7.34)	0.009
CRP, %	75.8 (–38.1; 353)	0.08 (–52.1; 178)	0.047
ALT, %	25.4 (–15.9; 78.8)	–19.3 (–42.9; 15.1)	< 0.001
AST, %	–13.6 (19.7; 139)	–20.5 (–47.7; 13.4)	0.15
GGT, %	11.7 (–24.3; 68.7)	–33.9 (–55.5; -3.52)	< 0.001
Renal function			
Serum creatinine, %	–20.4 (–34.2; –2.28)	–10.8 (–26.9; 6.60)	0.033
uACR, %	106 (–36.3; 465)	132 (9.77; 365)	0.52
eGFR, %	4.83 (–5.90; 34.7)	–2.09 (–9.17; 10.5)	0.010

Data are presented as mean and SD for normally distributed variables and the variables that remained skew after log-transformation are presented as median with 25th and 75th percentiles.
SD, standard deviation; HIV, human immunodeficiency virus; *n*, number of participants; WC, waist circumference; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; PP, pulse pressure, MAP, mean arterial pressure; HR, heart rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, glycated haemoglobin; GGT, γ-glutamyltransferase; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; uACR, urinary albumin creatinine ratio; eGFR, estimated glomerular filtration rate.

renal function with ART use. However, if the data are reviewed as a trajectory towards possible future outcomes, continued increases in eGFR may reach the hyperfiltration range, which precedes the development of renal disease. Additionally, this population is exposed to risk factors such as ageing, and use of tobacco, alcohol and antihypertensive medication, which may in the future increase their CVD risk.[24]

A previous study using the PURE study population reported dyslipidaemia in the newly diagnosed HIV-infected, ART-naïve black Africans.[15] Now, based on the 10-year follow-up data with 85% of the HIV-infected participants on ART, this current study reports an increase in HDL-C and TC levels and a decrease in TG:HDL-C in the HIV-infected compared to the uninfected controls.

In support of the increase in HDL-C levels, more of the HIV-infected men had elevated HDL-C than their uninfected counterparts at baseline. However, after the introduction of ART in 2010, fewer of the HIV-infected participants presented with lower HDL-C levels, while after 10 years, no difference was observed. Higher HDL-C is cardioprotective, and this finding is consistent with a study that reported an increase in HDL-C level over 96 weeks in HIV-infected patients on a first-line regimen, especially nevirapine (NVP).[25] The participants in this study were using NVP (Fig. 1), which is associated with favourable lipid changes.[26]

Table 4. Change in cardiometabolic characteristics of the HIV-infected and uninfected individuals over 10 years

	HIV infected			
	2005	*2010*	*2015*	p-*value*
Biochemical variables (*n* = 93–101)*				
TC, mmol/l	4.41 ±1.24	4.57 ±0.16	4.57 ±1.03	0.31
LDL-C, mmol/l	2.58 ±0.99	2.68±1.01	2.59 ±0.90	0.45
HDL-C, mmol/l	1.18 (1.09; 1.29)	1.18 (1.10; 1.27)	1.30 (1.22; 1.39)	0.017
TG, mmol/l	1.08 (0.98; 1.19)	1.07 (0.91; 1.27)	1.15 (0.21; 1.28)	0.63
TC:HDL-C ratio	3.58 (3.32; 3.85)	3.72 (3.45; 4.02)	3.41 (3.18; 3.65)	0.003
TG:HDL-C ratio	0.91 (0.80; 1.04)	0.91 (0.76; 1.09)	0.88 (0.77; 1.01)	0.88
Glucose, mmol/l	4.61 (4.44; 4.79)[a]	4.70 (4.45; 4.96)[b]	5.15 (5.01; 5.28)[ab]	< 0.001
HbA_{1c}, %	5.48 (5.40; 5.57)[a]	5.67 (5.58; 5.77)[ab]	5.46 (5.37; 5.55)[b]	< 0.001
CRP, mg/l	2.35 (1.69; 3.25)[ab]	3.47 (2.60; 4.63)[a]	4.16 (3.11; 5.58)[b]	0.002
ALT, U/l	17.0 (15.3; 18.9)	19.6 (17.5; 22.0)	21.1 (18.9; 23.7)	0.006
AST, U/l	31.9 (28.5; 35.7)	28.1 (25.5; 31.0)	28.8 (26.0; 31.9)	0.11
GGT, U/l	45.9 (39.2; 53.6)	44.4 (36.8; 53.6)	53.3 (43.7; 65.0)	0.046
Renal function				
Serum creatinine, µmol/l	69.4 (65.9; 73.1)[ab]	56.3 (53.8; 58.9)[a]	56.1 (53.2; 59.1)[b]	< 0.001
uACR, mg/mmol	0.93 (0.71; 1.23)[a]	-	1.92 (1.54; 2.39)[a]	< 0.001
eGFR, ml/min/1.73 m^2	106 (100; 112)[b]	122 (118; 127)[a]	118 (113; 122)[ab]	< 0.001
	Uninfected			
	2005	*2010*	*2015*	p-*value*
Biochemical variables (*n* = 102–113)*				
TC, mmol/l	4.99 ±1.19[a]	4.86 ±1.13[b]	4.27 ±1.08[ab]	< 0.001
LDL-C, mmol/l	2.74 ±1.09[a]	2.78 ±1.10[b]	2.20 ±1.33[ab]	< 0.001
HDL-C, mmol/l	1.59 (1.48; 1.71)[a]	1.47 (1.38; 1.57)	1.31 (1.14; 1.51)[a]	0.006
TG, mmol/l	1.01 (0.94; 1.10)	1.05 (0.97; 1.13)	0.99 (0.88; 1.11)	0.58
TC:HDL-C ratio, %	3.04 (2.84; 3.26)	3.21 (2.99; 3.44)	2.97 (2.72; 3.24)	0.007
TG:HDL-C ratio, %	0.63 (0.57; 0.72)[a]	0.71 (0.63; 0.80)	0.75 (0.66; 0.86)[a]	0.023
Glucose, mmol/l	4.81 (4.65; 4.96)	4.94 (4.76; 5.12)	5.04 (4.84; 5.25)	< 0.001
HbA_{1c}, %	5.48 (5.40; 5.57)[abc]	5.92 (5.79; 6.06)[abc]	5.65 (5.52; 5.79)[abc]	< 0.001
CRP, mg/l	2.35 (1.78; 3.10)	2.72 (2.087; 3.55)	2.75 (2.10; 3.59)	0.45
ALT, U/l	18.6 (16.7; 20.9)	16.8 (15.2; 18.5)	15.0 (13.4; 16.9)	0.001
AST, U/l	29.0 (25.5; 33.1)[a]	26.1 (23.5; 28.9)	23.6 (21.1; 26.4)[a]	0.002
GGT, U/l	58.8 (49.3; 70.1)[abc]	47.0 (38.6; 57.2)[abc]	37.9 (31.1; 46.0)[abc]	< 0.001
Renal function				
Serum creatinine, µmol/l	63.9 (61.7; 66.2)	59.3 (57.1; 61.5)[a]	57.7 (52.9; 62.9)[a]	0.027
uACR, mg/mmol	0.60 (0.48; 0.74)[a]	-	1.44 (1.17; 1.77)[a]	< 0.001
eGFR, ml/min/1.73 m^2	118 (114; 122)	121 (118; 124)	116 (106; 127)	0.53

Data are presented as mean and SD for normally distributed variables and for logarithmically transformed variables as geographic mean and 5th and 95th percentile. Means with same superscript differ significantly ($p < 0.05$).
*Data available for all three data collection time points were less than those for 2005 to 2015. SD, standard deviation; HIV, human immunodeficiency virus; *n*, number of participants; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, glycated haemoglobin; GGT, γ-glutamyltransferase; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase uACR, urinary albumin creatinine ratio; eGFR, estimated glomerular filtration rate.

Table 5. Percentage of cardiometabolic risk factors exceeding specific cut-offs of the HIV-infected and uninfected individuals over 10 years

	Cardiometabolic factors		
2005 baseline study	*HIV infected* n = *320*	*HIV uninfected* n = *320*	p-*value*
WC, *n* (%)			
Women ≥ 94 cm	16/198 (8.0)	19/194 (10)	0.55
Men ≥ 80 cm	17/117 (15)	17/116 (15)	0.98
Blood pressure ≥ 130/85 mmHg, *n* (%)	105/320 (32.8)	136/320 (42.5)	0.011
Glucose ≥ 5.6 mmol/l, *n* (%)	35/301 (12)	47/307 (15)	0.18
HDL-C, *n* (%)			
Women ≤ 1.29 mmol/l	34/124 (27.4)	50/161 (31)	0.504
Men ≤ 1.03 mmol/l	48/125 (38)	21/108 (19)	0.016
TG ≥ 1.7 mmol/l, *n* (%)	55/313 (18)	48/318 (15)	0.40
2010 follow-up study	n = *163*	n = *192*	
WC, *n* (%)			
Women ≥ 94 cm	6/114 (5)	21/117 (18)	0.003
Men ≥ 80 cm	9/47 (19)	12/71 (17)	0.75
Blood pressure ≥ 130/85 mmHg, *n* (%)	58/160 (36)	87/185 (47)	0.043
Glucose ≥ 5.6 mmol/l, *n* (%)	14/161 (9)	27/184 (15)	0.087
HDL-C, *n* (%)			
Women ≤ 1.29 mmol/l	44/115 (38)	66/113 (58)	0.002
Men ≤ 1.03 mmol/l	33/44 (75)	59/66 (89)	0.046
TG ≥ 1.7 mmol/l, *n* (%)	42/162 (26)	38/192 (20)	0.18
2015 follow-up study	n = *117*	n = *131*	
WC, *n* (%)			
Women ≥ 94 cm	18/73 (25)	36/95 (38)	0.504
Men ≥ 80 cm	11/25 (44)	17/53 (32)	0.31
Blood pressure ≥ 130/85 mmHg, *n* (%)	42/117 (36)	61/131 (47)	0.088
Glucose ≥ 5.6 mmol/l, *n* (%)	23/104 (22)	32/120 (27)	0.43
HDL-C, *n* (%)			
Women ≤ 1.29 mmol/l	39/83 (47)	30/77 (39)	0.31
Men ≤ 1.03 mmol/l	17/23 (75)	41/49 (84)	0.33
TG ≥ 1.7 mmol/l, *n* (%)	20/92 (22)	19/141 (13)	0.098

Data are presented as proportion and percentage.
HIV, human immunodeficiency virus; *n*, number of participants; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides. The cardiometabolic factors were defined using the International Diabetes Federation (IDF) definition as follows: central obesity: men ≥ 94 cm and women ≥ 80 cm; hyperglycaemia: fasting plasma glucose ≥ 5.6 mmol/l or previously diagnosed with type 2 diabetes; dyslipidaemia ≥ 1.7 mmol/l or specific treatment; dyslipidaemia (second criteria), HDL-C men < 1.03 mmol/l and women < 1.29 mmol/l or specific treatment; raised blood pressure ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic blood pressure or on treatment.

The decrease seen in TG:HDL-C in the HIV-infected participants over time may be attributed to the effect of the increase in HDL-C levels.[27] These findings suggest that increased longevity on ART provides benefits, and the low to moderate effect of ART on CVD risk factors might be modulated by the mean age of the participants being 52.4 ± 5.66 years at follow up.[28] It is well documented that older age is associated with higher CVD risk,[29] and the study participants were middle-aged, leaving several years for the consequences of CVD to take effect.

The 10-year continued elevation in circulating CRP levels in HIV-infected black Africans confirms the well-known inflammatory response due to HIV infection, which is marked by excess leukocytes and cytokines.[9] Early and effective ART initiation plays an important role in reducing immune activation and inflammation in HIV-infected individuals.[30] However, findings from randomised, controlled trials reported persistently elevated CRP levels in HIV-infected patients before and after ART use, and CRP elevation was associated with HIV disease progression.[31] The finding of this study supports persistent low-grade inflammation in HIV-infected patients, even after long-term ART, which may be a result of on-going viral replication or microbial translocation.[32] Moreover, CRP is associated with CVD risk and all-cause mortality not only in the general population,[33] but also in HIV-infected patients.[9]

Inflammation may be further aggravated in the presence of oxidative stress, which may be a consequence of both HIV infection and ART.[34] Higher levels of GGT were seen, a liver enzyme known to play an important role in maintaining glutathione homeostasis and normal redox status,[35] along with a greater increase in GGT over 10 years in the HIV-infected group. Where others reported that ART lowered serum GGT in HIV-infected patients,[10] the findings of this study did not support this, which could be attributed to the effects of the nucleosides.[10] The use of GGT applies beyond oxidative stress, as it is also a marker of non-fatty and alcohol-related liver disease.[36] Although self-reported alcohol use was high in our study, it did not differ between these groups.

Together with GGT, higher ALT and AST levels were reported at follow up and an increase in ALT over time in the HIV-infected participants compared to a decrease in uninfected counterparts. These results are in agreement with previous findings.[10] It should be noted, however, that ALT and GGT levels were not above the cut-off values of 40 and 50 U/l, respectively, for liver disease.[37,38] Administration of NRTIs is associated with mitochondrial toxicity, while NNRTIs are metabolised by the cytochrome P450, known to increase activities of co-administered ART and hence elevating the toxic effect on the hepatocytes.[39] As the HIV-infected participants will continue ART, it is expected that these liver enzymes will increase further over time, which warrants regular monitoring of liver function in the future.

In those with HIV, higher uACR and lower eGFR at baseline was indicated, while over 10 years, eGFR increased. This increase in eGFR is contrary to the normal expectations of a decrease with aging,[23] but aligns well with the findings of the Multicenter AIDS Cohort Study where an increase in eGFR in HIV-infected patients was defined as hyperfiltration (eGFR ≥ 140 ml/min/1.73 m^2).[40] This finding may indicate renal deterioration and may in future lead to the observed higher prevalence of renal failure in HIV-infected populations.[11] However, in this study the eGFR was not above the cut-off value as proposed by the Multicenter AIDS Cohort Study.

This increase for eGFR may also suggest a catch-up effect in renal function over time due to ART. Renal impairment occurs dependent or independent of HIV infection. In the former pattern, HIV alters renal function as a result of immune suppression and when ART is introduced, renal function improves by exerting its antiviral effects.[41] In the latter pattern, patients have improved immune function due to long-term ART use, which later results in nephrotoxicity, or as a result of pre-existing renal impairment and aging.[42] Although the renal function markers did not indicate renal disease over time, it is important that regular renal screening be done as this HIV-infected cohort is ageing and using life-long ART.

The findings of this study should be interpreted in the context of the strengths and limitations of our study design. Demographic and cardiometabolic profiling of HIV-infected and control participants were carefully performed over a period of 10 years, thereby contributing to longitudinal data in Africans living with HIV. HIV-infected participants (n = 20) that were newly diagnosed during the follow-up studies were also included. Regarding ART information, ART use was not available for 26 HIV-infected participants. Although this study is limited by a relatively small sample size, it is overcome somewhat by the longitudinal design of the study, but may not be representative of the HIV-infected population of South Africa.

Conclusion

South Africans living with HIV for 10 years presented with similar changes in blood pressure and body composition compared to their uninfected counterparts. However, HIV infection was accompanied by longitudinal changes in the lipid profile, which may indicate the future development of dyslipidaemia. Low-grade inflammation and oxidative stress are common in HIV-infected individuals using ART, and the changes seen may, together with the lipid changes, reflect the development of a pro-atherogenic profile, which is associated with increased risk of CVD. In addition, the trajectories of increased CRP levels, elevated liver enzymes and increased eGFR should be carefully monitored in light of HIV infection and ART use.

The authors are grateful to all participants who voluntarily took part in the study, the PURE-SA research team and the field workers, North-West University, South Africa, as well as Prof Lanthé Kruger (PURE South Africa), Dr S Yusuf (PURE International), the PURE project team at Hamilton Health Sciences at the McMaster University, ON, Canada, the South African Medical Research Council and the National Research Foundation, Department of Science and Technology, and Servier Medical Art.

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Relationship between obesity and blood pressure among employees in the Vhembe district municipality of Limpopo Province, South Africa

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Abstract

Objective: The aim of this study was to investigate the relationship between obesity and blood pressure among employees of the Vhembe district municipality of Limpopo province.

Methods: A cross-sectional study was conducted among 452 local government employees (207 males, 245 females) aged 24–65 years. Body mass index (BMI), blood pressure (BP) and waist circumference (WC) measurements, and waist-to-height ratio (WHtR) were assessed. Data were analysed using Statistical Package for Social Sciences (SPSS) statistics, version 21.

Results: The results showed that 27% of the participants were classified as overweight and 34% as obese, with females being more overweight and obese (29 and 48%, respectively) compared to males (24 and 17%, respectively). Twenty-five per cent of the participants were hypertensive, with females (27%) showing a higher prevalence compared to males (22%). Based on BMI categories, the obese group (35%) had a higher prevalence of hypertension in contrast to groups that were of normal weight (18%) and overweight (22%). The results also showed that systolic blood pressure (SBP) was positively ($p \leq 0.05$) correlated with BMI ($r = 0.15$), WC ($r = 0.26$) and WHtR ($r = 0.29$) in the normal and overweight groups (WC, $r = 0.23$ and WHtR, $r = 0.26$), and WHtR correlated with SBP ($r = 0.26$) and diastolic blood pressure (DBP) ($r = 0.19$).

Conclusion: The study showed a high prevalence of overweight, obesity and hypertension, with females more affected than their male counterparts. BMI, WC and WHtR were positively correlated with SBP in the normal and overweight groups, with WHtR positively correlated with both SBP and DBP in the overweight group. Therefore, it is recommended that intervention regimes designed to address obesity and hypertension should consider risk awareness for cardiovascular diseases, impaired quality of life and productivity among local government employees.

Keywords: obesity, hypertension, employees, blood pressure, body mass index

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Submitted 17/1/19, accepted 18/6/19
Published online 12/9/19
Cardiovasc J Afr 2019; **30**: 361–368 www.cvja.co.za

DOI: 10.5830/CVJA-2019-035

Obesity is one of the most important public health problems worldwide.[1] It is a major independent risk factor for chronic diseases, such as cardiovascular disease and diabetes mellitus, and is associated with high morbidity and mortality rates.[2] According to the World Health Organisation (WHO), up to 20% of the population in developed countries may suffer from obesity-associated hypertension, which may account for 78 and 65% of essential hypertension in males and females, respectively.[3,4] The WHO[4] reported that one in six adults is obese and one in three has elevated blood pressure (BP), with the highest prevalence recorded in Africa. Obesity and hypertension are among the preventable risk factors for cardiovascular disease that impose a considerable economic burden, particularly in developing countries.[5]

Hypertension is one of the 10 leading contributors to the global burden of disease and the most important risk factor for mortality worldwide,[4,6,7] and has been described as a silent killer due to its asymptomatic nature among sufferers.[8] Studies have reported that about nine million people die from hypertension annually.[9,10] The prevalence of hypertension in Africa has been reported in several previous studies.[9,11,12] Hypertension was once considered a disease of affluence but is now prevalent among the poor.[13] South Africa is facing a serious burden of hypertension.[14] More than 6.2 million South Africans are hypertensive, with 3.2 million having a BP of > 160 mmHg.[15]

Several studies have shown a clear association with BP increase and weight gain.[5,16,17] It has been reported that obese subjects have a 3.5 times increased likelihood of hypertension and that 60% of hypertension is attributable to an increase in adipose tissue stores.[2] Data from the National Health and Nutrition Examination Survey in 2004 indicated that the prevalence of hypertension among obese individuals with a body mass index (BMI) > 30 kg/m² was 42.5%, compared with 15.3% in lean individuals.[18] Visceral fat distribution is another genetic factor that contributes to the increase in BP levels among obese individuals.[19] In addition, environmental and behavioural factors, such as alcohol intake, cigarette smoking, timing of onset of childhood obesity, change in daily lifestyle habits and alteration in lipid profile may be implicated in visceral fat distribution and increased BP values.[20-22] Most studies suggest that centrally located body fat is a stronger determinant of BP elevation than peripheral body fat in both men and women.[21,23]

A positive correlation between BMI and BP has been reported among Ghanaian adults aged 30 to 50 years old.[24] Certain occupations, especially white-collar jobs, are characterised by sitting for long periods of time, such as employees in financial institutions and administration offices, and this predisposes individuals to a sedentary lifestyle.[25] These individuals tend to spend the majority of their adult working lives less engaged in physical activity outside of working hours, thereby predisposing them to obesity and diseases.[26] A study in India reported a higher prevalence of hypertension, which was more positively correlated to obesity among employees than the general population of the country.[27]

A recent systematic review among workers in West Africa reported a prevalence of hypertension of 12 to 69% among employees.[28] The prevalence of obesity ranged from 2% among automobile garage employees in Kumasi, Ghana,[29] to 42.1% among healthcare workers in Umuahia, Nigeria.[30] The prevalence of hypertension ranged from 27.9 to 78.9% among obese workers compared with 7.3 to 65.4% among non-obese employees in West Africa.[31] Among healthcare workers in a university teaching hospital, there appeared an unusual ratio in the association between obesity and hypertension, which was 2.2 ($p = 0.004$).[32] In Kaduna, civil servants younger than 40 years old who were overweight or obese were five times as likely to have hypertension compared with healthy-weight workers.[33] Schutte *et al*.[34] reported a prevalence of 48% overweight and obesity among South African employees from 18 companies participating in health-screening programmes. Cardiovascular risk factors, specifically diabetes and hypertension, were found to be associated with obesity among public service workers in Ondo State, Nigeria.[35]

This study will be first of its kind to study employees in the Vhembe district municipalities of the Limpopo Province to investigate the relationship between obesity and BP.

Methods

The research was based on a cross-sectional design on an available population sample of local government employees in the Vhembe district municipality of the Limpopo Province, South Africa. Participants voluntarily participated in the study.

There were 452 (men = 207; women = 245) participants from local government employees in the Vhembe district, which is one of the five districts of the Limpopo Province of South Africa (local government is a form of public administration in South Africa, which exists as the lowest tier of administration in the provinces). Vhembe district is located in the northern part of the country and shares its borders with the Beitbridge district in Matabeleland south, Zimbabwe. According to the 2001 census, 800 000 Vhembe district residents speak Tshivenda as their mother tongue, while 400 000 speak Tsonga and 27 000 speak Northern Sotho.[36] The majority of the participants in this study were employed as grounds maintenance workers, clerical workers, managers and councillors. The employees were categorised into three age groups as follows: 24–29, 30–44 and 45–65 years. Participants were included in the study if they were within the age categories and deemed healthy.

Standing height was measured to the nearest 0.1 cm, using a Harpenden portable stadiometer (Holtain Ltd, Crymych, Dyfed, UK). Body mass was measured using a portable calibrated scale (SECA) and recorded to the nearest 0.5 kg. BMI was calculated as body mass (kg) divided by height (m) squared (kg/m^2).

Waist circumference (WC) was measured using a steel tape measure and in accordance with the procedure recommended by the American College of Sports Medicine.[37] For men, low WC in this classification is defined as less than 94 cm, high is 94 to 102 cm, and very high is greater than 102 cm. For women, low WC is less than 80 cm, high is 80 to 88 cm, and very high is greater than 88 cm.[38,39] Waist-to-height ratio (WHtR) was determined from waist circumferences (cm) divided by height (cm). The norms for WHtR were as follows: normal is WHtR < 0.5, while WHtR > 0.5 indicates increased risk for both males and females.[40]

BP was measured by using an automated sphygmomanometer (Omron, Health Care, Inc, USA). The participants were seated, and systolic (SBP) and diastolic (DBP) blood pressure measurements were determined according to the protocols suggested by the American College of Sports Medicine (ACSM).[37]

The ACSM has identified thresholds above which individuals may be at an increased risk for cardiovascular disease.[37] The thresholds that were used to describe risk included the following:

- overweight = BMI between 25 and 29.9 kg/m^2; obesity = BMI ≥ 30 kg/m^2
- hypertension = SBP ≥ 140 mmHg and DBP ≥ 90 mmHg, as well as for participants on hypertension treatment.

The aim of the study was explained to the participants and their employers, who were also informed that the data would be treated confidentially and would only be used for the purposes of research. The participants were requested to complete and sign an informed consent form before participating in the study. The measurements took place during weekdays, as arranged with the participants. The researcher (a biokineticist registered with the Health Professions Council of South Africa: registration number BK 0016195-HPCSA) was assisted by well-trained research assistants conducting the measurements. The anthropometric measurements of height, weight, WC and BP were taken in allocated separate rooms for males and females. The study received ethical approval (Ref: NWU-00125-13-S1) from the ethics committee of North West University, Potchefstroom, South Africa.

Statistical analysis

Descriptive statistics were calculated for all variables according to gender. Numerical data are expressed as mean and standard deviation (mean ± SD) and categorical data are expressed as percentages. A *t*-test was used to determined differences in the means of variables (age, height, weight, BMI, WC, WHtR, and SBP and DBP between the study groups), and the chi-squared test was used to compare the prevalence of general obesity and central/abdominal obesity in men and women. The differences in BMI and WC across age groups were described by gender, and the chi-squared test was used to compare the prevalence of obesity between the various age groups. To determine the differences between the BMI categories/groups, an analysis of variance (ANOVA) was calculated for all variables. Descriptive characteristics of the hypertensive and normotensive groups were determined and compared. Pearson correlation coefficients were used to determine the relationship between obesity and BP among employees. All statistical analyses were performed with the SPSS, version 21. The statistical level of the *p*-values was set at $p \leq 0.05$.

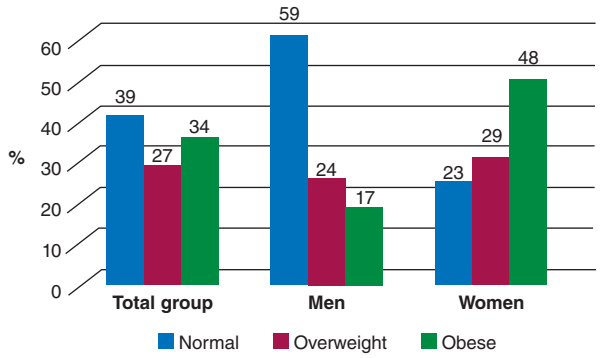

Fig. 1. BMI categories for the total group and by gender.

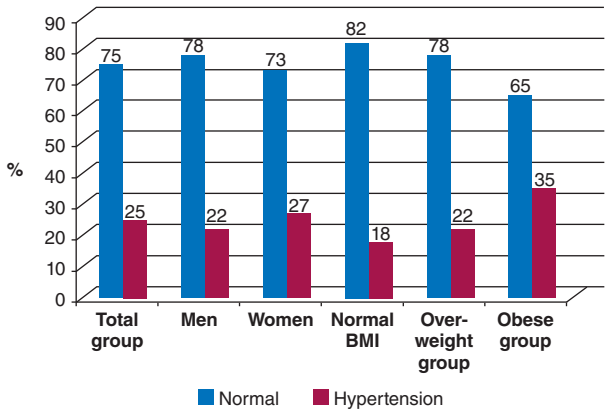

Fig. 2. Hypertension for the total group by gender and BMI categories

Results

Fig. 1 presents the percentage for BMI categories for the total group and by gender. The results show that of the total group, 39% had normal weight, 27% were overweight and 34% were obese. The findings also indicate that 29% of women were overweight compared to 24% of men. Similarly 48% of women were obese in comparison to 17% of men.

Fig. 2 presents the percentage of hypertension for the total group by gender and BMI categories. In the total group, the results show that 25% of the employees presented with hypertension in which the women (27%) were more affected than men (22%). When the data were analysed according to BMI categories, the results showed a significantly higher percentage of hypertension in both the overweight and obese groups.

Table 1 presents the percentages regarding the subjects' characteristics for the total, non-obese and obese groups. The women in the age group of 45 to 65 years had a higher prevalence of overweight (84.7%) and obesity (87.3%) compared to 76.6 and 82.9% of the men (Table 1). The results also show that participants with no education tended to be more overweight (71.1%) compared to those with qualifications, where women were 76.4% overweight and 66.1% obese, in contrast to men who were 63.3% overweight and 65.7% obese. The findings also indicate that 83.5% of grounds maintenance employees were overweight and 79.7% were obese in comparison to participants in other occupations, where women showed a higher preponderance of overweight (90.3%) and obesity (77.1%) compared to men who were 73.5% overweight. Accounting clerks showed a higher percentage of obesity (88.6%) within the obese category.

Presented in Table 2 are the means and standard deviations for overweight and obesity for the total group and by gender. As shown in the results, the mean height for the non-obese group was 167.94 ± 8.80 cm (from the total group of 178 participants). Men were taller on average (170.71 ± 7.19 cm) than women

Table 1. Subject characteristics of the men, women and total participants in the non-obese and obese groups

	Non-obese group, n (%)			*Obese group, n (%)*					
				Total participants		*Men*		*Women*	
	Total participants	*Men*	*Women*	*OV*	*OB*	*OV*	*OB*	*OV*	*OB*
Variables									
Age group (years)									
24–29	17 (9.6)	4 (3.3)	13 (23.6)	8 (7)	5 (3)	1 (2)	2 (5.7)	7 (9.7)	3 (2.5)
30–44	14 (7.9)	8 (6.5)	6 (10.9)	13 (11)	16 (11)	9 (18)	4 (11.4)	4 (5.6)	12 (10.2)
45–65	147 (82.6)	111 (90.2)	36 (65.5)	100 (83)	132 (86)	39 (76.6)	29 (82.9)	61 (84.7)	103 (87.3)
Qualification									
No formal education	124 (69.7)	92 (74.8)	32 (58.2)	86 (71.1)	101 (10)	31 (63.3)	23 (65.7)	55 (76.4)	78 (66.1)
Std 8	8 (4.5)	8 (6.5)	8 (14.5)	4 (8.3)	10 (6.5)	2 (4.1)	4 (11.4)	2 (2.8)	6 (5.1)
Matric	20 (11.2)	12 (9.8)	10 (18.2)	7 (5.8)	18 (12)	3 (6.1)	2 (5.7)	4 (5.6)	16 (13.6)
Diploma	17 (9.6)	7 (5.7)	1 (1.8)	9 (7.4)	16 (10.5)	5 (10.2)	4 (11.4)	4 (5.6)	12 (10.2)
Degree 1	2 (1.1)	1 (0.8)	1 (1.8)	2 (1.7)	3 (2)	2 (4.1)	1	-	2 (1.7)
Degree 3	1 (0.6)	1 (0.8)	2 (3.6)	5 (4.1)	4 (2.6)	3 (6.1)	1	2 (2.8)	3 (2.5)
Degree 4	3 (1.7)	1 (0.8)	1 (1.8)	7 (5.8)	–	3 (6.1)		4 (5.6)	
Certificate	2 (1.1)	1 (0.8)	–	1 (0.8)	1 (0.7)	-		1 (1.4)	1 (0.8)
Occupation									
General clerk	12 (6.7)	11 (8.9)	1 (1.8)	11 (9.1)	18 (11.8)	8 (16.3)	4 (11.4)	3 (4.2)	14 (11.9)
Accounting clerk	3 (1.7)	1 (0.8)	2 (3.6)	2 (1.7)	7 (4.6)	1 (2.0)	31 (88.6)	1 (1.4)	7 (5.9)
Grounds maintenance workers	160 (89.9)	111 (90.2)	49 (89.1)	101 (83.5)	122 (79.1)	36 (73.5)		65 (90.3)	91 (77.1)
Municipality manager (MM)	1 (0.6)	–	1 (1.8)	6 (6)	2 (1.3)	4 (8.2)		2 (2.8)	2 (1.7)
Councillors	2 (1.1)	–	2 (3.6)	1 (1)	4 (2.6)	–		1 (1.4)	4 (3.4)

OV = overweight; OB = obese, Std 8 = Standard eight (grade 10).

(161.76 ± 9.27 cm). The mean weight was 64.90 ± 7.97 kg for the total group, in which men were heavier (66.75 ± 7.93 kg) than women (60.75 ± 6.38 kg). Regarding BMI, the mean value for the total group was 22.99 ± 2.05 kg/m²; however, specific values were 22.89 ± 2.13 kg/m² for men and 23.23 ± 1.83 kg/m² for women.

Mean BP data for the total group were as follows: SBP (138.53 ± 23.10 mmHg), DBP (77.04 ± 13.62 mmHg), whereas corresponding values for men and women, respectively, were SBP 142.20 ± 23.05 mmHg and DBP 78.05 ± 14.53 mmHg, and SBP 130.31 ± 21.17 mmHg and DBP 74.80 ± 11.11 mmHg. The mean height for participants who were overweight and obese was 164.15 ± 8.39 cm and 160.87 ± 10.73 cm, respectively, for the total participants. In total, participants who were overweight and obese had a mean weight of 76.67 ± 7.77 and 92.85 ± 14.67 kg, respectively. However, the mean BMI for overweight and obese groups was, respectively, 28.42 ± 1.46 and 35.92 ± 4.92 kg/m². For the total group, the average SBP for overweight and obese participants, respectively, was 137.74 ± 21.71 and 145.76 ± 24.06 mmHg, with a mean DBP of 79.26 ± 11.26 and 84.90 ± 12.49 mmHg.

Table 3 presents ANOVA results for the variables of interest according to the three BMI categories. The results show significant group differences ($p = 0.05$) for height, with normal and overweight men being taller than underweight and obese counterparts, while no significant group differences ($p = 0.18$) were found among the women's BMI categories. Significant group differences ($p \leq 0.05$) were observed for body weight, BMI, WC and WHtR, with the overweight and obese groups having high mean values. Additionally, the results showed significant differences in the SBP and DBP for both overweight and obese women. No significant group differences ($p \geq 0.05$) were found in the blood pressure variables for men.

Provided in Table 4 are the descriptive data (mean, minimum, maximum and SD) for the overweight and obese groups by gender. The mean age and height of the participants in the obese group were as follows: men (51.84 ± 8.60 years; 168.34 ± 11.90 cm) and women (52.95 ± 9.07 years; 159.46 ± 6.94 cm). Corresponding data for body weight included the following: men (83.97 ± 13.43 kg) and women (83.80 ± 15.67 kg). The mean BMI of the obese group was 29.76 ± 4.81 kg/m² in men, and 32.91 ± 5.52 kg/m² in women, with a mean WC of 98.06 ± 11.96 and 99.41 ± 15.04 cm obtained for men and women, respectively. In the obese group the mean SBP was 140.44 ± 20.21 mmHg for men, and 143.61 ± 24.61 mmHg for women. However, the mean DBP was 80.23 ± 12.93 and 82.79 ± 12.93 mmHg for the men and women, respectively. The results also show that there was a significant difference ($p \leq 0.05$) in height, BMI and WHtR among men and women.

Table 5 presents the correlation coefficients for the normal, overweight and obese groups. In all three BMI groups, BW, WC, BMI and WHtR were significantly and positively related to each other. In the normal group, SBP was positively ($p \leq 0.05$) correlated with BMI ($r = 0.150$), WC ($r = 0.26$) and WHtR ($r = 0.29$). In the overweight category, WC was significantly ($p \leq 0.05$) and positively correlated with SBP ($r = 0.23$), and WHtR was positively associated with both SBP ($r = 0.26$) and DBP ($r = 0.19$).

Discussion

The purpose of this study was to investigate the relationship between obesity and BP among employees in the Vhembe district municipality of the Limpopo Province, South Africa. The study showed that 27 and 35% of the total participants were overweight and obese, respectively. These findings were higher in comparison to a study by Lategan, *et al.*,[41] which found that half of the participants from the black urban population of the Free State community had a BMI above normal (23% overweight and 32% obese). The results of this study concur with the findings of WHO,[42] which estimated that 45.1% of the South African population were overweight and obese. Schutte, *et al.*[34] reported a prevalence of 48% overweight and obesity among South African employees from 18 companies participating in health-screening programmes.

The findings of this study, according to gender, showed that females were more overweight and obese (29, 48%) compared to males (24, 17%). This is higher when compared to findings by the South African Demographic and Health Survey,[43] reporting that 18.7% of urban black men were overweight and 8.1% were obese, with 27.1% of urban black women being overweight and 33.8% obese. Our findings confirmed the trend that black South African women have substantially higher BMIs than their male counterparts. Overweight or obese individuals are at greater risk of developing metabolic (type 2 diabetes and dyslipidaemia) and non-metabolic disorders.[44]

The study also found a 25% prevalence of hypertension in the total group; this is lower when compared with a study by Maepa *et al*,[45] which reported a 39.5% prevalence of hypertension among employees in the gold mines of Gauteng's Harmony Gold Mining Company in South Africa. This also corresponds with findings by Owalabi *et al.*,[46] which revealed that 49.2% of the Buffalo City metropolitan municipality adults had a high prevalence of hypertension. The findings of the study are also

Table 2. Descriptive statistics (mean and standard deviations) of the men, women and total participants in the overweight and obese groups

	Non-obese group, mean ± SD				*Overweight and obese group, mean ± SD (n = 274)*						
	Total participants				*Total participants*		*Overweight*			*Obese group*		
	(n = 178)	*Men (n = 123)*	*Women (n = 55)*	p-*values*	*OV (n = 121)*	*OB (n = 153)*	*Men (n = 49)*	*Women (n = 72)*	p-*values*	*Men (n = 35)*	*Women (n = 118)*	p-*values*
Height	167.94 ± 8.80	170.71 ± 7.19	161.76 ± 9.27	< 0.001	164.15 ± 8.39	160.87 ± 10.73	170.22 ± 7.38	160.01 ± 6.26	< 0.001	165.60 ± 17.34	159.47 ± 7.31	0.003
Weight	64.90 ± 7.97	66.75 ± 7.93	60.75 ± 6.38	< 0.001	76.67 ± 7.77	92.85 ± 14.67	81.50 ± 7.68	73.38 ± 5.93	< 0.001	95.09 ± 14.77	92.19 ± 14.77	0.31
BMI	22.99 ± 2.05	22.89 ± 2.13	23.23 ± 1.83	0.30	28.42 ± 1.46	35.92 ± 4.92	28.09 ± 1.42	28.65 ± 1.46	0.04	34.97 ± 5.06	36.20 ± 4.87	0.19
WC	84.20 ± 11.02	85.24 ± 12.30	81.85 ± 6.92	0.05	93.92 ± 10.76	105.42 ± 14.42	96.53 ± 7.13	92.15 ± 12.39	0.03	105.81 ± 15.70	105.31 ± 14.08	0.86
SBP	138.53 ± 23.10	142.20 ± 23.05	130.31 ± 21.17	0.001	137.74 ± 21.71	145.76 ± 24.06	138.45 ± 18.07	137.25 ± 23.98	0.77	138.23 ± 21.06	147.99 ± 24.52	0.05
DBP	77.04 ± 13.62	78.05 ± 14.53	74.80 ± 11.11	0.14	79.26 ± 11.26	84.90 ± 12.49	80.67 ± 10.97	78.31 ± 11.43	0.26	79.57 ± 10.49	86.48 ± 12.63	0.004
WHtR	0.50 ± 0.07	0.50 ± 0.07	0.51 ± 0.05	0.58	0.57 ± 0.07	0.65 ± 0.08	0.57 ± 0.04	0.58 ± 0.08	0.43	0.62 ± 0.07	0.66 ± 0.08	0.04

OW = overweight; OB = obese.

Table 3. Participants' anthropometric and physiological characteristics according to BMI categories by gender

	Men				Women			
Variables	n	*Mean*	*SD*	p-*value of the differences*	n	*Mean*	*SD*	p-*value of the differences*
Height (cm)								
Underweight	15	169.73	9.94	0.05	1	169.00	.	0.18
Normal	123	170.71	7.19		55	161.76	9.27	
Overweight	49	170.22	7.38		72	160.01	6.26	
Obese	35	165.60	17.34		118	159.46	7.31	
Total	222	169.73	9.81		246	160.18	7.55	
Body weight (kg)								
Underweight	15	49.51	5.77	< 0.001	1	51.00	.	< 0.001
Normal	123	66.75	7.93		55	60.75	6.38	
Overweight	49	81.50	7.68		72	73.38	5.93	
Obese	35	95.09	14.77		118	92.19	14.63	
Total	222	73.31	15.35		246	79.49	17.09	
BMI (kg/m^2)								
Underweight	15	17.17	1.23	< 0.001	1	17.85	.	< 0.001
Normal	123	22.89	2.13		55	23.23	1.84	
Overweight	49	28.09	1.42		72	28.65	1.46	
Obese	35	34.97	5.07		118	36.20	4.87	
Total	222	25.55	5.58		246	31.01	6.45	
WC (cm)								
Underweight	15	73.47	4.56	< 0.001	1	79.00	.	< 0.001
Normal	123	85.24	12.30		55	81.85	6.92	
Overweight	49	96.53	7.13		72	92.15	12.39	
Obese	35	105.81	15.70		118	105.31	14.08	
Total	222	90.18	14.63		246	96.11	15.56	
SBP (mmHg)								
Underweight	15	138.80	27.28	0.65	1	156.00	.	< 0.001
Normal	123	142.20	23.05		55	130.31	21.17	
Overweight	49	138.45	18.07		72	137.25	23.98	
Obese	35	138.23	21.06		118	147.99	24.52	
Total	222	140.52	21.98		246	140.93	24.63	
DBP (mmHg)								
Underweight	15	83.27	15.13	0.44	1	92.00	.	< 0.001
Normal	123	78.05	14.53		55	74.80	11.11	
Overweight	49	80.67	10.96		72	78.30	11.43	
Obese	35	79.57	10.49		118	86.48	12.63	
Total	222	79.22	13.29		246	81.50	12.91	
WHtR								
Underweight	15	0.43	0.02	< 0.001	1	0.46	.	< 0.001
Normal	123	0.50	0.08		55	0.50	0.05	
Overweight	49	0.56	0.04		72	0.57	0.07	
Obese	35	0.62	0.07		118	0.65	0.08	
Total	222	0.53	0.08		246	0.60	0.09	

BMI = body mass index, WC = waist circumference. SBP = systolic blood pressure, DBP = diastolic blood pressure, WHtR= waist-to-height ratio, *n* = number, SD = standard deviation.

Table 4. Descriptive statistics of age, height, BMI, WC, SBP, DBP and WHtR for the overweight and obese group by gender

Variables	n	*Min*	*Max*	*Mean*	*SD*	*F*	p-*value*
Age, years							
Men	108	25.0	65.0	51.84	8.60	1.096	0.30
Women	201	24.0	65.0	52.95	9.07		
Height, cm							
Men	108	107.0	189.0	168.34	11.90	68.607	< 0.001
Women	201	135.0	182.0	159.46	6.94		
Weight, kg							
Men	108	55	132	83.97	13.43	0.009	0.93
Women	201	51	172	83.80	15.67		
BMI, kg/m^2							
Men	108	25.10	55.11	29.76	4.81	24.941	< 0.001
Women	201	25.09	64.06	32.91	5.52		
WC, cm							
Men	108	70	170	98.06	11.96	0.645	0.42
Women	201	37	152	99.41	15.04		
SBP, mmHg							
Men	108	91.0	193.0	140.44	20.21	1.308	0.25
Women	201	86.0	229.0	143.61	24.61		
DBP, mmHg							
Men	108	54.0	115.0	80.23	11.12	3.041	0.08
Women	201	54.0	141.0	82.79	12.93		
WHtR							
Men	108	0.42	0.91	0.5786	0.06	18.969	< 0.001
Women	201	0.23	0.94	0.6215	0.09		

BMI = body mass index, WC = waist circumference. SBP = systolic blood pressure, DBP = diastolic blood pressure, WHtR= waist-to-height ratio, *n* = number, SD = standard deviation.

Table 5. Correlation coefficients (*r*) for normal, overweight and obese groups

Groups	*BW*, r	*BMI*, r	*WC*, r	*SBP*, r	*DBP*, r	*WHtR*, r
Normal						
BW (kg)	–	0.51**	0.50**	0.05	–0.02	0.09
BMI	0.51**	–	0.42**	0.15*	0.004	0.52**
WC	0.50**	0.42**	–	0.26**	0.11	0.82**
WHtR	0.09	0.52**	0.82**	0.29**	0.14	–
Overweight						
BW (kg)	–	0.22*	0.51**	0.01	0.08	–0.09
BMI	0.22*	–	0.23*	0.17	0.23*	0.44**
WC	0.51**	0.23*	–	0.23*	0.18	0.71**
WHtR	–0.09	0.44**	0.71**	0.26**	0.19*	–
Obese group						
BW (kg)	–	0.57**	0.59**	0.02	0.09	0.19*
BMI	0.57**	-	0.47**	0.04	0.11	0.57**
WC	0.59**	0.47**	–	0.15	0.07	0.78**
WHtR	0.19*	0.57**	0.78**	0.14	0.08	–

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).
BW = body weight, BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, WHtR = waist-to-height ratio.

lower when compared to a study by Day *et al.*,[47] which reported a 40% prevalence of hypertension among adults in South African provinces during 2010. Peer *et al.*[48] also reported a lower prevalence of hypertension (38.9%) among black urban South African adults between the ages of 24 and 65 years in Cape Town. The study showed that women (27%) had a higher prevalence of hypertension compared to males (22%). This is lower than the study by Ntuli *et al.*[49] in adults in a rural community of Dikgale in the Limpopo Province, which showed that 42% of males and 41% of females were hypertensive.

The findings of our study are also similar to those of the South Africa Demographic and Health Survey (SADHS),[50] which reported that using a cut-off of 140/90 mmHg and gender adjustment, 25% of men and 26% of women had hypertension. Based on BMI categories, our study showed that obese groups (35%) had a high prevalence of hypertension when compared to the normal (18%) and overweight groups (22%). These findings are similar to a study by Dua *et al.*,[51] which found that the prevalence of high BP was greater in those with high BMI. This has also been reported in other studies.[52,53] The WHO[4] reported that hypertension was globally responsible for 45% of deaths due to cardiovascular disease and 51% of deaths due to stroke.

According to Ibrahim and Damasceno,[54] as well as the WHO,[4] an estimated one billion people worldwide are hypertensive, and this number is expected to rise to 1.56 billion by 2025.

These studies also found that all measures of body composition (WC, BMI and WHtR) significantly correlated with WC and WHtR. BMI and WC positively correlated with SBP in the normal group. The same trend was observed in other studies, where a statistically significant association was found between hypertension and BMI among employees working at Port Said University.[55] The results of the study also found that, in the overweight group, WC correlated significantly with SBP, and WHtR correlated positively with both SBP and DBP. These findings correspond with those of Dua *et al.*,[51] who showed a statistically significant positive correlation between all the anthropometric measures and BP parameters (SBP and DBP). These findings are also in agreement with other studies, which found that anthropometric variables such as BMI, WC and WHtR were frequently positively associated with BP among employees in West Africa.[28] Obesity emerged as a strong predictor of hypertension among employees in Ghana.[31]

The high prevalence of overweight/obesity in this study linked to the prevalence of hypertension agrees with the International Study of Salt and Blood Pressure,[56] which reported a strong, significant, independent association between BMI and BP. From the literature, it was revealed that obesity is associated with more pronounced changes in BP during a 24-hour cycle and a higher SBP, DBP and pulse pressure, indicating autonomic dysfunction or hypertension.[57] All these risk factors may contribute to the increase in prevalence of chronic diseases and absenteeism among employees.[58,59]

The major constraint of the study was the difficulty in collecting data from all the municipalities that participated. Inclusion of all employees from the Vhembe district would have enriched the data collected. In addition, it was not feasible to collect 24-hour BP data from the participants due to logistical challenges. This would have shed more light on the observed relationships between WC and WHtR measures. It would be important in future studies to address these challenges.

Conclusion

Females showed a higher percentage of obesity and hypertension than their male counterparts. The obese group showed a high prevalence of hypertension compared with the other groups. Body composition measures were associated with BP parameters (more especially, BMI, WC and WHtR), which showed a positive significant relationship in both normal and overweight groups. Therefore, this study recommends that intervention regimes designed to address the risk of obesity and hypertension should focus on the awareness of cardiovascular diseases, impaired quality of life, and low productivity associated with obesity and hypertension among local government employees in the Vhembe district of Limpopo Province.

The willingness of the Vhembe local municipality employees to participate in the study is highly appreciated. The University of Venda biokineticist interns: Walter, Precious, Gudani and Merlyn and third-year biokinetics students Tsakani, Fulufhelo, Pearl, Rixongile, Ruth and Emmanuel are acknowledged for their roles in data collection and capturing. Furthermore, Ms Frazer Maake is thanked for her support in organising satellites within the Vhembe district where the study took place. The financial support by the University of Venda towards the study is acknowledged.

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Bedtime BP meds may cut heart risk by almost half : large randomised study

Blood pressure medication may confer a larger benefit if taken at night, rather than in the morning. A 'robust' Spanish study of more than 19 000 patients found that taking the medication so that it works overnight cuts the risk of heart-related death and disease nearly in half.

'The same medication ingested at different times of the day actually has different pharmacological properties, behaving like totally different medications,' said the study's lead author, Ramón Hermida, director of the Bio-engineering and Chrono-biology Labs at the University of Vigo in Spain.

NBC News reports Hermida and his research team randomly selected half of the study participants to take their blood pressure pills upon waking up in the morning. The other half made the medication part of their bedtime routine. The team then tracked the patients for six years, periodically monitoring their blood pressure levels continuously in 48-hour blocks.

The differences in outcomes were striking: compared with the group who took their pills in the morning, the night-timers had a more than 40% lower risk of experiencing a heart attack, heart failure, stroke or needing procedures to open clogged coronary arteries. What's more, their risk of dying from heart problems during the study period was cut by 66%. By taking your blood pressure medications before going to bed, you're preventing high blood pressure during sleep, which is a significant risk factor for cardiovascular disease, Hermida is quoted in the report as saying.

Normally, a person experiences 'nocturnal dipping' while asleep at night. Blood pressure 'dips' by about 10 to 20%. But that doesn't happen in some people, and others may even experience an increase in blood pressure during sleep, said Dr Luke Laffin, a preventive cardiologist at the Cleveland Clinic who was not involved in the research. 'It makes sense that if we give blood pressure medicines at night, we may catch some of those people who have the non-dipping patterns, or elevated blood pressures at night,' said Laffin, 'and protect them from more cardiovascular disease.'

The report says previous studies had hinted that better blood pressure control at night might offer a benefit. 'This was the piece that was missing,' Dr Renato Lopes, a professor of medicine at Duke University School of Medicine, said. 'For the first time in a very large, randomised fashion, this study really gave us impressive results,' said Lopes, who was not involved in the research.

The report says while the results are encouraging, researchers say patients with high blood pressure should speak with their doctors before making any changes to their blood pressure medication routines. 'It is important to understand that this may not apply to medications that need to be taken more than once a day, or for blood pressure medications that are being prescribed for other problems such as angina,' Dr Tim Chico, professor of cardiovascular medicine at the University of Sheffield, said.

And there are other caveats, the report says. The new research had participants take all of their blood pressure medications at once, either at night or in the morning, rather than some in the morning and some at night. But some cardiologists say many patients may need a more tailored approach. 'For most people, a combination of a couple medicines in the morning and a couple in the evening means you're going to do better, eliminate side effects and generally have better control of your blood pressure over 24 hours,' Laffin said. And people may not want to take certain kinds of blood pressure medications at night, such as diuretics, because they increase urination.

The report says the study included only white participants, so it's unclear whether the apparent benefits would be as effective for African Americans, who have consistently higher uncontrolled blood pressure and heart disease death rates. The findings also may not apply to people who are awake all night, such as shift workers.

Meanwhile, simply making sure to take your blood pressure medications overall has been shown to reduce the risk of heart attack and stroke significantly. Anyone with a measurement over 130/80 mmHg is considered to have high blood pressure, according to guidelines from the American Heart Association and the American College of Cardiology.

The time of day a person measures his or her blood pressure may also be key. Readings tend to be higher first thing in the morning, so many doctors recommend those keeping track of blood pressure at home take measurements once in the morning, and once in the evening.

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Availability and administration of benzathine penicillin G for the prevention of rheumatic fever in Africa: report of the Working Group on Penicillin, Pan-African Society of Cardiology Task Force on Rheumatic Heart Disease

Sulafa Ali, Aidan Long, Jean B Nikiema, Geoffrey Madeira, Rosemary Wyber

Abstract

Methods: Penicillin is the cornerstone of management for rheumatic heart disease (RHD), an important public health problem in Africa. An online survey was used to collect data from African health workers about availability and administration of penicillin.

Results: There were 30 respondents from 14 countries. Unavailability of benzathine penicillin G (BPG) was reported by 30% of respondents. Skin testing was practiced by 40% of respondents, 30% did not have administration guides and only 30% had emergency kits available. The interval of BPG for secondary prophylaxis varied between two and four weeks. Major adverse reactions were observed by 30% of respondents, including anaphylactic shock/death in six cases. Forty-three per cent of respondents reported that health workers had concerns about BPG administration, including worry about reactions, pain and the viscosity of the solution, and 50% were not confident to manage BPG allergy.

Conclusion: BPG availability should be addressed and African health workers' knowledge and practices need to be augmented.

Keywords: penicillin, Africa, availability, administration

Submitted 5/11/18, accepted 14/7/19

Cardiovasc J Afr 2019; **30**: 369–372 www.cvja.co.za

DOI: 10.5830/CVJA-2019-042

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Rheumatic heart disease (RHD) affects about 33 million people worldwide and leads to 320 000 deaths annually; most of these cases occur in sub-Saharan Africa and Asia.[1] Penicillin is the principal antibiotic for prevention of acute rheumatic fever (ARF) and RHD. Benzathine penicillin G (BPG) is a long-acting formulation of penicillin that can be administered as a single-dose treatment for bacterial pharyngitis and as three- to four-weekly secondary prophylaxis of ARF. The four-weekly interval was found to be less effective in reducing rheumatic fever relapses when compared with two-weekly intervals, therefore some countries use a two-weekly regimen.[2] Other indications for BPG include treatment of syphilis, particularly prevention of mother-to-child transmission, and management of hyposplenism in sickle cell disease.

BPG has been included in each iteration of the World Health Organisation (WHO) Essential Medicines list since the list was developed.[3] Therefore BPG is expected to be available in most low- and middle-income countries where RHD is prevalent. However, reports of shortages are widespread and use of the drug has been further complicated by concerns about quality, adverse events and optimal administration techniques.[4]

In 2016 the Pan-African Society of Cardiology (PASCAR) initiated a broad RHD control agenda with support from the African Union, codified in the Addis Ababa Communiqué. The PASCAR approach focused on seven key actions to eradicate RHD from Africa.[5] The second of these actions was to address the issues surrounding BPG and the Penicillin Working Group was formed. The objective of the Penicillin Working Group in the long term is to help establish safe and efficacious BPG and oral penicillin supply and use at primary-care level in African countries.

This survey represents the first output of the Working Group to document penicillin availability and utility in African countries. This pragmatic approach is intended to identify priorities for improving the use of penicillin in Africa.

Methods

An online survey was designed by the Working Group and formulated in Survey Monkey. The survey questions can be viewed online at https://www.surveymonkey.com/r/PVTFGHK. The survey tool addressed five key domains: availability, brands and prices, administration, adverse reactions and health workers concerns and needs. The questionnaire was sent to the PASCAR RHD community (160 people) through e-mails and re-circulated three times. Participants were asked to invite their colleagues who work with RHD to fill in the questionnaire. Ethics approval was not considered necessary or feasible for this low-risk survey across a number of jurisdictions.

Results

The total number of respondents was 30 (18% of the people contacted), representing 14 countries (Fig. 1). Most respondents (87%) were doctors working in public referral centres. RHD was the commonest indication for BPG administration (86%); other reported clinical indications include syphilis and sickle cell disease.

BPG was reported to be not regularly available by 30% of respondents (Fig. 2). All but one respondent indicated BPG is on the national essential-drug list (96.6%) and on the free-drug list (58%). Oral penicillin is included on the essential-drug list in 65% and on the free-drug list in 40% of respondents' countries.

Most respondents recognised that one to three brands are available, but some countries reported 10 brands (Uganda), six brands (Tanzania) and five brands (Mozambique). Reported retail purchase price for a 1.2-million international unit (IU) vial ranged between US$0.5 and US$1. In 10 countries (71%) BPG was listed as a 'free drug'.

Skin testing before BPG administration is practiced by 40% of respondents' centres. Skin testing is performed prior to the first injection by 20% and before each injection by 20% of respondents (Fig. 3). Skin testing is mostly done with dilute BPG (85%). Only 30% use controls for skin testing. Positive tests were observed by 20% of respondents. Centres that perform skin testing were in Angola, Nigeria, Sudan, Egypt, Zambia and Mozambique.

Of the respondents, 30% did not have a guide to the administration of BPG in their centre. In centres with a guide, utilisation of the resource was estimated at 80%.

Fig. 1. Geographic location of respondents to the penicillin survey in alphabetical order: 1. Angola; 2. Egypt; 3. Ethiopia; 4. Liberia; 5. Mozambique; 6. Niger; 7. Nigeria; 8. Rwanda; 9. South Africa; 10. Sudan; 11. Tanzania; 12. Uganda; 13. Zambia; 14. Zimbabwe.

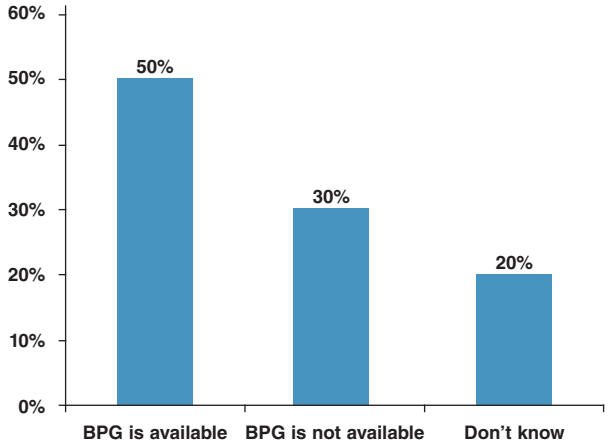

Fig. 2. Availability of benzathine penicillin (BPG).

Only 30% had emergency kits containing adrenaline available when BPG is administered.

There was a large variation between countries in interval of BPG injections for secondary prophylaxis. BPG was mostly given four weekly (60%), but 10% of respondents were administering BPG every two weeks.

Minor reactions were observed by 33% of respondents and major reactions by 30%. Major reactions included death in six cases reported from Nigeria, Zimbabwe, Rwanda, Sudan and Tanzania.

With regard to health workers' concerns and needs, 43% of respondents reported that health workers do have concerns about BPG administration. These concerns include worry about reactions, pain, viscosity of the solution and the difficulty to inject it. Twenty-three per cent of respondents reported that they had concerns about the quality of BPG.

Half of respondents reported that they do not feel confident to manage a patient with BPG allergy. Most respondents (86%) would like to have a refresher course on BPG administration and 95% would like to have an administration guide.

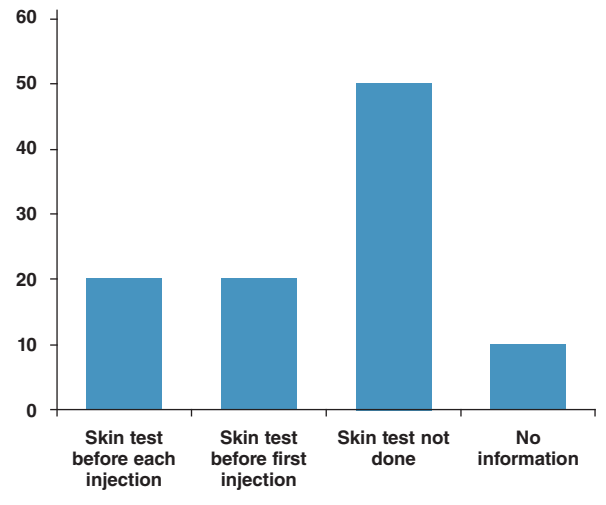

Fig. 3. Skin testing before BPG administration.

Discussion

This pragmatic survey included 14 countries with responses from North, South, East, West and Central Africa. Most respondents work in governmental hospitals that typically treat patients with RHD. This survey unmasked major barriers to the use of BPG in African countries where RHD constitutes a major public health problem and was documented to be the most common indication for BPG use.

Shortages of BPG at the point of care were reported in nearly a third of countries surveyed. This is similar to the 2013 global survey of clinicians in 24 countries when 42% (16/39) of respondents indicated problems with BPG supply.[6] Similarly, a more recent survey conducted by the WHO and the Clinton Health Access Initiative (CHAI) of 81 countries in America and Africa revealed that at least 41% of countries experienced BPG shortages, which were attributed to shortfalls in supply, demand and procurement.[6] The market analysis by CHAI highlights the perceived issues with quality and safety, leading to underutilisation of BPG by health staff.[4,6,7] Substitution behaviour may increase the use of alternative, less effective and more expensive antibiotics. In turn, orders for BPG have decreased, leading to delays in production and distribution.

The beliefs and preferences of people who provide, administer and receive BPG injections drive supply. Therefore supporting safe and appropriate use of BPG is important for stabilising demand and the market. Clinical guidelines and administration guides are important parts of supporting health workers. This survey revealed that although some countries reported that they do have BPG administration guidelines, they are not universally used. A clear need for training courses and resources was also identified. The PASCAR Penicillin Working Group is developing a task aid for BPG administration to respond to this need but ongoing support and education is needed to ensure this effective medication is safely used.

One of the areas of greatest confusion in use of BPG centres on skin testing. In some countries there is a belief that skin testing is needed to assess for risk of penicillin allergy prior to BPG administration. This study indicates that 40% of respondents use some kind of skin testing with dilute BPG. In addition to Africa, we are aware of other countries that use dilute BPG skin testing, including Iran,[8] Nepal[9] and India (pers commun). Despite this widespread practice, there is no evidence that skin testing is useful in reducing adverse reactions to BPG. It is possible that the practice stems from the 2001 WHO guidelines on ARF and RHD, which suggest that health workers need to be trained on skin testing before giving BPG injections for secondary prophylaxis.[10] In this reference there was no specification of the type of skin test. This recommendation might explain the widely practiced use of dilute BPG for skin testing.

The standard test for BPG allergy is conducted using benzylpenicilloyl polylysine (major determinant), penicillin G diluted with normal saline to 10 000 units/ml (minor determinant), positive and negative controls.[11] It is indicated in patients with a prior history of hypersensitivity to penicillin and it is not recommended for routine use prior to BPG injection. This test is not expected to be readily available in African primary healthcare settings therefore there is no need to include it as a guideline.

In contrast to the widespread use of skin testing, emergency kits containing adrenaline were reported to be available to only 30% of respondents. Prompt administration of adrenaline is the mainstay of treating anaphylaxis. Ensuring that adrenaline and other resuscitation equipment are available when BPG is administered is important for safe use of the medication. Similarly, training of health workers on management of anaphylaxis will increase their confidence, as has been reported from the Zambian experience.[12]

The survey showed variations in BPG interval for secondary prophylaxis. Most countries follow the WHO recommendation of three- to four-weekly injections however some respondents administer BPG two weekly. This emphasises the need for standardised administration guidelines and may require conducting research to study the best interval for BPG to be effective for secondary prophylaxis.

Adverse reactions to BPG are not rare and have been one of the barriers to the use of the drug. The commonest minor adverse reaction to BPG is pain at the site of injection. There is some evidence that this can be managed by using an anaesthetic solution such as lidocaine 2% as diluent for the BPG powder.[13] However, this practice is not endorsed by manufacturers and clinical guidelines are not yet in place to support the use of local anaesthetic.

Major adverse reactions have also been reported, including deaths associated with BPG administration. A third of respondents in this survey identified major adverse reactions associated with BPG. This result is similar to the World Heart Federation survey in 2013 that included 39 physicians, where 26% reported serious adverse reactions related to BPG, including deaths.[6]

The mechanism of these deaths is not entirely understood. Anaphylaxis can cause death following injection, however other mechanisms such as inadvertent intravenous injection and arrhythmias need to be considered. Sudden deaths without signs of anaphylaxis have been reported and may be related to arrhythmias in patients who have a severe valve dysfunction.[14]

Improving health workers' knowledge and practices can largely decrease these adverse events and improve workers' confidence in dealing with them. As is seen in this report, health workers' reluctance to give BPG and the lack of confidence were common and directly related to their fear of adverse reactions. Further improvement is sorely needed in order to overcome such serious reactions.

This survey has a number of limitations. The number of participants is small. Clinicians with concerns and adverse experiences with BPG may have been more inclined to respond, leading to bias over-representing concerns. Although respondents may not have been representative, it is clear that shortages of BPG and concerns about use persist in a number of places across the African continent.

Conclusion

This survey demonstrates that shortages of BPG supply occur in Africa and this can limit use of the drug for prevention and management of RHD. Skin testing is quite widespread despite the lack of evidence that it can reduce the risk of major adverse events. In contrast, lifesaving access to emergency kits and adrenaline to manage anaphylaxis are limited. Adverse reactions do occur and health workers reported that they are not confident in managing these. Safe and reliable supplies of BPG are critical for managing the ongoing burden of RHD in Africa. Penicillin is

the only intervention proven to alter the natural history of RHD and save lives. Improving access to this essential medicine must be prioritised by governments and clinicians must be supported to use it confidently and safely.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We acknowledge the tremendous effort of Ms Janette Lombard the PASCAR office administrator for compiling the survey and analysing the data. The PASCAR Working Group on BPG acknowledges the contribution of survey participants.

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Commenting on the research, Professor Paul Leeson, professor of cardiovascular medicine, at the University of Oxford, said in a report in *The Daily Telegraph:* 'This study has the potential to transform how we prescribe blood pressure medication. The findings are likely to be relevant to most people who take tablets for high blood pressure.

Dr Richard Francis, head of research, Stroke Association added: 'We're pleased to see this research, which could potentially change the way we prevent strokes in the future. This is a robust study that shows that people who take their blood pressure medication at night have better blood pressure control and have reduced risk of a cardiovascular event such as a stroke or heart attack. 'Hopefully we can see studies like this recreated in the UK and combined with existing evidence, this could lead to a review of current guidelines on treating high blood pressure.'

Vanessa Smith, from the British Heart Foundation, said in a BBC News report: 'Although this study supports previous findings in this area, further research among other ethnic groups and people who work shift patterns would be needed, to truly prove if taking blood pressure medication at night is more beneficial for cardiovascular health. If you're currently taking blood pressure medication, it's important to check with your GP or pharmacist before changing the time you take it. There may be specific reasons why your doctor has prescribed medication in the morning or night.'

Source: Medical Brief 2019

SEASON'S GREETINGS

A warm thank you from the management and staff of Clinics Cardive Publishing (publishers of the *Cardiovascular Journal of Africa* and the *South African Journal of Diabetes & Vascular Disease*) to our authors, reviewers and clients for your continued support and collaboration.

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