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From the Editor's Desk

Bayauli *et al*. (page 56) show an association between chronic kidney disease in diabetes and left ventricular hypertrophy. Left ventricular hypertrophy is an important marker of disease in African countries and can be a target in health programmes that deal with hypertension and diabetes. Other interesting points in this article are the high prevalence of the metabolic syndrome, dylipidaemia and hyperuricaemia. It is clear from this article and from articles in the previous issue of the journal that there are clear markers of disease in African countries that can be the targets of public health programmes, which will provide a cost-effective and meaningful reduction in morbidity rates. National governments in African countries should be directing their health ministries to create public health programmes based on this clear data coming from researchers in those countries. Programmes are established in the Western world and can be adapted to the African setting.[1] The Indian experience points to the need for investment in public health infrastructure and educational programmes for medical staff and patients.[2]

Onen has made a strong case for the creation of public health programmes against non-communicable disease in the article about the epidemiology of ischaemic heart disease in sub-Saharan Africa (page 88). It is clear that there is a steady worsening of the risk factors for cardiovascular disease and a concerted effort is needed to prevent and manage these factors.

Huisamen *et al.* demonstrate the antihypertensive and cardio-protective effect of *Prosopis glandulosa* (page 61). Its cardiovascular effects outweigh its antidiabetic effects in this study, but other studies show an interesting effect on insulin and glucose.[3] *P glandulosa* is widely available in Africa and biochemical analysis may yield novel drugs in both the hypertension and diabetes fields.

Ferris and Crowther explain the complexities of fat metabolism (page 81). With rising obesity rates, it is important to re-examine fat's various roles, such as its thermo-regulatory role and endocrine function, and its links to insulin resistance and cardiovascular disease. The lipolytic products of fat have even been shown to be involved in signalling to non-adipose cells in the body.[4]

Sirolimus is a macrolide antibiotic that has potent anti-proliferative effects and is useful for reducing stent re-stenosis.[5] Qiao *et al*. (page 68) analysed trials that compared sirolimus-eluting stents with bare-metal stents in diabetic patients. They showed that the rates of major cardiac events and target lesion revascularisation were markedly reduced, although overall mortality rates were unchanged. Overall safety and effectiveness were better with the sirolimus-eluting stents.

Sherman and Weich introduce guidelines for the use of transcatheter aortic valve implantation (TAVI) (page 97). Guidelines are important in health resource-limited environments such as South Africa. As our understanding of the use of these devices evolves and costs decline, the overall usage of transcatheter valve replacements will probably increase and become routine in its application. Although older patients generally do well with conventional aortic valve replacement, the TAVI is a useful alternative where patients have a high operative and/or anaesthetic risk.[6]

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Left ventricular hypertrophy and geometry in type 2 diabetes patients with chronic kidney disease: an echocardiographic study

MP BAYAULI, FB LEPIRA, PK KAYEMBE, JR M'BUYAMBA-KABANGU

Abstract

Objective: **We assessed left ventricular structural alterations associated with chronic kidney disease (CKD) in Congolese patients with type 2 diabetes.**

Methods: **This was a cross-sectional study of a case series. We obtained anthropometric, clinical, biological and echocardiographic measurements in 60 consecutive type 2 diabetes patients (37 females, 62%) aged 20 years or older from the diabetes outpatient clinic, University of Kinshasa Hospital, DRC. We computed creatinine clearance rate according to the MDRD equation and categorised patients into mild (CrCl > 60 ml/min per 1.73 m^2), moderate (CrCl 30–60 ml/ min per 1.73 m^2) and severe CKD (< 30 ml/min per 1.73 m^2). Left ventricular hypertrophy (LVH) was indicated by a LV mass index (LVMI) > 51 g/$m^{2.7}$ and LV geometry was defined as normal, or with concentric remodelling, eccentric or concentric hypertrophy, using relative wall thickness (RWT) and LVMI.**

Results: **Compared to patients with normal kidney function, CKD patients had higher uric acid levels (450 ± 166 vs 306 ± 107 µmol/l; $p \leq 0.001$), a greater proportion of LVH (37 vs 14%; $p \leq 0.05$) and longstanding diabetes (13 ± 8 vs 8 ± 6 years; $p \leq 0.001$). Their left ventricular internal diameter, diastolic (LVIDD) was (47.00 ± 6.00 vs 43.00 ± 7.00 mm; $p \leq 0.001$), LVMI was (47 ± 19 vs 36.00 ± 15 g/$m^{2.7}$; $p \leq 0.05$) and proportions of concentric (22 vs 11%; $p \leq 0.05$) or eccentric (15 vs 3%; $p \leq 0.05$) LVH were also greater. Severe CKD was associated with increased interventricular septum, diastolic (IVSD) (12.30 ± 3.08 vs 9.45 ± 1.94 mm; $p \leq 0.05$), posterior wall thickness, diastolic (PWTD) (11.61 ± 2.78 vs 9.52 ± 1.77 mm; $p \leq 0.01$), relative wall thickness (RWT) (0.52 ± 0.17 vs 0.40 ± 0.07; $p \leq 0.01$) rate of LVH (50 vs 30%; $p \leq 0.05$), and elevated proportions of concentric remodelling (25 vs 15%; $p \leq 0.05$) and concentric LVH (42 vs 10%; $p \leq 0.05$) in comparison with patients with moderate CKD. In multivariable adjusted analysis, hyperuricaemia emerged as the only predictor of the presence of LVH in patients with CKD (adjusted OR 9.10; 95% CI: 2.40–33.73).**

Conclusion: **In keeping with a higher rate of cardiovascular events usually reported in patients with impaired renal function, CKD patients exhibited LVH and abnormal LV geometry.**

Keywords: type 2 diabetes, chronic kidney disease, left ventricular hypertrophy, prevalence, predictors

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Prevention of cardiovascular disease (CVD) requires early detection and correction of predisposing conditions and risk factors in susceptible subjects.[1] Diabetes is a major risk factor for CVD, the prognosis of which lies not only in the level of plasma glucose but also in associated factors such as left ventricular hypertrophy (LVH).[2] The latter develops frequently among diabetic patients, including blacks, and has been identified as a powerful marker of impaired prognosis.[2] Besides hyperglycaemia, various conditions such as aging, hypertension, obesity, central obesity, dyslipidaemia and physical inactivity are known to alter LV structure.[2]

Several reports have indicated that chronic kidney disease (CKD) is independently associated with the presence of LVH on echocardiography, suggesting that CKD might be related to LV mass index (LVMI).[3-5] Individuals with LVH have eccentric or concentric hypertrophy as a result of both pressure and volume overload.[4] Moderate to severe CKD affects 15 to 33% of diabetic patients and predicts the occurrence of CVD.[6,7] Therefore, diabetic patients with CKD might be at a high risk for LVH and subsequent CVD in comparison with those without renal dysfunction.[6,7]

Such an association holds more risk for black people, whose high propensity to diabetic nephropathy has often been documented.[1] There is a need to document the impact of renal function on CV morbidity and mortality in diabetic patients with CKD, particularly blacks.[1] The aim of the present study was to evaluate the association between CKD and LV structural alterations in a clinic-based sample of consecutive Congolese patients with type 2 diabetes mellitus.

Methods

We enrolled in the present study consecutive type 2 diabetes subjects aged 20 years and older attending the outpatient clinic at the University of Kinshasa Hospital. Ethical approval was obtained from the institutional ethics review board and informed consent was obtained from the study participants. Exclusion criteria included ischaemic heart disease (IHD), acute coronary syndrome

(ACS), congestive heart failure (CHF, NYHA class II or greater), valvular heart disease, cerebral infarction or transient ischaemic attack (TIA).

Self-reported physical activity, alcohol use and smoking habits, known duration of diabetes mellitus, current treatments and measures of adiposity [body mass index (BMI) and waist circumference] were obtained in all patients. Overweight and obesity were classified as BMI ≥ 25 kg/m² and ≥ 30 kg/m², respectively. Central obesity was categorised as waist circumference > 102 cm in men and > 88 cm in women.

Blood pressure (BP) was measured in the supine position using a mercury sphygmomanometer with an appropriate cuff on the left arm; the average of two readings was used for statistical analysis. Pulse pressure (PP) calculated as systolic blood pressure (SBP) minus diastolic blood pressure (DBP) was considered increased when > 60 mmHg.[8] Hypertension was defined as BP > 140/90 mmHg or currently on antihypertensive treatment. Heart rate was counted over a full minute.

A 12-hour overnight fasting venous blood sample was collected for measurement of total cholesterol and its sub-fractions [low-density lipoprotein cholesterol (LDL-C) high-density lipoprotein cholesterol (HDL-C)], triglycerides (TG), plasma glucose, serum uric acid and creatinine levels. LDL-C was calculated according to the Friedewald formula.[9] Dyslipidaemia was an LDL-C level ≥ 2.6 mmol/l or HDL-C < 1.03 mmol/l or TG > 1.69 mmol/l.

According to the NCEP-ATP III guidelines,[10] the metabolic syndrome (MS) was, in addition to diabetes, the presence of two of the followings risk factors: BP > 130/85 mmHg or current antihypertensive treatment, central obesity as defined above, HDL-C < 1.03 mmol/l and/or TG > 1.69 mmol/l.

We computed glomerular filtration rate [creatinine clearance (CrCl)] using the MDRD equation.[11] Chronic kidney disease (CKD) was a CrCl rate < 60 ml/min per 1.73 m²; it was stratified into mild (CrCl > 60 ml/min per 1.73 m²), moderate (CrCl: 30–60 ml/min per 1.73 m²) and severe (CrCl < 30 ml/min per 1.73 m²).[12] A uric acid level > 416 µmol/l defined hyperuricaemia. Proteinuria was a 24-hour urine protein excretion rate > 0.3 g.

Table 1. Clinical characteristics of the whole group and diabetics with and without CKD.

Characteristic	Whole group (*n* = 60)	Normal renal function (*n* = 70)	*CKD* (*n* = 32)
Gender:	M/F 23/37	11/17	12/20
Age (years)	58 ± 8	59 ± 8	58 ± 8
Duration DM (years)	11 ± 8	8 ± 6	13 ± 8***
Central obesity (%)	62	32	30
AHT (%)	80	37	43
MS (%)	58	28	30
Antidiabetic drugs (%)	97	45	52
Antihypertensive drugs (%)	67	25	42**
Smoking (%)	10	7	3
BMI (kg/m²)	26 ± 5	27 ± 6	26 ± 5
Waist (cm)	95 ± 12	96 ± 13	95 ± 12
SBP (mmHg)	148 ± 26	148 ± 29	149 ± 23
DBP (mmHg)	84 ± 13	86 ± 15	82 ± 11
PP (mmHg)	64 ± 21	61 ± 23	67 ± 19
Heart rate (beats/min)	83 ± 15	83 ± 20	86 ± 12

Data are expressed as mean ± SD or relative frequency in per cent.
CKD, chronic kidney disease; M, male; F, female; DM, diabetes mellitus; AHT, arterial hypertension; MS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$in comparison with normal renal function.

Table 2. Biological characteristics of the patients and data according to renal function.

Characteristic	Whole group (*n* = 60)	Normal renal function (*n* = 28)	*CKD* (*n* = 32)
TC (mmol/l)	5.61 ± 1.62	5.74 ± 1.40	5.62 ± 1.71
LDL-C (mmol/l)	3.80 ± 1.54	3.90 ± 1.42	3.73 ± 0.78
HDL-C (mmol/l)	1.45 ± 0.67	1.44 ± 0.51	1.53 ± 0.84
TG (mmol/l)	1.60 ± 1.30	1.84 ± 1.80	1.33 ± 0.78
Glucose (mmol/l)	8.10 ± 3.31	8.27 ± 2.77	7.80 ± 3.80
Uric acid (µmol/l)	410 ± 178	309 ± 107	500 ± 166***
CrCl (ml/min/173 m²)	64 ± 41	97 ± 35	35 ± 18
24-h proteinuria (g)	0.79 ± 1.72	0.07 ± 0.164	1,42 ± 2,17

Data are expressed as mean ± SD
CKD, chronic kidney disease; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CrCl, creatinine clearance.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ in comparison with normal renal function.

Echocardiographic examination was performed with the patient in the partial left lateral decubitus position using an Acuson 128XP/10˝ machine with a 3.5-MHz transducer. Two-dimensional guided M-mode measurements were obtained as recommended by the American Society of Echocardiography (ASE).[13]

We used the Devereux modified cubed formula to calculate left ventricular mass (LVM).[14] To account for gender and body size variations, LVM was indexed to height$^{2.7}$, with a boundary of 51 g/m$^{2.7}$ to define LVH in both genders.[15] Relative wall thickness (RWT) was calculated as 2 × PWTD (posterior wall thickness, diastolic)/LVIDD (left ventricular internal diameter, diastolic). It was considered increased when > 0.45.[16] RWT and left ventricular mass index (LVMI) were used to characterise LV geometry as normal (normal LVMI and normal RWT), concentric remodelling (normal LVMI and increased RWT), concentric hypertrophy (increased LVMI and increased RWT) and eccentric hypertrophy (increased LVMI and normal RWT). LV ejection fraction (LVEF) was calculated using Tiechloz's formula.[17]

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or relative frequency in per cent. The distribution of duration of hypertension and triglyceride levels being positively skewed, the non-parametric Mann–Whitney test was used for these variables. Chi-square and Student *t*-tests were used for comparing categorical and normally distributed continuous variables, respectively.

Multiple regression models and the likelihood ratio method were performed with LVH as the dependent variable for the assessment of the strength and independence of association with risk factors. Adjusted odds ratio (aOR) were calculated for each variable from a model which included all these variables; the resulting aOR allowed the direct comparison of the independent effects of these variables to decide which variable has the greater effect on LVH. All statistical analyses were performed with SPSS for Windows, version 18.0. A *p*-value ≤ 0.5 was considered statistically significant.

Results

Tables 1 and 2 show clinical and biological characteristics of patients according to renal function. Mean age and duration of diabetes were 58 ± 8 and 11 ± 8 years, respectively for the whole group. BMI, waist circumference, SBP and DBP, and plasma glucose levels averaged 26 ± 5 kg/m^2, 95 ± 12 cm, 148 ± 26 mmHg, 84 ± 13 mmHg, and 8.10 ± 3.31 mmol/l, respectively. Diabetes was frequently associated with other CV risk factors, among which hypertension (80%) was the commonest. Clustering of risk factors into the metabolic syndrome was observed in 58% of patients.

Besides antidiabetic therapy, 97% of patients were receiving BP-lowering drugs. CKD was observed in 32 patients (53%), 20 of whom (62%) had a CrCl rate of 30 ml/min per 1.73 m^2 or higher. Compared to those with normal renal function, the duration of diabetes was longer (13 ± 8 vs 8 ± 6 years; $p \leq 0.001$), the proportion of patients on current antihypertensive drugs greater (42 vs 25%; $p < 0.05$) and the level of uric acid higher (450 ± 166 vs 306 ± 107 µmol/l; $p \leq 0.001$) in CKD patients. The two subgroups were similar for the other variables.

Table 3 summarises echocardiographic measurements by renal function status and Table 4 by the severity of renal dysfunction. Patients with CKD had increased LVIDD (47.00 ± 6.00 vs 43.00 ± 7.00 mm; $p \leq 0.001$), LVMI (47.00 ± 19 vs 36.00 ± 15.00 mm; $p \leq 0.05$) and higher proportions of LVH (37 vs 14%; $p \leq 0.05$); they also showed higher proportions of concentric (22 vs 11%; p ≤ 0.05) and eccentric (15 vs 3%; $p \leq 0.05$) LVH. Compared to patients with moderate CKD, those with severe CKD had increased interventricular septum thickness, diastolic (IVSD) (12.30 ± 3.08 vs 9.45 ± 1.94 mm; $p \leq 0.001$), RWT (0.52 ± 0.17 vs 0.40 ± 0.07 mm; $p \leq 0.01$) and higher proportions of LVH (50 vs 30%; $p \leq 0.05$). Concentric remodelling (25 vs 15%; p ≤ 0.05) and concentric hypertrophy (42 vs 10%; $p \leq 0.05$) were the geometric patterns most frequently encountered in patients with severe CKD. Between groups, systolic function indices did not differ.

In multivariable adjusted analysis, the probability of LVH among CKD patients was increased by hyperuricaemia (aOR 9.10; 95% CI: 2.40–33.74) for the presence versus the absence of hyperuricaemia.

Table 3. M-mode echocardiographic data in the whole group and diabetics with and without CKD.

Characteristic	Whole group (n = 60)	Normal renal function (n = 28)	*CKD* (n = 32)
LV dimension			
LVIDD (mm)	44.83 ± 6.62	43.00 ± 7.00	47.0 ± 6.00***
LVIDS (mm)	29.67 ± 8.43	28.04 ± 7.7	2 31.09 ± 8.98
IVSD (mm)	10.42 ± 2.60	10.30 ± 2.41	11.00 ± 3.48
PWTD (mm)	9.98 ± 2.26	10.00 ± 2.00	10.00 ± 2.30
RWT	0.46 ± 0.13	0.47 ± 0.12	0.45 ± 0.13
LVMI (g/m$^{2.7}$)	41.83 ± 17.72	36.00 ± 15.00	47.00 ± 19.00*
EF (%)	68.25 ± 19.06	69.24 ± 17.02	67.39 ± 20.91
FS (%)	0.34 ± 0.13	0.34 ± 0.13	0.34 ± 0.14
LV geometry			
Normal (%)	43	43	44
Concentric remodelling (%)	30	43	19*
Concentric hypertrophy (%)	17	11	22*
Eccentric hypertrophy (%)	10	3	15*

Data are expressed as mean ± SD or relative frequency in per cent.
CKD, chronic kidney disease; LVIDD, left ventricular internal diameter, diastolic; LVIDS, left ventricular internal diameter, systolic; IVSD, interventricular septum, diastolic; PWTD, posterior wall thickness, diastolic; RWT, relative wall thickness; LVMI, left ventricular mass index; EF, ejection fraction; FS, fraction shortening.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ in comparison with normal renal function.

Table 4. Severity of renal dysfunction and M-mode echocardiographic data among diabetics with CKD.

	CrCl 30–60 ml/min (n = 20)	CrCl < 30–60 ml/min (n = 20)
LV dimension		
LVIDD (mm)	46.75 ± 5.72	46.75 ± 6.79
LVIDS (mm)	30.50 ± 9.76	32.08 ± 7.80
IVSD (mm)	9.45 ± 1.94	12.30 ± 3.08*
PWTD (mm)	9.52 ± 1.77	11.61 ± 2.78**
RWT	0.40 ± 0.07	0.52 ± 0.17**
LVMI (g/m$^{2.7}$)	43.52 ± 15.74	52.41 ± 22.40
FS (%)	0.35 ± 0.15	0.32 ± 0.11
LV geometry		
Normal, %	55	25*
Concentric remodelling (%)	15	25*
Concentric hypertrophy (%)	10	42*
Eccentric hypertrophy (%)	20	8*

Data are expressed as mean ± SD or relative frequency in per cent.
CKD, chronic kidney disease; CrCl, creatinine clearance; LVIDD, left ventricular internal diameter, diastolic; LVIDS, left ventricular internal diameter, systolic; IVSD, interventricular septum, diastolic; PWTD, posterior wall thickness, diastolic; RWT, relative wall thickness; LVMI, left ventricular mass index; EF, ejection fraction; FS, fraction shortening.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ in comparison with moderate CKD.

Discussion

The key finding of the study was that the elevated prevalence of chronic kidney disease in our diabetic patients was associated with abnormal cardiac structure. The alteration in renal function was moderate in the majority of cases. Left ventricular mass index, the frequency of left ventricular hypertrophy and uric acid levels were higher in CKD patients in whom multivariable adjusted analysis indicated uric acid as the only predictor of LVH.

The elevated prevalence of moderate to severe CKD has been reported in 15 to 23% of diabetic patients in whom it predicts the occurrence of CVD.[18,19] The mechanisms by which chronic hyperglycaemia may induce cardiovascular and renal dysfunction include enhanced polyol pathway flux, altered redox state, increased formation of diacylglycerol (DAG) and subsequent activation of protein kinase C (PKC) isoforms, and accelerated non-enzymatic formation of advanced glycation end products (AGEs).[20] The DAG–PKC pathway affects cardiovascular and renal structure and function in many ways, e.g. the regulation of endothelial permeability, vascular tone, cell growth, angiogenesis, and cytokine and leucocyte activation.[20] Moreover, insulin resistance/hyperinsulinaemia-induced activation of the sympathetic nervous and renin–angiotensin–aldosterone systems could contribute to cardiovascular and renal damage through oxidative stress and inflammation.[21-23]

Alteration in kidney function predominated in patients with a longer duration of diabetes, enhancing the effect of both chronic hyperglycaemia and the ageing process.[3,24] The latter is associated with changes in vascular structure and function due to clustering of multiple risk factors, including insulin resistance/hyperinsulinaemia, oxidative stress and inflammation.[25] Arterial stiffness, an independent predictor of morbidity and mortality, has been reported to increase with age and is associated with high systolic and pulse pressure.[3,24,26] Moreover, the decrease in the number of nephrons, which occurs with ageing, may result in hyperfiltration, hypertrophy and elevation in glomerular capillary pressure.[27]

The high prevalence of LVH in CKD patients found in our study agrees with that of other studies.[28-31] LVH in CKD is thought to result partly from uraemia-associated risk factors such as anaemia, calcium-phosphate products and hyperhomocysteinaemia.[4] Moreover, renal dysfunction activates the renin–angiotensin–aldosterone system, with subsequent formation of angiotensin II, known to be essential for the development and progression of LVH.[32] The risk of CVD and death increases with the decline in glomerular filtration rate (GFR) and the major increase in risk occurs at a GFR < 60 ml/min per 1.73 m^2.[4]

LVH has been reported to predispose to ischaemic heart disease, arrhythmias and congestive heart failure.[33] Our results indicate that patients with severe CKD had higher proportions of abnormal LV geometry, with concentric remodelling and concentric hypertrophy as the most frequent pattern. Both eccentric and concentric hypertrophy may occur in individuals with CKD.4 Eccentric hypertrophy is thought to result from volume overload, leading to cardiomyocyte drop out. Concentric hypertrophy is typically the result of hypertension and increased afterload and is exacerbated by anaemia, hyperparathyroidism and high angiotensin II concentrations. Eccentric and concentric hypertrophy have different impacts on the prognosis.[4] Concentric hypertrophy confers the worst prognosis, followed by eccentric hypertrophy and concentric remodelling.[33]

Moderate CKD and a high proportion of hypertension could explain the pre-eminence of concentric hypertrophy observed in the present study. In Nigerian hypertensive patients, Aje *et al*. reported greater systolic, diastolic, pulse and mean blood pressure among patients with concentric hypertrophy in comparison with those with normal geometric patterns.[34]

In our study, hyperuricaemia emerged as the only predictor of LVH in CKD patients. The mechanisms that could account for increased uric acid levels in CKD include overproduction to counteract oxidative stress and endothelial dysfunction, the severity of diabetes and/or hypertension, impaired renal uric acid clearance, and insulin resistance/hyperinsulinaemia-induced proximal renal tubular reabsorption of ·sodium and urate.[35,36] The association between hyperuricaemia and LVH could rely upon an association of uric acid with other risk factors, either isolated or combined in the metabolic syndrome.[32] The coexistence of hyperuricaemia and LVH has been recognised as an independent and powerful predictor of CVD.[36-38]

The interpretation of the results of our study is confounded by some limitations. The cross-sectional design of the work precludes any causal relationship between CKD and associated risk factors. Moreover, the sample size did not allow sufficient power to detect additional associations. One wonders to what extent the conclusions of this clinic-based study could be extrapolated to the general population, given the bias in the referral of patients. The findings of our study bear, however, some clinical implications for CKD identification, treatment protocol and estimated prognosis in hypertensive patients.

Conclusion

This study has shown that LVH is common among type 2 diabetes patients with CKD. Concentric LVH was the geometric LV pattern most frequently encountered and its frequency increased with the decline in renal function. Hyperuricaemia emerged as the unique independent predictor of the risk of LVH.

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During prolonged low-intensity exercise, caffeine alters blood glucose levels

The effects of caffeine versus maltodextrin during exercise were observed in patients with type 2 diabetes. Researchers examined the effects on blood pressure (BP), heart rate (HR) and blood glucose (BG) levels associated with the intake of caffeine in comparison to maltodextrin (CHO) during prolonged periods of low-intensity exercise in patients with type 2 diabetes.

Researchers conducted a pilot study on eight individuals with type 2 diabetes who were aged 55 ± 10 years. The participants either received 1 g/kg of CHO or 1.5 mg/kg of caffeine before undergoing exercise. They then exercised for 40 minutes, executed at 40% HR reserve, and recovered for 10 minutes.

Their BP and exertion, assessed by the Borg scale, were checked every two minute, and their BG levels were checked every 10 minutes. The ANOVA test was used for statistical analysis, and a p-value < 0.05 indicated statistically significant results.

Neither of the treatments produced significant changes in BP and HR. However, 1.5 mg/kg caffeine significantly reduced BG levels by 75 mg/dl (65% CI; $p < 0.05$) as opposed to 1 g/kg maltodextrin, which produced no significant change in BG levels during the 40-minute period of exercise.

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Cardioprotective and anti-hypertensive effects of *Prosopis glandulosa* in rat models of pre-diabetes

B HUISAMEN, C GEORGE, D DIETRICH, S GENADE

Abstract

Aim: **Obesity and type 2 diabetes present with two debilitating complications, namely, hypertension and heart disease. The dried and ground pods of *Prosopis glandulosa* (commonly known as the Honey mesquite tree) which is part of the Fabaceae (or legume) family are currently marketed in South Africa as a food supplement with blood glucose-stabilising and anti-hypertensive properties. We previously determined its hypoglycaemic effects, and in the current study we determined the efficacy of *P glandulosa* as anti-hypertensive agent and its myocardial protective ability.**

Methods: **Male Wistar rats were rendered either pre-diabetic (diet-induced obesity: DIO) or hypertensive (high-fat diet: HFD). DIO animals were treated with *P glandulosa* (100 mg/kg/day for the last eight weeks of a 16-week period) and compared to age-matched controls. Hearts were perfused ex vivo to determine infarct size. Biometric parameters were determined at the time of sacrifice. Cardiac-specific insulin receptor knock-out (CIRKO) mice were similarly treated with *P glandulosa* and infarct size was determined. HFD animals were treated with *P glandulosa* from the onset of the diet or from weeks 12–16, using captopril (50 mg/kg/day) as the positive control. Blood pressure was monitored weekly.**

Results: **DIO rats and CIRKO mice: *P glandulosa* ingestion significantly reduced infarct size after ischaemia–reperfusion. Proteins of the PI-3-kinase/PKB/Akt survival pathway were affected in a manner supporting cardioprotection. HFD model: *P glandulosa* treatment both prevented and corrected the development of hypertension, which was also reflected in alleviation of water retention.**

Conclusion: ***P glandulosa*** **was cardioprotective and infarct sparing as well as anti-hypertensive without affecting the body weight or the intra-peritoneal fat depots of the animals. Changes in the PI-3-kinase/PKB/Akt pathway may be causal to protection. Results indicated water retention, possibly coupled to vasoconstriction in the HFD animals, while ingestion of *P glandulosa* alleviated both. We concluded that treatment of pre-diabetes, type 2 diabetes or hypertension with *P glandulosa* poses possible beneficial health effects.**

Keywords: *Prosopis glandulosa*, hypertension, cardioprotection, PKB, insulin resistance

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Obesity and type 2 diabetes present with two debilitating complications, namely, hypertension and heart disease. The dried and ground pods of *Prosopis glandulosa* (commonly known as the Honey mesquite tree) which is part of the Fabaceae (or legume) family are currently marketed as a food supplement with blood glucose stabilising and anti-hypertensive properties in South Africa. In the past, the pods of this tree were used as the primary foodstuff for the residents of the south-western regions of the North American deserts and these trees are still widely distributed across a large portion of the south-western United States.[1] The pods are composed of 80% carbohydrate, 13% protein, 25% fibre and 3% fat, and grinding of the plant is thought to improve its use.[2]

Obesity is currently classified as a pandemic and is recognized as the leading cause in the development of the metabolic syndrome. The metabolic syndrome is described as a cluster of pathophysiology outlined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) and the European Group for the Study of Insulin Resistance, to include insulin resistance or glucose intolerance (pre-diabetes), type 2 diabetes, hypertension and atherogenic dyslipidaemia.[3,4] In addition, all of these factors can be considered independent risk factors for the development of cardiovascular disease.[3]

According to the World Health Organisation (WHO), non-communicable diseases such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes are currently (updated June 2011) the leading causes of mortality in the world.[5] This invisible epidemic is an under-appreciated cause of poverty and hinders economic development in many countries. The burden is growing and the number of people, families and communities afflicted is increasing.

The time-line for development of overt type 2 diabetes is described as developing over many years. The cardiovascular consequences of this so-called 'ticking clock' hypothesis, starting from obesity and culminating in type 2 diabetes, is present from the early pre-diabetic stages.[6]

In view of the scarcity and cost of modern oral hypoglycaemic agents, plant-based therapies for the treatment of diabetes are gaining considerable prominence.[7] According to these authors more than 400 plant species have been described as having hypoglycaemic activity. However, not all of these substances have been researched scientifically to validate their efficacy.

We have researched a product from one such plant species, consisting solely of the dried and ground pods of the plant *P glandulosa*, for hypoglycaemic properties.[8] In addition, potent

anti-infective and anti-parasitic compounds have also been isolated from this plant.[9]

In view of the hypoglycaemic effects of *P glandulosa*, as well as its ability to partially restore the function of pancreatic tissue and increase cardiomyocyte insulin sensitivity,[7] we set out to determine the cardiovascular effects of treatment, using a wellcharacterised rat model of obesity and pre-diabetes with known cardiovascular insufficiency and endothelial dysfunction.[10,11] In addition, using a rat model of high-fat feeding known to develop hypertension,[12] we determined whether *P glandulosa* had any effects on the development of high blood pressure.

Models

Diet-induced obesity (DIO)

As described previously,[10] Wistar rats (180–200 g) were randomly divided into a control and diet group. The DIO group was fed a diet of normal rat chow supplemented with sucrose and condensed milk for a basic period of eight weeks. From weeks eight to 16 the rats were treated with *P glandulosa* (100 mg/kg/day) set in jelly/gelatine blocks and given to each one individually according to the weight of the animal.[8] This was done to ensure absolute compliance and dose control. The dose of *P glandulosa* was calculated as previously described.[8]

The diet to induce pre-diabetes in the animals was based on hyperphagia.[13] Animals were anaesthetised with sodium pentobarbital (160 mg/kg, intra-peritoneally) before experimentation. At the time of sacrifice, their body weight and the weight of the intra-peritoneal fat were noted and trunk blood was collected for biochemical analyses. For Western blot analyses, the hearts were removed, immediately snap-frozen in liquid nitrogen and stored at –80°C.

High-fat diet (HFD)

To induce high blood pressure, the rats were fed a diet containing the following per kg of food: cooking fat 400 g, fructose 100 g, casein 100 g, cholesterol 10 g, and rat chow pellets 390 g. Blood pressure was monitored on a weekly basis over 16 weeks. Treatment with *P glandulosa* (100 mg/kg/day) given in jelly blocks was either started at the onset of the diet to study the effect on prevention of the development of hypertension, or after a period of 12 weeks of the HF diet to study its anti-hypertensive effects. Rats treated with captopril (50 mg/kg/day) from the onset of the diet were included as a positive control. All animals were also placed individually in metabolic cages in order to collect urine samples.

CIRKO mice

A mouse model of animals with a cardiac conditional ablation of the insulin receptor was used in conjunction with their C57Bl6 littermates.[14] Mice were fed normal chow and treated with *P glandulosa* at a similar dose to that of the rats for a period of eight weeks before experimentation.

Methods

Animals had free access to food and water and were kept on a 12-hour day/night cycle in the Central Research Facility of the Faculty of Health Sciences of the University of Stellenbosch. The study conformed to the revised South African National Standard for the Care and Use of Animals for Scientific Purposes (South African Bureau of Standards, SANS 10386, 2008) and was registered with the Committee for the use of animals in research of the University of Stellenbosch – numbers P05/11/013 and P07/11/020.

The *P glandulosa* plant material was originally obtained from naturally growing plants. The material was handled according to a patented and standardised procedure[8] and pre-packed in capsules for human consumption, which we emptied and weighed. The voucher specimen was reported previously.[8]

Plasma glucose levels were determined in the fasting state. Blood was obtained via a tail prick and glucose levels were determined using a conventional glucometer (Cipla MedPro). Plasma was stored at –80°C in a Snijders Scientific Ultracool (Tilburg, the Netherlands) and insulin levels were determined using a coat-a-count assay (Diagnostic Products).

Intra-peritoneal glucose tolerance curves (IPGTTs) were generated in the animals after an 18-hour fast. Animals were injected intra-peritoneally with 1 g/kg of a 50% sucrose solution and blood glucose levels were monitored over a 120-min period. After removal, the hearts were arrested in ice-cold Krebs Henseleit (KH) medium (in mM: NaCl 119, $NaHCO_3$ 25, KCl 4.75, KH_2PO_4 1.2, $MgSO_4.7H_2O$ 0.6, Na_2SO_4 0.6, $CaCl_2.2H_2O$ 1.25, glucose 10) and immediately (within 30 sec) mounted onto the aortic cannula of a perfusion rig. The pulmonary vein was connected to a second cannula in order to perform perfusions in the working-heart mode with a preload of 15 cm H_2O and an afterload of 100 cm H_2O, as described previously.15 The perfusion medium was continuously gassed with 95% O_2/5% CO_2. Hearts were fitted with a temperature probe and the temperature was kept constant at 36.5–37°C.

After a stabilisation period of 30 min, rat hearts were subjected to 35-min regional ischaemia by coronary artery ligation, followed by reperfusion for one hour, as described previously.[15] Infarct size was determined according to a well-established protocol,[15] followed by planimetry, and expressed as a percentage of the area at risk. Planimetry was performed blind by a third party.

Mouse hearts were perfused retrogradely, meaning via the aorta without a connection to the pulmonary vein. After the 30-min stabilisation period, the hearts were subjected to 20-min normothermic ischaemic cardiac arrest (NICA) by stopping all perfusion. This was followed by one hour of reperfusion, after

which the infarct development through the whole heart was determined as described above.

To measure blood pressure, rats were placed in restraining holders with a dark nose cone to calm them. The restrainers were placed on a heating pad (32 ± 2°C) to warm the rat and maintain blood flow to the tail. Animals were placed in the restrainers for at least five minutes before monitoring the blood pressure using a computerised tail-cuff blood pressure monitor (Kent Scientific Corporation, Connecticut, USA). Prior to commencement of the experiment, rats were subjected to the above procedure daily for at least a week to train the animals for the procedure and to avoid stress in the rats during experimental determinations.

Animals were placed individually in metabolic cages and the volume of urine was determined over a period of 24 hours.

Western blotting

Frozen tissues were pulverised with a liquid nitrogen pre-cooled mortar and pestle and then extracted in lysis buffer containing in mM: Tris-HCl 20 (pH 7.5), EGTA 1, EDTA 1, NaCl 150, Na_2VO_3 1, beta-glycerophosphate 1, sodium-pyrophosphate 2.5, PMSF 0.3, Triton X-100 1% (v/v) plus 10 µg/ml leupeptin and aprotinin, respectively, using a Polytron PT10 homogeniser, 2 × 4 sec, at

Table 1. Biometric data – model 1: DIO.

	Control	Control + *P glandulosa*	DIO	DIO + *P glandulosa*
Weight	433.7 ± 9.3	438.6 ± 9.3	507.7 ± 22.9***	534.3 ± 11.7***
Intra-peritoneal fat	18 ± 2.7	11 ± 1.8	28.0 ± 1.74***	34 ± 1.4***
Blood glucose (mmol/l)	5.42 ± 0.17	5.4 ± 0.18	6.4 ± 0.17*	5.6 ± 0.19
Serum insulin (µU/ml)	17.12 ± 0.8	14.07 ± 1.50	34.33 ± 9.06*	35.93 ± 10.21*
HOMA-IR	4.73 ± 0.71	3.40 ± 0.40	8.96 ± 2.65*	7.88 ± 3.30*

*$p < 0.05$ vs the respective control; ***$p < 0.001$ vs the respective control. Analysis by two-way ANOVA, $n = 6$/group.

setting 4. Lysates were cleared from particulate matter by centrifuging for 15 min at 14 000 rpm in a microfuge (Eppendorf Mini-spin plus, Hamburg, Germany) and the protein content was determined by the method of Bradford.[16] Samples were diluted in Laemmli sample buffer, boiled for 5 min and stored at –80°C.

Equal amounts of cytosolic proteins were separated on a SDS poly-acrylamide gel and electro-transferred to ImmobilonTM-P PVDF membranes. Transfer and equal loading of proteins was determined with Ponceau red reversible stain. The membranes were blocked for two hours in Tris-buffered saline (TBS) containing 0.1% Tween-20 and 5% non-fat milk powder and incubated overnight in the primary antibodies (diluted in TBS–Tween according to the manufacturer's instructions). The following antibodies from cell signalling were used: insulin receptor beta-subunit, phospho-PI3K P85 (Tyr458), total and phospho-PTEN (Ser380/Thr382/383), total and phospho-PKB/Akt (Ser473), Glut 1 and Glut 4.

Blots were stripped using a 5-min incubation in 2% NaOH after washing in distilled water and re-probed with a beta-tubulin antibody to confirm equal loading. Bands were visualised using the ECL detection system and quantified by laser-scanning densitometry with suitable software (Silk Scientific Inc, USA). For comparison purposes, total pixels of bands were expressed as a ratio of the mean of the controls on the same blot.

Statistical analysis

Data are presented as mean ± SEM and were analysed using either a one-way or two-way ANOVA followed by a Bonferroni post-hoc test for differences between groups. The blood pressure effects were analysed using a repeated-measures two-way ANOVA. Statistical significance was set at $p < 0.05$.

Results

After the 16-week diet animals from model 1 (DIO) presented with significantly increased body- and intra-peritoneal fat weight (Table 1). As summarised in Table 1, these animals had significantly elevated blood glucose and insulin levels, leading to an increased homeostatic model assessment of insulin resistance index (HOMA-IR), indicative of whole-body insulin resistance.

In neither control nor DIO animals did the treatment with *P glandulosa* have any effect on the body weight or the intraperitoneal fat weight of the animals. After treatment of the DIO animals with *P glandulosa*, the blood glucose levels were no longer significantly elevated compared to the treated controls but the HOMA-IR was still significantly higher. However, as shown in Fig. 1, the two-hour blood glucose values after intra-peritoneal glucose tolerance analyses were significantly lower in the treated DIO animals, underscoring a slight effect on blood glucose handling, as previously reported.[8]

Infarct size

After 16 weeks of the obesity-inducing diet, the ex vivo perfused hearts of the DIO animals presented with significantly larger infarct sizes, calculated as percentage of the area at risk, than the hearts from the control animals (DIO 49.48 ± 3.25 vs control 40.62 ± 2.21%, $p < 0.05$, $n = 17$ per group). The area at risk did not differ between the groups and averaged 54.13 ± 2.21%.

An eight-week treatment regime with *P glandulosa* in conjunction with the diet significantly improved the ability of the hearts to withstand a period of ischaemia, and smaller infarcts developed. There was no significant effect in the hearts from control rats (Fig. 2). Two-way ANOVA indicated a significant effect of the treatment on infarct size ($p < 0.01$).

To confirm these results and rule out any effect of insulin levels on the cardioprotective role of *P glandulosa*, we used a mouse model with a conditional ablation of the insulin receptor in cardiomyocytes.[14] Subjecting these animals and their normal C57Bl6 littermates to ex vivo perfusion and NICA, followed by reperfusion, we found that the hearts of both control and CIRKO mice were protected by the *P glandulosa* treatment. This was demonstrated by the significantly smaller infarct size observed (Fig. 3). The effect of this treatment was highly significant ($p < 0.001$, $n = 9$ per group) as indicated by two-way ANOVA.

Analyses of proteins forming part of the insulin-signalling cascade

Protection against myocardial damage induced by ischaemia–

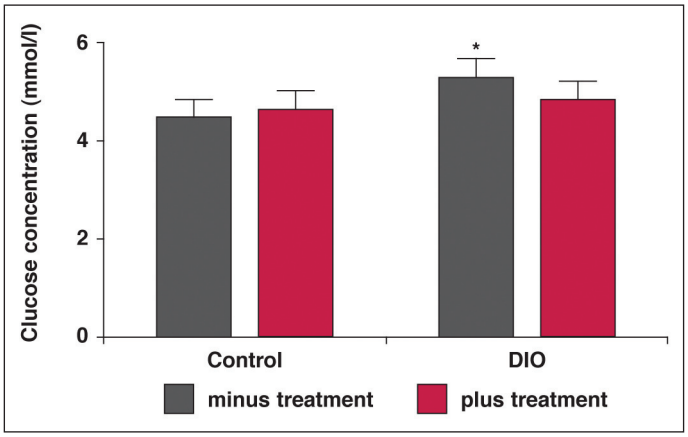

Fig. 1. DIO or control chow-fed rats for 16 weeks with *P glandulosa* treatment for the last eight weeks were subjected to intra-peritoneal glucose-tolerance testing after an 18-hour fast. Blood was collected by tail prick and analysed over a 120-min period using a commercial glucometer. Data given are the 120-min values. *$p < 0.05$ vs control and DIO plus treatment, $n = 6$ per group.

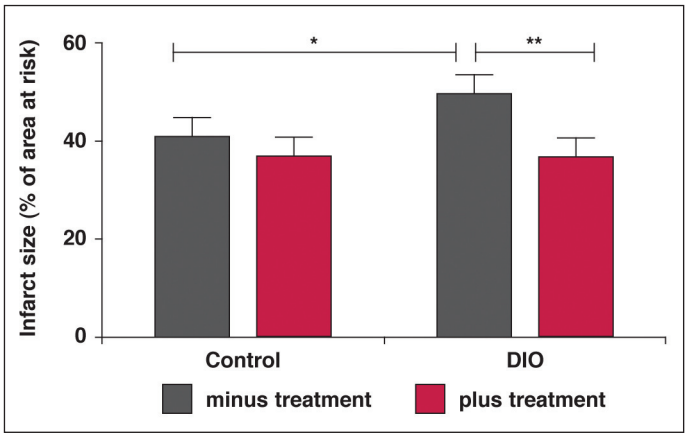

Fig. 2. After the 16-week diet plus P glandulosa treatment, isolated hearts from DIO rats were perfused ex vivo in the working-heart mode. They were subjected to regional ischaemia as described in Methods. Infarct size was determined as a percentage of the area at risk of infarction. *$p < 0.05$, **$p < 0.01$, $n = 15–17$ per group.

reperfusion and culminating in the formation of an infarct has been ascribed, among others, to the activity of the phosphatidylinositol-3-kinase (PI-3K) pathway. In view of the previously reported improvements in insulin sensitivity of cardiomyocytes, induced by *P glandulosa* treatment,[8] we systematically analysed the proteins involved in this signalling cascade.

As summarised in Table 2 and shown in Fig. 4, hearts from the DIO animals presented with a significantly lower phosphorylated:total ratio of the central protein in this cascade, protein kinase B or Akt. This ratio was significantly improved by treatment. In addition, the expression of the p85 regulatory subunit of the PI-3K enzyme was significantly lower in hearts from the DIO animals, whereas this was not the case after treatment.

Treatment also resulted in a lower expression of the phosphatase and tensin homologue deleted on chromosome 10 (PTEN) with a higher state of phosphorylation of this enzyme (Fig. 5). Phosphorylation of PTEN further inactivates this enzyme, responsible also for the dephosphorylation of PKB/Akt.[17,18]

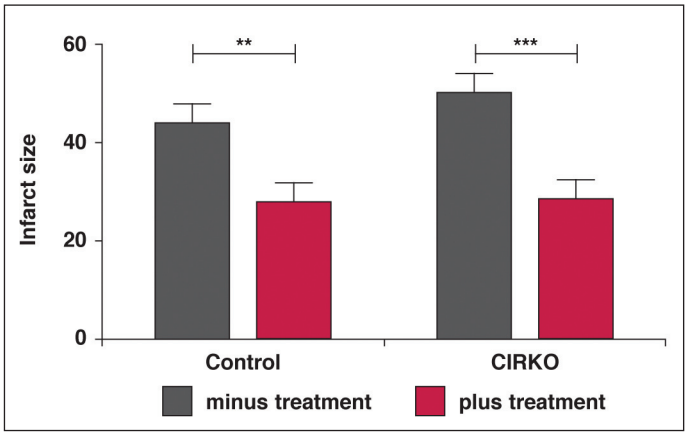

Fig. 3. After the eight weeks of treatment, hearts were removed from the CIRKO mice and perfused ex vivo in the Langendorff mode and subjected to NICA as described in Methods. Infarct size was determined throughout the whole heart and expressed as a percentage of the total surface. **$p < 0.01$, ***$p < 0.001$, $n = 9$ per group.

Anti-hypertensive effects

As the DIO diet does not cause high blood pressure, we used a modification of a high-fat diet to induce hypertension in the animals.[12] As can be seen in Fig. 5, these animals developed a significant elevation of their blood pressure within four weeks (HFD 135.88 ± 2.0 vs control 125.85 ± 1.9 mmHg, $p < 0.05$, $n = 8$ per group).

We either pre-treated the animals with *P glandulosa*, starting at the onset of the diet, or we allowed the animals to become severely hypertensive (12 weeks) and then started the treatment. We included a group of animals treated with the angiotensin converting enzyme (ACE) inhibitor captopril from the onset of the diet, as a positive control in this study.

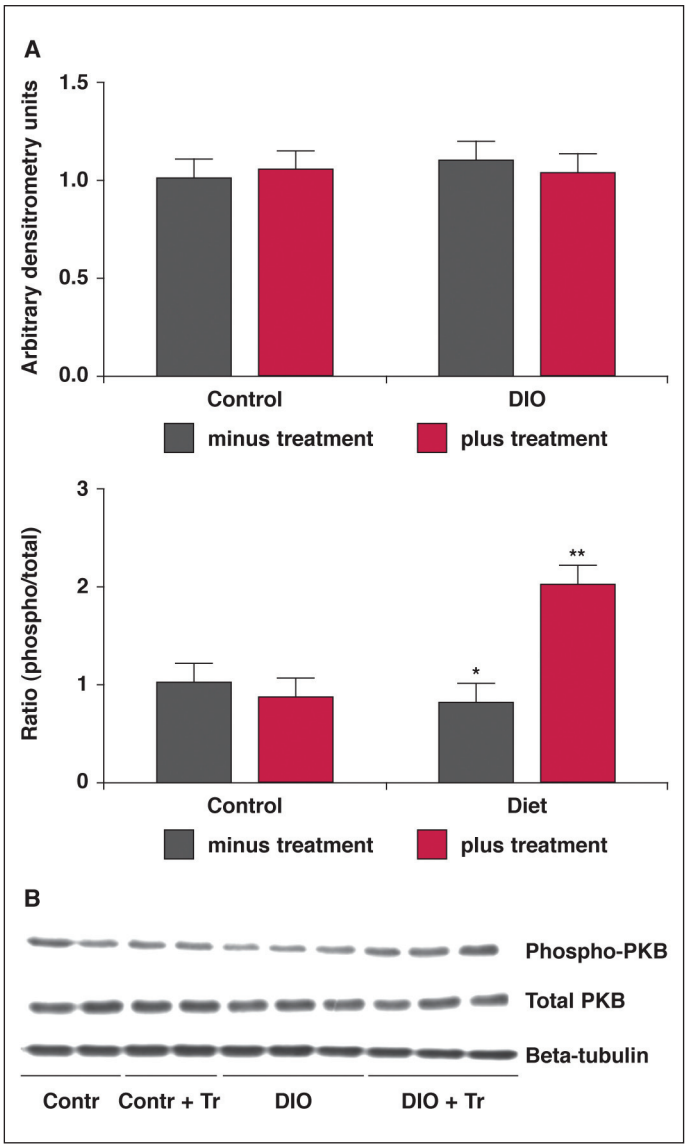

Fig. 4. Hearts from the treated and untreated DIO animals were removed without any intervention and stored in liquid nitrogen. Tissue lysates were prepared and Western blotting was performed as described in Methods. **A**: bar charts of the expression of PKB protein as well as the ratio of phosphorylated vs total protein. *$p < 0.05$ vs control; **$p < 0.01$ vs untreated DIO, $n = 6$ individual hearts analysed per group. **B** is a representative blot depicting these proteins and beta-tubulin, used as an indicator of equal loading.

Table 2. Summary of the western blot analyses of the proteins involved in the insulin signal transduction pathway with arrows indicating the effect induced by the diet alone or the diet in combination with *P glandulosa* treatment. Hearts were freeze-clamped in the basal state without any interventions.

Protein	Effect of diet	Effect of treatment
Glut 1	↔	↔
Glut 4	↔	↔
IR-beta	↔	↔
PKB/Akt	P/T ↓	P/T ↑
p85	↓	↔
PTEN	↔	T ↓ P/T ↑

P = phosphorylated protein, T = total protein; P/T = the ratio of phosphorylated to total protein, *n* = 6 individual hearts per group.

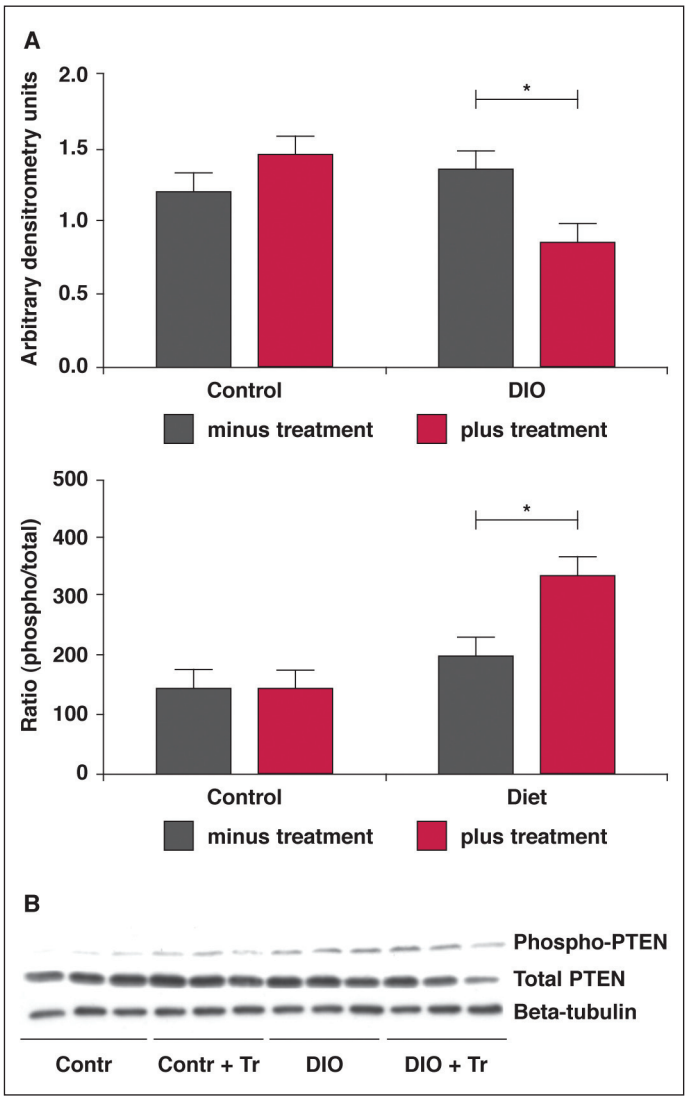

Fig. 5. Hearts from the treated and untreated DIO animals were removed without any intervention and stored in liquid nitrogen. Tissue lysates were prepared and Western blotting was performed as described in Methods. **A**: bar charts of the expression of the PTEN protein as well as the ratio of phosphorylated vs total protein. *$p < 0.05$, $n = 6$ individual hearts analysed per group. **B** is a representative blot depicting these proteins and beta-tubulin, used as an indicator of equal loading.

As can be seen in Fig. 6A, captopril prevented the development of hypertension in the animals. Similarly, *P glandulosa* treatment prevented the development of high blood pressure in these animals when given in conjunction with the high-fat diet. *P glandulosa* treatment did not significantly affect the animals on the control diet (Fig. 6B). In addition, treatment of already hypertensive animals (week 12) with *P glandulosa* normalized their blood pressure within two weeks.

Effects on urine production

Measuring the urine output of the animals by keeping them separately in metabolic cages showed that after the 12-week treatment period, the urine output of animals on the control diet was 17.37 ± 0.8 ml while those on the high-fat diet had a significantly lower urine output of 9.8 ± 0.55 ml ($p < 0.001$, $n = 9$ per group).

Captopril treatment elevated the urine output to 15 ± 0.9 ml. Treatment with *P glandulosa* also elevated urine output to 13.68 ± 0.80 ml ($p < 0.01$, $n = 9$ per group) (Fig. 7).

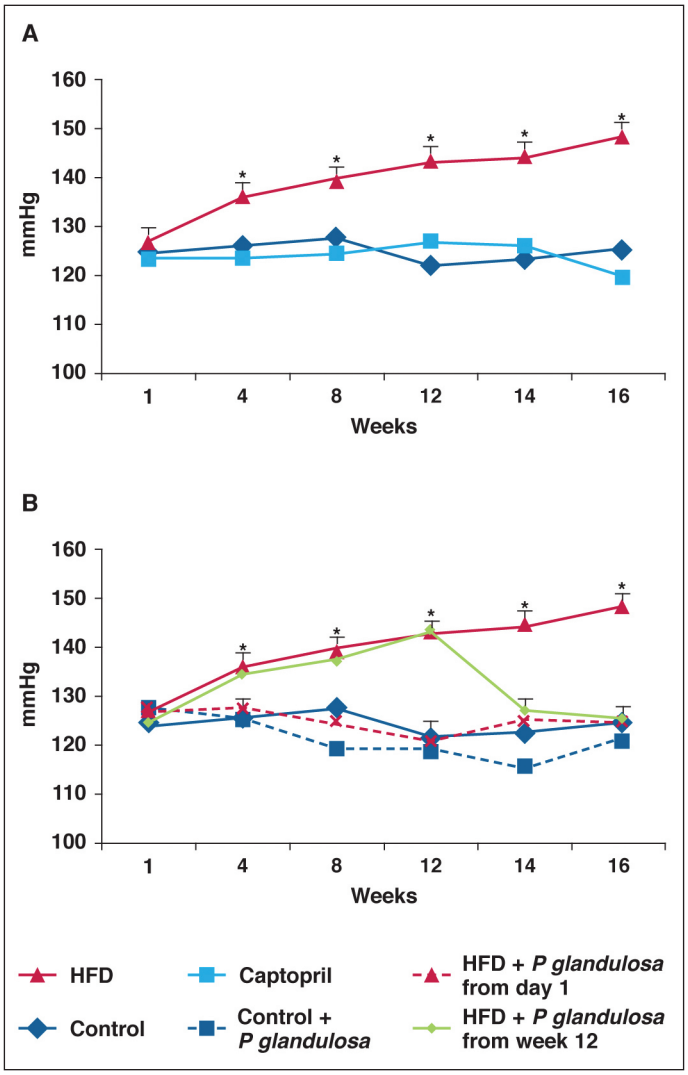

Fig. 6. Rats were fed a high-fat diet for 16 weeks and blood pressure was monitored on a weekly basis as described in Methods. *$p < 0.001$ vs control and captopril, $n = 9$ per group. **A**: HFD vs captopril, **B**: HFD vs P glandulosa treatment.

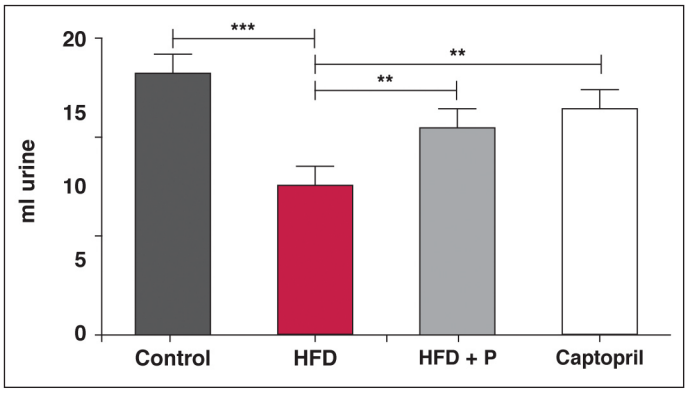

Fig. 7. Rats on the high-fat diet were individually placed in metabolic cages for the collection of urine over a 24-hour period. Data were collected at 12 weeks after the diet was started. $^{**}p < 0.01$, $^{***}p < 0.001$, $n = 9$ per group.

Discussion

Currently, the world is suffering from a silent epidemic starting with obesity and culminating in type 2 diabetes.[3] Two of the most debilitating complications of obesity, especially centrally located obesity, responsible for the high morbidity and mortality associated with such patients are hypertension and heart disease.[19,20] In view of the need for effective medication to supplement lifestyle changes to control these disease states, utilisation of plant-based therapies are currently strongly advocated.[7,21] Such therapies offer potentially cost-effective management but need scientific validation of their effects.

Previous studies from our laboratory demonstrated that the dried and ground pods of the *P glandulosa* tree have a potential benefit in the management of both type 1 and type 2 diabetes.8 In view of the insulin-sensitising effects on isolated cardiomyocytes from rats treated with *P glandulosa*, we aimed to determine whether this product has any cardioprotective or anti-hypertensive effects.

In this study, we used three different animal models. The first was a model of pre-diabetes (DIO), as also indicated by the biometric data presented in Table 1. These animals were fed an obesity-inducing diet containing only 16% fat.[11,13] DIO animals become insulin resistant but not diabetic, as the blood glucose levels never rose above ~ 6.5 mmol/l. This was however significantly higher than the levels found in the control, chow-fed animals. In order to keep the blood glucose levels low, the animals presented with high plasma insulin concentrations.

Although *P glandulosa* treatment did not significantly alter these parameters, the clinically important two-hour blood glucose values after a glucose tolerance test were significantly higher in the DIO animals and were effectively lowered by the treatment (Fig. 1). This underscores the slight effect on blood glucose handling previously reported.[8]

Determination of infarct size in ex vivo perfused rat hearts as a measure of myocardial damage incurred by ischaemia followed by reperfusion, is taken as the gold standard to prove cardioprotection.[15] We previously showed that hearts from the DIO rats developed larger infarct sizes when subjected to regional ischaemia followed by reperfusion.[10]

After eight weeks of treatment of DIO rats or CIRKO mice with *P glandulosa*, it was clearly demonstrated that there was an infarct-sparing effect elicited by ingestion of this plant material (Figs 2, 3). As the CIRKO mice do not possess a myocardial insulin receptor, the protection found in these animals confirmed the results obtained in the rat model and underscores that protection does not occur via the insulin-secretory effects of *P glandulosa*, as previously reported.[8]

One of the best-described and researched mechanisms of protection of the heart against ischaemia–reperfusion injury and infarction is activation of the PI-3K, PKB/Akt pathway, normally activated by various extracellular substances.[22-24] Activation of this pathway has several anti-apoptotic effects, leading to limitation of the development of an infarct after ischaemia.

In addition, activation of PKB/Akt is a pre-requisite for glucose uptake by the heart.[25] Myocardial glucose is taken up via the two transporters Glut 1 and Glut 4. An improved ability to import and utilise glucose is cardioprotective when the heart is subjected to the absence of oxygen, as induced by ischaemia. The heart then uses the energy generated by glycolysis to protect itself.

Measurement of the expression of both Glut 1 and Glut 4 showed no differences between hearts from control and DIO rats. However, the lower ratio of phosphorylated to total protein of PKB/Akt found in hearts from the DIO animals may have been detrimental during an ischaemic incident. In addition, there was lower expression of the p85 subunit of PI-3K documented in these hearts, which may have exacerbated this effect.

Both of these detrimental changes were improved by *P glandulosa* treatment. The changes documented in the phosphatase PTEN will further the positive effects found in both PI-3K and PKB/Akt as the lower expression and elevated phosphorylation of this enzyme will elevate the activity of PKB/Akt when the latter is stimulated.[18] PTEN normally inactivates PKB/Akt.[17] These changes may play a central role in the protection that *P glandulosa* treatment confers on the heart.

The second rat model was aimed at specifically inducing the development of hypertension. A modification of a high-fat diet was used (HFD).[12] These animals, in contrast to the DIO animals, developed severe hypertension within a four-week period, as shown in Fig. 6A and B. Not only was *P glandulosa* treatment able to prevent the development of hypertension when given in conjunction with the high-fat diet, but it normalised elevated blood pressure within two weeks.

The hormonal effects associated with a high-fat diet in rats, namely elevated vasopressin as well as activation of the renin–angiotensin system, leading to elevated aldosterone levels may both be involved in the development of hypertension in these animals.[26-28] Vasopressin, the anti-diuretic hormone leads to water retention and therefore the development of high blood pressure. In addition, it is associated with vasoconstriction.[28] Similar effects can be expected from elevated sympathetic activity, leading to elevated aldosterone levels. Measuring the 24-hour urine output of the HFD animals underscored this, as the HFD animals had a significantly lower urinary output than the controls.

According to Lee and Blaufox,[29] a volume of 16–17 ml urine can be expected from normal animals in the weight range of our experimental rats (control 258.49 ± 15.03 vs HFD 327 ± 12.90 g, $p < 0.05$, $n = 14$ per group) while a high-fat diet will result in concentration of this volume, indicating water retention. It can also be speculated that, in parallel with the latter effect, there will be vasoconstriction, contributing to the observed hypertension.

The treatment with *P glandulosa* was able to alleviate this, thereby adding to the myocardial protection observed. To highlight this argument, in the present study both the ACE inhibitor and

P glandulosa treatment significantly improved urinary flow of the animals, in conjunction with lowering the blood pressure. Although this was not measured in the current study, we speculate that vasopressin production and aldosterone levels were elevated in the HFD rats. *P glandulosa* treatment may affect the levels of either of these hormones, or it may provide a different, hitherto unrecognised mechanism of lowering blood pressure in the animals.

Conclusion

The present study has confirmed our previous results that the dried and ground pods of the *P glandulosa* tree have anti-hyperglycaemic effects. In addition we have conclusively shown that this treatment was cardioprotective, as determined by the infarct-sparing effects, and anti-hypertensive without affecting the body weight or the intra-peritoneal fat depots of the animals. The results indicated that key proteins involved in the cardioprotective PI-3-kinase/PKB/Akt pathway were affected in a manner that may be causal to this protection.

With regard to the anti-hypertensive effects, the results indicated water retention, possibly coupled with vasoconstriction in the HFD animals, while ingestion of *P glandulosa* alleviated both water retention and hypertension. Treatment of pre-diabetes, type 2 diabetes or hypertension with *P glandulosa* therefore poses potentially beneficial health effects besides its antihyperglycaemic effects.

Acknowledgements

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Efficacy and safety of sirolimus-eluting stents versus bare-metal stents in coronary artery disease patients with diabetes: a meta-analysis

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Abstract

Objective: **To compare by meta-analysis the efficacy and safety of sirolimus-eluting and bare-metal stents in coronary artery disease (CAD) patients with diabetes.**

Methods: **PubMed, MEDLINE and EMBASE were searched from 1971 to 2012. Data on the efficacy and safety of sirolimus-eluting and bare-metal stents in patients with diabetes were collected. A meta-analysis was then performed on a total of 1 259 CAD patients with diabetes from six studies. The odds ratio (OR) was used for comparison. Subgroup analysis was performed according to the sample size, year of study, subjects' geographic area and study method.**

Results: **Compared with those in the bare-metal stent group (BMS), the subjects in the sirolimus-eluting stent (SES) group had a reduced risk for major cardiac events [OR 0.42, 95% confidence interval (CI): 024–0.74, $p < 0.01$] and target-lesion revascularisation (OR 0.26, 95% CI: 0.11–0.59, $p < 0.01$). There was no difference for myocardial infarction (OR 0.92, 95% CI: 0.61–1.40, $p > 0.05$) or mortality (OR 1.19, 95% CI: 0.74–1.92, $p > 0.05$). Subgroup analysis showed a significant difference for overall risk of major cardiac events between SES and BMS when the sample size was ≤ 90 (OR 0.28, 95% CI: 0.16–0.48, $p < 0.01$), when it was a randomized control trial (RCT) (OR 0.28, 95% CI: 0.19–0.42, $p < 0.01$), or when it was performed on European subjects (OR 0.45, 95% CI: 0.27–0.77, $p < 0.01$). The sensitivity was not different when one study was removed at a time.**

Conclusion: **Our study confirmed that SES are safer and more effective than BMS in CAD patients with diabetes, as far as major cardiac events are concerned.**

Keywords: sirolimus-eluting stent, bare-metal stent, diabetes, meta-analysis, efficacy, safety

According to Nodari *et al.*, compared to patients without diabetes, those with diabetes mellitus (DM) had increased cardiovascular morbidity and mortality, and were more likely to develop congestive heart failure (CHF).[1] Van Nunen used coronary stents for revascularisation in acute cardiac events and improved the prognosis, with a high success rate and favourable early outcome.[2]

The traditional bare-metal stent (BMS) was initially widely used, with considerable efficacy and safety. However, longterm outcome and restenosis rate has been very discouraging.[3] Recently, sirolimus-eluting stents (SES) have been increasingly used for treating restenosis after having used BMS, as well as for treating the native coronary narrowing.[4-7]

For coronary arterial disease (CAD) patients with diabetes, the outcome, efficacy and safety of SES and BMS remain controversial,[8-16] mainly due to small sample sizes or low statistical power. Meta-analysis, combining results of several studies and producing a single estimate of major events with enhanced precision, has been considered a powerful tool for summarising inconsistent results from different studies.[17-20] Heterogeneity and publication bias can be detected with funnel plots and other methodologies.[21-26]

To clarify this controversy, in this study, we performed a meta-analysis and subgroup analysis, along with heterogeneity and publication-bias analysis, and compared the major cardiac events, target-lesion revascularisation, myocardial infarction and mortality rate in CAD patients with diabetes who were treated with SES or BMS.

Methods

PubMed, MEDLINE, EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google scholar were searched. The following keywords were used, 'sirolimus-eluting stents', 'bare-metal stents', 'coronary arterial disease', 'diabetes', 'diabetic', 'safety', 'efficacy', 'study' and 'trial'. The time period was limited from 1 January 1971 to 31 December 2012. The language published in was limited to English only. References of the articles were also checked for additional studies.

Studies included were randomised, controlled trials (RCT) and non-RCT conducted in coronary artery disease patients with diabetes treated with SES or BMS (studies with these two methods compared), regardless of the sample size. Excluded studies were those investigating patients with CAD or DM in only case reports or review articles, duplicated articles, and those with no comparison of SES and BMS.

After the investigators were trained, the data-mining form was developed and modified. The data included study details such as first author, year of study, year of publication, geographical area of subjects, demographics of subjects, and events with follow up after being treated with SES or BMS. According to the standard protocol, two investigators (A and B) mined the data independently, which was reviewed by the third one (C). Discrepancies were resolved through internal and external discussions (with the original investigators).

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S Afr J Diabetes Vasc Dis 2016; **13**: 68–73

Statistical analysis

Analysis was performed with software review manager 5.1 (Cochrane collaboration, http://ims.cochrane.org/revman) and comprehensive meta-analysis (Englewood, NJ); $p < 0.05$ was regarded as statistically significant. Meta-analysis was performed in fixed- or random-effect models.

Odds ratios (OR) and 95% confidence intervals (CI) were estimated in each study. Pooled ORs were obtained using the Mantel–Haenszel method in a fixed-effect model, and the DerSimonian–Laid method in a random-effects model.[24] The significance of pooled ORs was determined by the Z-test. Cochrane's Q-statistic was used to assess within- and between-studies variations. A $p < 0.10$ on the Q-statistic was regarded as heterogeneity across the studies. I^2 was also used to test heterogeneity with the formula:

$$I^2 = \frac{(Q - df)}{Q} \times 100\%$$

where $I^2 < 25\%$ means no heterogeneity; $I^2 = 25$–50% means moderate heterogeneity; $I^2 > 50\%$ means large or extreme heterogeneity.[27]

The random-effects model was also used for evaluating the possibility of heterogeneity of studies. Publication bias was evaluated with Egger's test and funnel plots,[28] which compensate for each other's drawbacks. If there is evidence of publication bias, the funnel plot is noticeably asymmetric. For the Egger's test the significance level was set at 0.05. Sensitivity analysis was also performed to test reliability of the results, by removing one study at a time and repeating the meta-analysis.

Results

As shown in Fig. 1, among 3 658 articles potentially relevant to the search terms (PubMed: 1 103; MEDLINE: 765; Springer: 650; Elsevier Science Direct: 880; Cochrane Library: 50; Google Scholar: 210), 323 potentially relevant studies were selected after the duplicates were removed. When the abstracts were screened, 276 were excluded (65 were review articles, 156 were not diabetic patients, 55 did not report on BMS data). Among the remaining 47, another 41 were excluded (25 only reported on BMS data without comparisons, 16 were excluded due to unavailable data). Finally, six studies were included in this meta-analysis.

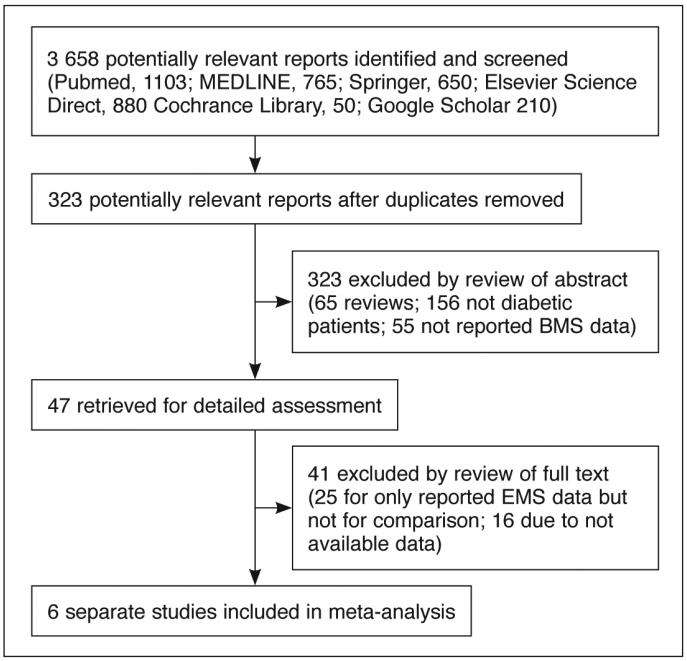


Fig. 1. Flow chart of selection of the studies.

The characteristics of the included studies are presented in Table 1. These six studies were conducted from 2002 to 2006 and published between 2005 and 2008, three in Europeans, two in Americans, and one in Asians and Americans. A total of 1 259 CAD subjects with diabetes (SES 614 and BMS 645) were included, with an average age of 65 years. The sample sizes ranged from 83 to 458, and the studies were RCTs and non-RCTs.

Table 1. Characteristics of studies included in the meta-analysis.

Study	Study year	Country	Ethnicity	Study method	Follow up (years)	SES group		BMS group	
						Sample size	Age (years)	Sample size	Age (years)
Aoki J, *et al.*	2002–2003	Netherlands	European	Non-RCT	1	112	63 ± 10	118	64 ± 11
Jimenez-Quevedo P, *et al.*	2003	United States	America	RCT	1	80	65.4 ± 8	80	67.9 ± 9
Baumgart D, *et al.*	2002–2004	Germany	European	RCT	1	94	66 ± 9	96	66 ± 10
Daemen J, *et al.*	2002–2003	United States	America	Non-RCT	1	206	62.0 ± 10	252	62.7 ± 10
Chan C, *et al.*	2002–2004	United States and Asia	America and Asian	RCT	1	54	58.7 ± 9.7	29	62.5 ± 10.3
Maresta A, *et al.*	2004–2006	Italy	European	RCT	1	68	71 ± 9	70	69 ± 9

Table 2. Pooled odds ratio for the SES versus the BMS group.

Subgroups	Random model				Test of heterogeneity			Egger's test for publication bias	
	No. of studies	OR (95% CI)	Z	*p*-value	*Q*	*p*-value	12 (%)	*t*	*p*-value
Overall effects	6	0.42 (0.24–0.74)	3.00	< 0.01	20.14	< 0.01	75.2	–4.19	0.014
Sample size ≤ 90	3	0.28 (0.16–0.48)	4.60	< 0.01	2.39	0.303	16.3	–3.66	0.62
Sample size > 90	3	0.61 (0.31–1.21)	1.42	0.15	8.70	0.013	77.0	–9.26	0.20
RCT	4	0.28 (0.19–0.42)	6.14	< 0.01	2.40	0.495	0.0	–2.36	0.531
Non-RCT	2	0.87 (0.61–1.24)	0.76	0.446	0.92	0.338	0.0	–5.29	–
European	3	0.45 (0.27–0.77)	2.95	< 0.01	3.71	0.156	46.1	–7.98	0.46
American and Asian	3	0.37 (0.11–1.27)	1.58	0.115	15.55	< 0.01	87.1	–5.92	0.23

The efficacy of SES versus BMS is presented in Table 2. As shown, the pooled OR was 0.42 (95% CI: 0.24–0.74, $p < 0.01$) for SES versus BMS. This suggests that, after the data had been pooled, SES were more effective than BMS in CAD patients with diabetes. However, there was publication bias ($t = –4.19$, $p < 0.05$).

As shown in Fig. 2A, the pooled OR was 0.42 (95% CI: 0.24–0.74, $p < 0.01$) for overall events, suggesting that SES had a better outcome compared with BMS, with a greater reduction in risk for major cardiac events. However, there were heterogeneities between the studies ($Q^2 = 20.14$, $I^2 = 75.0\%$, $p < 0.1$) and publication bias, as shown in Fig. 2B (asymmetric funnel plot). This was further confirmed with Egger's linear regression test, shown in Table 2 ($t = –4.19$, $p < 0.05$).

As shown in Fig. 3, the pooled OR was 0.26 (95% CI: 0.11–0.59, $p < 0.01$) for SES versus BMS, suggesting that SES had a better revascularisation rate for target lesions compared with BMS. However, there were heterogeneities between the studies ($Q^2 = 24.44$, $I^2 = 80.0\%$, $p < 0.1$) and publication bias ($t = –6.44$, $p < 0.05$).

As shown in Fig. 4, the pooled OR was 0.92 (95% CI: 0.61–1.40, $p > 0.05$) for SES versus BMS, suggesting that the overall risk for myocardial infarction was not significantly different between these two groups. There was no heterogeneity between the studies ($Q^2 = 4.37$, $I^2 = 0\%$, $p > 0.1$) but there was publication bias ($t = –3.44$, $p < 0.05$).

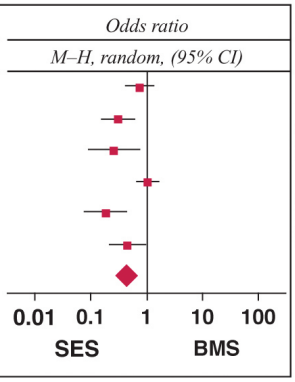
As shown in Fig. 5, the pooled OR was 1.19 (95% CI: 0.74–1.92, $p > 0.05$) for SES versus BMS, suggesting that the overall risk of mortality was not significantly different between the groups. There was no publication bias ($t = –1.69$, $p > 0.05$) or heterogeneities between the studies ($Q^2 = 3.88$, I2 = 0.0%, $p > 0.1$).

Subgroup analyses were stratified by sample size, subjects' geographical area and study method. As shown in Table 2 and Fig.

A

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
Aoki J, *et al.*	27	112	37	118	18.5	0.70 (0.39–1.24)
Baumgart D, *et al.*	15	94	38	96	17.2	0.29 (0.15–0.58)
Chan C, *et al.*	8	54	12	29	12.8	0.25 (0.09–0.71)
Daemen J, *et al.*	44	206	54	252	20.1	1.00 (0.64–1.56)
Jimenez-Quevedo P, *et al.*	8	80	31	80	15.0	0.18 (0.07–0.41)
Maresta A, *et al.*	15	68	28	70	16.4	0.42 (0.20–0.90)
Total (95% CI)		614		645	100.0	0.42 (0.24–0.74)
Total events	117		200			

Heterogeneity: Tau² = 0.36; Chi² = 20.14, df = 5 ($p = 0.001$); $I^2 = 75\%$
Test for overall effect: $Z = 3.00$ ($p = 0.003$)



B

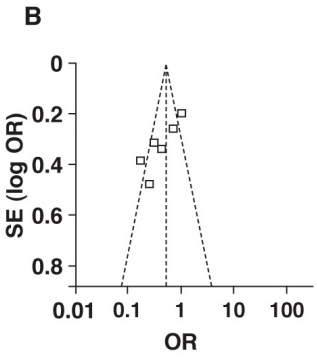


Fig. 2 A: Forest plots of studies with major adverse cardiac events in the SES group versus the BMS group. **B**: Funnel plots of studies with major adverse cardiac events in the SES group versus the BMS group.

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
Aoki J, *et al.*	9	112	23	118	17.9	0.36 (0.16–0.82)
Baumgart D, *et al.*	3	94	24	96	14.6	0.10 (0.03–0.34)
Chan C, *et al.*	7	54	10	29	15.7	0.28 (0.09–0.85)
Daemen J, *et al.*	28	206	35	252	19.9	0.98 (0.57–1.67)
Jimenez-Quevedo P, *et al.*	5	80	28	80	16.4	0.12 (0.04–0.34)
Maresta A, *et al.*	4	68	21	70	15.5	0.15 (0.05–0.45)
Total (95% CI)		614		645	100.0	0.26 (0.11–0.59)
Total events	56		141			

Heterogeneity: Tau² = 0.83; Chi² = 24.44, df = 5 ($p = 0.0002$); $I^2 = 80\%$
Test for overall effect: $Z = 3.22$ ($p = 0.001$)

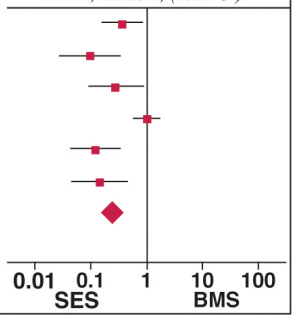


Fig. 3. Forest plots of studies with target-lesion revascularisation events in the SES group versus the BMS group.

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
Aoki J, *et al.*	18	112	14	118	25.1	1.42 (0.67–3.02)
Baumgart D, *et al.*	4	94	5	96	10.4	0.81 (0.21–3.11)
Chan C, *et al.*	1	54	2	29	5.6	0.25 (0.02–2.94)
Daemen J, *et al.*	10	206	11	252	20.7	1.12 (0.47–2.69)
Jimenez-Quevedo P, *et al.*	2	80	6	80	12.8	0.32 (0.06–1.62)
Maresta A, *et al.*	11	68	14	70	25.4	0.77 (0.32–1.85)
Total (95% CI)		614		645	100.0	0.92 (0.61–1.40)
Total events	46		52			

Heterogeneity: Chi² = 4.37, df = 5 ($p = 0.50$); $I^2 = 0\%$
Test for overall effect: $Z = 0.37$ ($p = 0.71$)

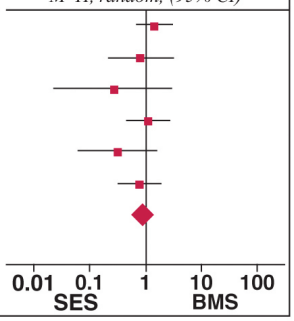


Fig. 4. Forest plots of studies with myocardial infarction events in the SES group versus the BMS group.

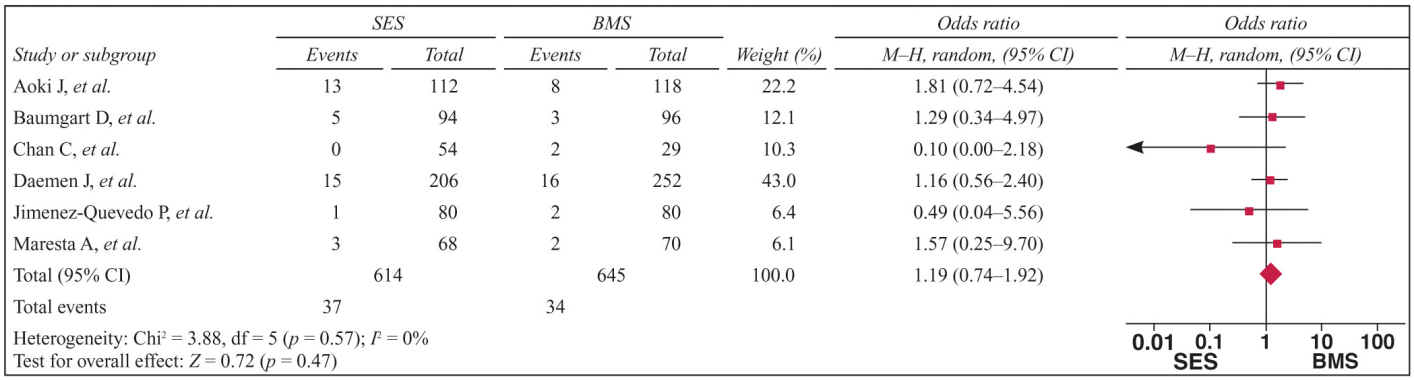


Fig. 5. Forest plots of studies with mortality events in the SES group versus the BMS group.

6A–C, the pooled OR was 0.28 (95% CI: 0.16–0.48, $p < 0.01$, Fig. 6A) for SES versus BMS in studies whose sample size was above 90, with heterogeneities between the studies ($Q^2 = 8.7$, $I^2 = 77\%$, $p < 0.1$). The pooled OR was 0.61 (95% CI: 0.31–1.21, $p > 0.05$, Fig. 6A) in studies whose sample size was 90 or less, without heterogeneities between the studies ($Q^2 = 2.39$, $I^2 = 16\%$, $p > 0.1$).

The pooled OR was 0.45 (95% CI = 0.27–0.77, $p < 0.01$, Fig. 6B) in studies whose subjects were European, without heterogeneities between the studies ($Q^2 = 3.71$, $I^2 = 46\%$, $p > 0.1$). The pooled OR was 0.37 (95% CI: 0.11–1.27, $p > 0.05$, Fig. 6B) in studies whose subjects were American and Asian, with heterogeneities between the studies ($Q^2 = 15.55$, $I^2 = 87\%$, $p < 0.1$).

The pooled OR was 0.28 (95% CI: 0.19–0.42, $p < 0.01$, Fig. 6C) in studies whose study method was RCT, without heterogeneities between the studies ($Q^2 = 2.4$, $I^2 = 0\%$, $p > 0.1$). The pooled OR was 0.87 (95% CI: 0.61–1.24, $p > 0.05$, Fig. 6C) in studies whose method of study was non-RCT, without heterogeneities between the studies ($Q^2 = 0.92$, $I^2 = 0\%$, $p > 0.1$).

By removing one study at a time, a sensitivity analysis was performed and the model was rerun to determine the effect on each estimate. It showed that the above meta-analysis estimates did not change significantly after removal of each study, implying that these results were statistically reliable.

Discussion

A growing number of studies has shown the efficacy and safety of SES versus BMS for treating CAD patients with diabetes,[9,29] but the outcome has been controversial. In this analysis, we retrieved six studies, which included 1 259 CAD subjects with diabetes, and performed a meta-analysis. It showed that the SES group had a significant reduction in major adverse cardiac events, as well as target-lesion revascularisations, compared with the BMS group. There was no significant difference for myocardial infarction or mortality.

These results are consistent with a recent study that suggested a significant reduction in target-vessel revascularisations with SES, but with similar mortality rates.[9] Unlike this study, in which the incidence of myocardial infarction was higher, our analysis showed no difference for myocardial infarctions between the groups.

Another recent study conducted in Europeans confirmed the efficacy of SES compared with BMS, along with comparable

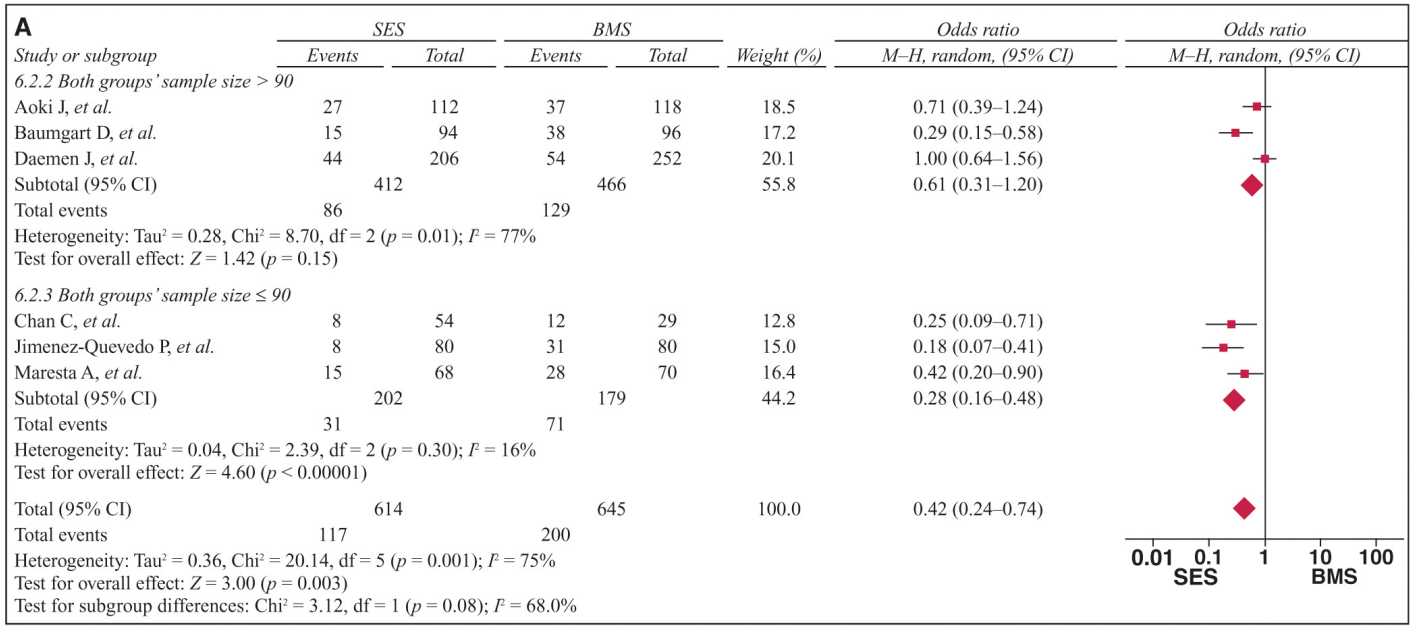
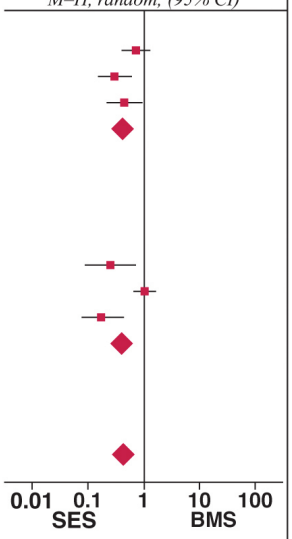


Fig. 6. A: Forest plots of sample size subgroups.

B

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
1.1.1 European Subgroup						
Aoki J, *et al.*	27	112	37	118	18.5	0.70 (0.39–1.24)
Baumgart D, *et al.*	15	94	38	96	17.2	0.29 (0.15–0.58)
Maresta A, *et al.*	15	68	28	70	16.4	0.42 (0.20–0.90)
Subtotal (95% CI)		274		284	52.1	0.45 (0.27–0.77)
Total events	57		103			
Heterogeneity: Tau² = 0.10, Chi² = 3.71, df = 2 (p = 0.16); I^2 = 46%						
Test for overall effect: Z = 2.95 (p = 0.003)						
1.1.2 American and Asian						
Chan C, *et al.*	8	54	12	29	12.8	0.25 (0.09–0.71)
Daemen J, *et al.*	44	206	54	252	20.1	1.00 (0.64–1.56)
Jimenez-Quevedo P, *et al.*	8	80	31	80	15.0	0.18 (0.07–0.41)
Subtotal (95% CI)		340		361	47.9	0.37 (0.11–1.27)
Total events	60		97			
Heterogeneity: Tau² = 1.02, Chi² = 15.55, df = 2 (p = 0.0004); I^2 = 87%						
Test for overall effect: Z = 1.58 (p = 0.11)						
Total (95% CI)		614		645	100.0	0.42 (0.24–0.74)
Total events	117		200			
Heterogeneity: Tau² = 0.36, Chi² = 20.14, df = 5 (p = 0.001); I^2 = 75%						
Test for overall effect: Z = 3.00 (p = 0.003)						
Test for subgroup differences: Chi² = 0.09, df = 1 (p = 0.77); I^2 = 0%						



C

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
5.1.1 RCT						
Baumgart D, *et al.*	15	94	38	96	17.2	0.29 (0.15–0.58)
Chan C, *et al.*	8	54	12	29	12.8	0.25 (0.09–0.71)
Jimenez-Quevedo P, *et al.*	8	80	31	80	15.0	0.18 (0.07–0.41)
Maresta A, *et al.*	15	68	28	70	16.4	0.42 (0.20–0.90)
Subtotal (95% CI)		296		275	61.4	0.28 (0.19–0.42)
Total events	46		109			
Heterogeneity: Tau² = 0.00, Chi² = 2.40, df = 3 (p = 0.49); I^2 = 0%						
Test for overall effect: Z = 6.14 (p = 0.00001)						
5.1.2 Non-RCT						
Aoki J, *et al.*	27	112	37	118	18.5	0.70 (0.39–1.24)
Daemen J, *et al.*	44	206	54	252	20.1	1.00 (0.64–1.56)
Subtotal (95% CI)		318		370	38.6	0.87 (0.61–1.24)
Total events	71		91			
Heterogeneity: Tau² = 0.00, Chi² = 0.92, df = 1 (p = 0.34); I^2 = 0%						
Test for overall effect: Z = 0.76 (p = 0.45)						
Total (95% CI)		614		645	100.0	0.42 (0.24–0.74)
Total events	117		200			
Heterogeneity: Tau² = 0.36, Chi² = 20.14, df = 5 (p = 0.001); I^2 = 75%						
Test for overall effect: Z = 3.00 (p = 0.003)						
Test for subgroup differences: Chi² = 16.81, df = 1 (p < 0.0010); I^2 = 94.1%						

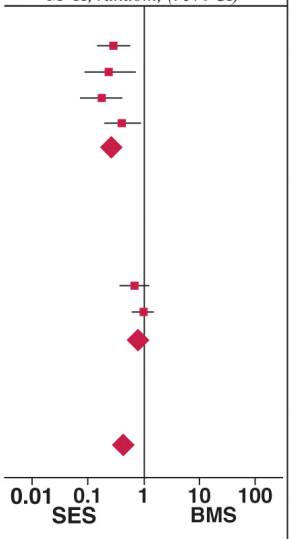


Fig. 6. B: Forest plots of ethnicity subgroups. **C**: RCT or non-RCT subgroups.

mortality rates and myocardial infarctions,[11] which further proved the validity of our analysis. The efficacy and safety of SES have been receiving more and more supportive reports.[30-33]

The uniqueness of our analysis and findings is that it proved the efficacy and safety of SES in CAD patients with diabetes.

Heterogeneity is one major concern with regard to the validity of meta-analyses.[26,34] Non-homogeneous data can easily give misleading results. In our study, the Q and I^2 statistics were performed to test heterogeneity. For all samples, there was significant heterogeneity for major adverse cardiac events in the SES and BMS groups.

We further conducted subgroup analysis according to sample size, ethnicity and study method. It demonstrated that in the studies where sample size was ≤ 90, method was a RCT and population was European, the overall major cardiac events were significantly different between the SES and BMS groups.

Heterogeneity between the studies was decreased after stratifying the samples. No significant heterogeneity was observed with RCTs, suggesting an RCT is important for good results. More high-quality RCTs are therefore warranted.

Another concern for meta-analyses is publication bias, due to selection of the studies included. In this study, using funnel plots and Egger's test,[28,35,36] we found publication bias for overall major cardiac events, target-lesion revascularisations and myocardial infarction, but not for overall mortality. Furthermore, the sensitivity analysis confirmed there was no change if one study was removed at a time. Although more studies would have produced better results, overall, our results were statistically reliable.

Conclusion

This meta-analysis suggested that, compared with BMS, SES are more effective and safer for reducing major cardiac events in CAD patients with diabetes. This may indicate the direction for future trials and clinical implementation.

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The protective effect of topical rifamycin treatment against sternal wound infection in diabetic patients undergoing on-pump coronary artery bypass graft surgery

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Abstract

Objectives: **The aim of this study was to investigate the protective effect of topical rifamycin SV treatment against sternal wound infection (SWI) in diabetic patients undergoing on-pump coronary artery bypass graft (CABG) surgery.**

Methods: **One hundred and fifty-nine diabetic patients who were scheduled to undergo isolated on-pump CABG surgery were included. Eight were excluded for various reasons. Of the 151 patients, 51 were on insulin therapy and 100 were on oral anti-diabetics. The risk of mediastinitis was assessed using the American College of Cardiology/American Heart Association 2004 guideline update for CABG surgery. According to the risk scores, patients were divided into two comparable groups: the rifamycin group (*n* = 78) received topical rifamycin treatment after on-pump CABG surgery, and the control group (*n* = 73) received no topical treatment.**

Results: **Deep sternal wound infection (mediastinitis) was not observed in either group (0/78 vs 0/73, *p* = 1.0). No superficial sternal wound infection was observed in the rifamycin group, however, it did occur in one patient in the control group (0/78 vs 1/73, *p* = 0.303). Wound culture was performed and coagulase-negative staphylococci were observed. The infection regressed on initiation of antibiotic therapy against isolated bacteria and the patient was discharged after a full recovery.**

Conclusion: **Although the difference in rate of superficial sternal wound infection (SSWI) in the rifamycin and control groups was not statistically significant, locally applied rifamycin SV during closure of the sternum in the CABG operation may have had a protective affect against SWI.**

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Keywords: rifamycin, sternal wound infection, on-pump CABG

Sternal wound infection (SWI) is a rare complication occurring after coronary artery bypass graft (CABG) surgery. Sternal wound infection occurs in one to 3% of patients and has a mortality rate of up to 40%. It is also associated with prolonged hospital stay and increased healthcare costs.[1-4]

According to the American College of Cardiology/American Heart Association (ACC/AHA) 2004 guideline update for CABG surgery, the risk of mediastinitis is evaluated before CABG surgery using factors, such as age of patient, the presence of obesity, diabetes or chronic obstructive pulmonary disease (COPD), the need for dialysis, an ejection fraction (EF) < 40%, and being scheduled for emergency surgery.[5]

In studies by Khanlari *et al*. and Kloos *et al*., patients with SWI were divided into two subgroups: superficial sternal wound infection (SSWI) and deep sternal wound infection (DSWI).[6,7] While SSWI involves only subcutaneous tissue, DSWI is associated with sternal osteomyelitis and sometimes with infected retrosternal space (termed mediastinitis). These researchers reported that DSWI occurred in 0.25 to 2.3% of patients.[6,7]

Rifamycin SV is a relatively effective agent for the treatment of gram-positive bacteria, *Mycobacterium tuberculosis* and certain gram-negative bacteria. Rifampicin, derived from rifamycin SV, is readily absorbed after oral administration and possesses higher antimicrobial activity against *Staphylococcus aureus, S epidermidis, Streptococcus viridans* and *Mycobacterium tuberculosis,* even in very low doses. In nly one study in the literature has the use of antibiotics containing rifampicin been suggested to improve outcomes in staphylococcal deep-wound infections.[6]

In the present study, we aimed to investigate the protective effects of topical rifamycin SV treatment on SWI after on-pump CABG surgery in diabetic patients.

Methods

One hundred and fifty-nine diabetic patients who were scheduled to undergo isolated CABG surgery in the Department of Cardiovascular Surgery, Mevlana University between July 2008 and July 2011 were prospectively enrolled. Of these patients, eight were excluded due to use of the intra-operative beating-heart technique, a need for revision in the post-operative period, or death. In the remaining 151 patients, the risk of mediastinitis was assessed according to the ACC/AHA 2004 guideline update for CABG surgery.[5]

We grouped the patients according to their mediastinitis risk scores into two comparable groups: the rifamycin group consisted of 78 patients (52 male, mean age 62 ± 8 years) who received local antibiotic rifamycin SV i.m. (Rif® 250 mg/3-ml ampoule) on the sternal region after CABG surgery, and the control group consisted

of 73 patients (45 male, mean age 61 ± 8 years). They did not receive a local antibiotic.

The local ethics committee approved the study. Written informed consent was obtained from the patients. It was determined prior to the initiation of the study that patients developing SSWI would be treated by the administration of antibiotics alone. Patients developing DSWI would be treated by the administration of antibiotics plus surgery.

During the pre-operative period, all patients were assessed for the risk of mediastinitis according to the ACC/AHA 2004 guideline for CABG surgery,[5] using eight parameters including age, presence of obesity, diabetes or COPD, the need for dialysis, ejection fraction (EF) < 40%, and scheduled for emergency surgery. Baseline characteristics, parameters used to assess the risk of mediastinitis, and post- and intra-operative data of the patients are presented in Table 1.

Skin cleansing was performed in all patients prior to surgery. Combined insulin therapy with regular human insulin (Humulin® R 100 U/ml) and insulin glargine (Lantus® 100 U/ml) was administered to control blood glucose levels below 200 mg/dl during pre-, intra- and postoperative periods. Insulin infusion was initiated in patients as required. The standard prophylactic antibiotic regimen used in our clinic was administered to patients, that is 1 g cefazolin sodium (Cefamezin-IM/IV®) 30 minutes before surgery and 1 g every eight hours after surgery for 48 hours.

Cardiopulmonary bypass (CPB) duration, cross-clamping times and number of grafts in both groups are shown in Table 1. Only left internal mammary artery grafts were used in all patients. Meticulous aseptic techniques were used during the operation and unnecessary use of electrocautery and excessive perfusion in CPB were avoided.

All patients were kept in the intensive care unit for 24 hours and the patients were referred to a regular ward within the second 24 hours after drains and arterial catheters were removed. Central venous catheters were removed on the second postoperative day. The patients were discharged on postoperative day 6 ± 3.

In the rifamycin group, mediastinum, sternum and suprasternal tissues were irrigated after surgery using rifamycin SV i.m. (Rif® 250 mg/3-ml ampoule) diluted with 10 ml isotonic solution. In the control group, irrigation was not performed. The two groups were compared with regard to risk for sternal infection.

Table 1. Baseline clinical characteristics of the study groups.

	Group 1 (*n* = 78)	Group 2 (*n* = 78)	*p*-value
Age (years)	62 ± 8	61 ± 8	0.605
Sex (F/M)	26/52	28/45	0.635
BMI (kg/m²)	28.9 ± 4.6	29.1 ± 4.2	0.796
Mediastinitis risk score	0.7 ± 0.4	0.7 ± 0.4	0.570
Number of grafts (*n*)	3.2 ± 1.0	3.3 ± 1.0	0.557
CABG time (min)	104 ± 30	105 ± 27	0.896
Cross-clamp (min)	70 ± 21	71 ± 20	0.687
24-hour drainage (ml)	508 ± 200	549 ± 317	0.350
Total drainage (ml)	515 ± 202	587 ± 334	0.113
COPD	6 (7.7%)	4 (5.5%)	0.746
Dialysis	2 (2.6%)	3 (4.1%)	0.673
Ejection fraction (< 40%)	13 (16.7%)	12 (16.4%)	0.856
Urgent surgery	1 (1.3%)	3 (4.1%)	0.353
Emergency surgery	0 (0%)	0 (0%)	1.0
Sternal infection	0 (0%)	1 (1.4%)	0.303

Categorical variables are expressed as number (percentage) and continuous variables as mean = SD. BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease.

Statistical analysis

Statistical analysis was performed using statistical package for social sciences 13.0 (SPSS Inc, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the distribution of numerical parameters. Continuous variables are presented as mean ± standard deviation. For comparison of independent continuous variables, the Student's *t*-test or Mann-Whitney *U*-test was used where appropriate. Categorical data were compared using the Fisher's exact test or chi-square test. For all statistics, a p-value < 0.05 was considered statistically significant.

Results

There were no significant differences between the two groups in terms of baseline characteristics and mediastinitis risk percentages (Table 1).

The patients were followed up for the development of SWI for 30 days after the surgery. In neither group did DSWI occur. While no SSWI was observed in the rifamycin group, it was observed in one patient in the control group (0/78 vs 1/73, $p = 0.303$). This patient, who used oral anti-diabetic medication, was 75 years old and had a serum creatinine level below 2.5 mg/dl, had a low risk profile (total risk score: 3 and pre-operative mediastinitis risk percentage: 0.5%), according to the ACC/AHA 2004 guideline.[5]

Wound culture was performed and coagulase-negative staphylococci (CoNS) were observed. The patient was put on appropriate antibiotic therapy with sodium fusidate (Stafine® tablet 500 mg) three times daily and rifampicin (Rifcap® capsule 150 mg) twice daily. The infection regressed and the patient was discharged after a full recovery.

The amount of drainage in the control group, particularly in four patients, was higher than in the patients in the rifamycin group, however, the difference was not statistically significant. This was attributed to the pre-operatively administered antiplatelet agents rather than to surgical reasons, and re-exploration was not required. However, none of the four patients developed sternal infection. None of the patients required re-exploration due to bleeding, tamponade or for other reasons.

Discussion

Rifamycin was first isolated in 1957 from a fermentation culture of *Nocardia mediterranei* and used as a novel antibiotic compound. Rifamycin SV is a relatively effective agent for the treatment of gram-positive bacteria, *Mycobacterium tuberculosis* and certain gram-negative bacteria. Rifampicin, an orally active agent that possesses higher antimicrobial activity, is derived from rifamycin SV. It has lower antimicrobial activity compared to its orally active derivative of rifampicin; however, both are effective against gram-positive cocci, especially staphylococci. Moreover, they possess higher antimicrobial activity against *Staphylococcus aureus, S epidermidis, Streptococcus viridans* and *Mycobacterium tuberculosis*, even in very low doses. There is only one study reporting improved outcomes in DSWI with the use of rifampicin.[6]

CoNS are part of normal skin flora.[7] They are omnipresent and cause infection in patients as well as in hospital staff.[7,8] CoNS are multiple-drug-resistant pathogens that can infect deep surgical wounds and have the potential to threaten life.[9] Stahle *et al*.[10]

reported the rate of CoNS in surgical wound infections as 14%. It is known that CoNS are also the predominant bacteria in DSWI.[11]

SWI are divided into two subgroups: superficial sternal wound infection (SSWI) and deep sternal wound infection (DSWI). While SSWI involves only subcutaneous tissue, DSWI is associated with sternal osteomyelitis and sometimes with infected retrosternal space (termed mediastinitis).[12] Studies have reported that DSWI occurs in 0.25 to 2.3% of patients.[13-17]

While re-opening and debridement of the mediastinum is required in the treatment of DSWI, administration of antibiotics is generally sufficient to treat SSWI. In the present study, only one patient (1/151, 0.66%) in the control group developed SSWI and was treated with the administration of antibiotics.

DSWI occurring after CABG operation has a multifactorial aetiology, with a potential risk of death and high hospital costs.[18] Many studies have suggested the underlying aetiology of DSWI occurring after CABG to be obesity, advanced age, prolonged CPB duration, diabetes, high creatinine levels, use of bilateral internal mammary artery grafts, and unnecessary use of electrocautery.[14,18-21] Recent studies have suggested that DSWI is associated with obesity and re-operation, and also indicated that use of bilateral internal mammary artery grafts, duration and complexity of the operation, and diabetes are other risk factors.[22]

It is well known that mobilisation of the internal mammary artery causes sternal devascularisation and the resultant ischaemia contributes to sternal dehiscence or infection.[14,22] In the present study, according to the ACC/AHA 2004 guideline,[5] the pre-operative mediastinitis risk percentage of one patient who developed SSWI was 0.5%, due to the risk factors, advanced age and the presence of diabetes. Although this patient was not a dialysis patient, he/she had a high creatinine level (2.5 mg/dl).

In a 10-year retrospective study of 5 440 patients who underwent cardiac surgery, Khanlari *et al*.[6] evaluated 100 patients with staphylococcal DSWI developing after cardiac surgery. They reported that a rifampicin-containing antibiotic regimen significantly improved the outcomes during a one-year follow-up period.

Many factors have been implicated in the occurrence of DSWI after cardiac surgery. However, there is no consensus on which is the most important and best predictive factor.[23] On the other hand, diabetes has emerged as a significant risk factor of cardiovascular surgeons, for the development of DSWI after CABG operation. In terms of the pathophysiological consequences of diabetes, microvascular changes and elevated blood glucose levels impair the healing process of surgical wounds.[24,25] The present study is distinctive in that it examined patients who were on oral anti-diabetic agents or insulin therapy.

Conclusion

Although the difference in the rate of superficial sternal wound infection between the rifamycin and control groups was not statistically significant, locally applied rifamycin SV during closure of the sternum after CABG surgery may have had a protective affect against SWI.

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Mean platelet volume is associated with myocardial perfusion defect in diabetic patients

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Abstract

Aim: **Our aim was to evaluate whether there was a relationship between mean platelet volume and myocardial perfusion defect in diabetic patients using myocardial perfusion imaging.**

Method: **Forty-four diabetic patients with myocardial perfusion defect (group 1) and 44 diabetic patients without myocardial perfusion defect (group 2), matched for age and gender, were retrospectively examined. Levels of mean platelet volume (MPV) in the two groups were assessed.**

Results: **MPV was higher in group 1 than group 2 patients (8.76 ± 0.76 and 8.25 ± 0.78 fl), respectively, p = 0.003). Levels of glucose, triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, haemoglobin (Hb) and glycosylated haemoglobin (HbA_{1c}), and body mass index (BMI) in the two groups were not statistically significantly different. Multivariate logistic regression analyses showed that MPV was the only variable independently associated with myocardial perfusion defects (OR: 2.401, 95% CI: 1.298–4.440, p = 0.013).**

Conclusion: **This study showed that higher MPV was associated with myocardial perfusion defects. Higher MPV in diabetic patients was independently related to myocardial perfusion defects and may be an indicator of myocardial ischaemia.**

Keywords: myocardial perfusion defect, mean platelet volume, diabetes mellitus

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Diabetes mellitus (DM) is considered a coronary artery risk equivalent.[1] DM is associated with an increased risk of cardiovascular morbidity and mortality.[2,3] DM may cause myocardial perfusion defects involving the main coronary artery and myocardial microvascular circulation. Myocardial perfusion imaging (MPI) is a useful non-invasive tool to determine whether there is a myocardial perfusion defect.[4]

Platelet volume is a marker of platelet activation and function and is measured as mean platelet volume (MPV).[5] MPV has become a prognostic factor in coronary heart disease and may eventually be accepted as a parameter of platelet activity.[6] MPV is emerging as a new risk factor for vascular complications of DM of which atherothrombosis plays a crucial role.[7]

However, to the best of our knowledge, there have been no reports in the literature to evaluate the relationship between MPV and myocardial perfusion defect using MPI in patients with diabetes. Our aim was to evaluate whether there was a relationship between myocardial perfusion defect using myocardial perfusion scintigraphy and MPV in selected diabetic patients.

Methods

Eighty-eight patients with type 2 diabetes who had MPI between January and May 2013 in Bozok and Gaziosmanpaşa universities were retrospectively examined. Eighty-eight patients were enrolled in the study and divided into two groups, matched for age and gender: the myocardial perfusion defect group (group 1) and a group with no myocardial perfusion defect (group 2). Group 1 consisted of 44 subjects (14 men and 30 women, mean age: 61.75 ± 7.86 years). Group 2 consisted of 44 subjects (12 men and 32 women, mean age: 60.48 ± 9.28 years).

Patients with a history of myocardial infarction, unstable angina pectoris, cardiac surgery, angiographically proven coronary artery disease, endocrine disorder without diabetes, systemic inflammatory disease, rhythm disorder, any medication that could affect the MPV, suspicious scintigraphy results due to breast attenuation, and aperture and fixed (scar) perfusion defects were excluded.

The blood samples were withdrawn following a 12-hour fast. Glucose, creatinine and lipid profiles were determined using standard methods. For both groups, we measured the MPV from blood samples that were obtained following venipuncture. The blood was collected in tripotassium EDTA tubes. We analysed the blood samples using an automatic blood counter within one hour of drawing the blood.

The patients underwent a two-day stress/rest single-photon-emission tomography and gated GSPECT study using adenosine with a standard weight-based infusion protocol (140 µg/kg/min). The six-minute adenosine infusion was begun and 740 MBq (20 mCi) of MIBI was injected after three minutes. After a 45-minute delay, a stress set of images was acquired.

At rest, before receiving technetium-99m methoxy isobutyl

isonitrile (99mTc-MIBI), the patients were given one to two tablets of sublingual nitroglycerin (0.4 mg), five minutes apart and they were injected with 740 MBq (20 mCi) of MIBI. A GSPECT study was performed 45 minutes later.

GSPECT data were acquired in the supine position with the double-head SPECT-γ camera equipped with a high-resolution low-energy collimator. The obtained data were projected as myocardial tomographic slices in short-axis, vertical long-axis and horizontal long-axis views. Electrocardiogram gating was applied to the cardiac cycle with eight frames per cardiac cycle. The myocardium was divided into 17 segments following the American Society of Nuclear Cardiology/American College of Cardiology/American Heart Association guidelines.[8]

GSPECT dates were processed and analysed using 4D-MSPECT software, which determines the extent and severity of left ventricular perfusion defect size and the extent of reversible (ischaemia) or fixed (scar) perfusion defects.[9] The programme assigned a score of 0 to 4 to each segment based on activity level: 0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = absence of detectable tracer uptake. Abnormal perfusion, motion and thickening were defined as a score of ≥ 2.

The summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were calculated based on the conventional 17-segment model. The summed difference score (SDS), indicating the extent of reversible perfusion defects, was obtained by calculating the differences between the SSS and SRS.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 software. Parametric values are given as mean ± standard deviation and non-parametric values as a percentage. To compare parametric continuous variables, the Student's *t*-test was used; to compare non-parametric continuous variables, the Mann-Whitney *U*-test was used. Categorical data were compared by chi-square distribution. Stepwise multivariate logistic regression models were created to determine independent variables for myocardial perfusion defect. For multivariate regression, variables with a *p*-value < 0.1 in univariate analysis were selected. Two-tailed *p*-values < 0.05 were considered to indicate statistical significance.

Table 1. Baseline characteristic of the patients.

	Group 1	Group 2	*p*–value
Age (years)	60.02 ± 9.28	60.81 ± 8.02	0.660
Women (%)	72.7	68.2	0.408
HT (%)	72.7	86.4	0.093
HL (%)	47.7	56.8	0.281
Aspirin (%)	34.1	29.5	0.410
BMI (kg/m²)	31.41 ± 6.23	30.41 ± 5.7	0.446
Glucose (mg/dl)	131.79 ± 40.553	151.16 ± 54.213	0.070
TG (mg/dl)	192.36 ± 116.48	171.71 ± 87.321	0.600
TC (mg/dl)	190.04 ± 42.25	178.83 ± 46.73	0.258
HDL-C (mg/dl)	40.58 ± 5.911	38.68 ± 6.08	0.167
LDL-C (mg/dl)	118.77 ± 28.75	108.28 ± 33.82	0.133
Hb (g/dl)	13.16 ± 1.40	13.42 ± 1.46	0.399
MPV (fl)	8.76 ± 0.76	8.25 ± 0.78	0.003
HbA_{1c} (%)	8.67 ± 0.68	8.35 ± 0.86	0.094

HT: hypertension; HL: hyperlipidaemia TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: lowdensity lipoprotein cholesterol; Hb: haemoglobin; MPV: mean platelet volume; HbA_{1c}: glycosylated haemoglobin.

Results

Baseline characteristic of the patients are given in Table 1. Levels of glucose, triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, haemoglobin (Hb) and glycosylated haemoglobin (HbA_{1c}), and body mass index (BMI) in the two groups were not statistically significantly different. The MPV level was higher in group 1 than in group 2 patients (8.76 ± 0.78 and 8.25 ± 0.78 fl, respectively, $p = 0.003$). Levels of MPV in the two groups are shown in Fig. 1.

Univariate analysis showed that MPV, and HbA_{1c} and glucose levels were significantly involved in myocardial perfusion defects. Multivariate logistic regression analyses showed that MPV was the only variable independently associated with myocardial perfusion defect (OR: 2.401, 95% CI: 1.298-4.440, $p = 0.013$) (Table 2).

Discussion

This study showed that there was a relationship between myocardial perfusion defect and MPV. MPV was higher in the group with myocardial perfusion defects, compared to the one without myocardial perfusion defects. Patients with diabetes develop vascular complications, including macrovascular complications [coronary artery disease (CAD), peripheral vascular disease and stroke] and microvascular complications [diabetic nephropathy (DN), diabetic retinopathy (DR) and peripheral neuropathy].[10] Continuous hyperglycaemia may cause endothelial dysfunction and vascular lesions, resulting in diabetic vascular complications.[11,12]

Type 2 diabetes is a substantial risk factor in atherosclerotic cardiovascular disease.[13,14] Cardiovascular disease (CVD) is the leading cause of death in patients with type 2 DM.[15] Asymptomatic CAD is common in patients with DM and is a strong predictor of future poor outcome of coronary vascular events, as well as early death.[16,17] DM is associated with generalised endothelial dysfunction and small-vessel abnormalities.[18,19]

Perfusion defects are substantial predictors of coronary events in patients with known or suspected coronary heart disease (CHD).20 It is proposed that concomitant abnormalities of perfusion imaging scans in patients with diabetes with normal coronary angiograms

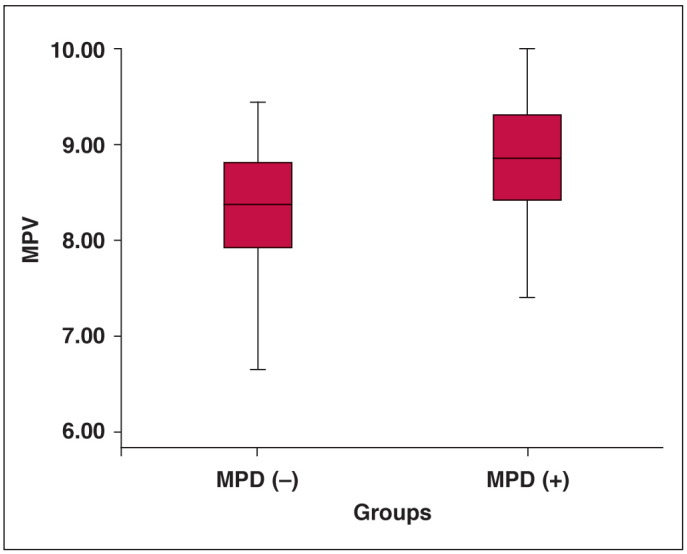

Fig. 1. MPV levels in the two groups.

Table 2. Univariate and multivariate regression analyses of independent variables for MPD.

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
MPV (fl)	2.401	1.298–4.440	0.005	2.484	1.215–5.081	0.013
Glucose (mg/dl)	1.009	0.999–1.029	0.072	1.008	0.997–1.019	0.178
HbA_{1c} (%)	1.800	0.993–3.474	0.08	1.984	0.980–4.018	0.064
Age (years)	1.011	0.963–1.061	0.664			
Gender	1.244	0.497–3.16	0.641			
HT (mg/dl)	2.375	0.801–7.043	0.119			
BMI (km/m2)	0.991	0.92–1.067	0.820			
TC (mg/dl)	0.994	0.984–1.004	0.256			
TG (mg/dl)	0.998	0.994–1.002	0.360			
HDL-C (mg/dl)	0.948	0.878–1.023	0.167			
LDL (mg/dl)	0.989	0.975–1.003	0.134			
Hb (%)	1.138	0.845–1.534	0.395			

may be caused by micro-angiopathy or endothelial dysfunction. Accordingly, it reflects an increased likelihood of future coronary events.[21]

The majority of studies on ischaemia have used SPECT MPI. An analysis of the diagnostic accuracy of pharmacologically induced stress MPI reported a mean sensitivity and specificity of 88 and 77%, respectively.[22]

Platelet volume is a marker of platelet activation and function, and is measured using MPV.5 Platelets that have dense granules are more active biochemically, functionally and metabolically. Large platelets secrete high levels of prothrombogenic thromboxane A2, serotonin, beta-thromboglobulin and procoagulant membrane proteins such as P-selectin and glycoprotein IIIa.[5,23] Platelets secrete a large number of substances that are crucial mediators of coagulation, inflammation, thrombosis and atherosclerosis.[24,25] It is also well known that large platelets are a risk factor for developing coronary thrombosis, leading to myocardial infarction.[19,23,26,27]

Measurement of platelet activation and/or aggregation may provide prognostic information in patients at risk for or following a cardiovascular event.[28,29] Reports have revealed that there is a close relationship between MPV and cardiovascular risk factors, including impaired fasting glucose levels, diabetes mellitus, hypertension, hypercholesterolaemia, obesity and the metabolic syndrome.[30-32] Increased platelet activity is reported to play a role in the development of vascular complications in diabetic patients.[18]

MPV was increased in patients with SCF complex and cardiac syndrome X, both being related to microvascular defects and endothelial dysfunction.[33,34] In the present study, we showed that MPV was associated with myocardial perfusion defect, using MPI in diabetic patients.

In our study, MPV was increased in the myocardial perfusion defect group compared to those without myocardial perfusion defects. DM not only involves the main coronary artery but also the microvascular circulation, leading to myocardial perfusion defects. Perfusion defects are significant predictors of coronary events in patients with known or suspected CHD.[20]

The main limitation of our study was the small sample size, which could result in low statistical power for equivalency testing, leading to false-negative results. Second, because of the retrospective nature of data collection, the angiographic results of the patients were not evaluated. MPI may reflect myocardial perfusion defects but it was not able to show the anatomical status of the coronary artery. We cannot extend our results to the general population due to our broad exclusion criteria.

Conclusion

MPV levels were higher in the diabetic patients with myocardial perfusion defects than in those without myocardial perfusion defects. In diabetic patients, increased MPV may be an independent marker of myocardial perfusion defects, which are associated with adverse coronary events.

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Peripheral neuropathy associated with cardiovascular disease and stroke in type 2 diabetes patients

Testing for peripheral neuropathy may provide a way to identify individuals at higher risk for cardiovascular events.

Jack Brownrigg, a PhD student at St George's, University of London, UK, who conducted the research at St George's Vascular Institute, is quoted in a press release from St George's as saying, 'While the risk of cardiovascular disease is known to be higher in patients with diabetes, predicting which patients may be at greatest risk is often difficult. We looked at data on individuals with no history of cardiovascular disease and found that those with peripheral neuropathy were more likely to develop cardiovascular disease.'

Robert Hinchliffe, senior lecturer and consultant in vascular surgery at St George's, who co-led the study with Prof Kausik Ray, said: 'While loss of sensation in the feet is known to be a key risk factor for foot ulcers, it may also provide additional useful information to guide patient management. This is the first study to show that it can also indicate an increased risk of cardiovascular problems like heart attacks or strokes.'

'The good news is that peripheral neuropathy can be easily identified by simple tests carried out in GP surgeries. The results of the study warrant further investigation as to whether even greater control of risk factors, including blood pressure and blood sugar, can prevent or delay the onset of cardiovascular disease. There is likely an unmet potential to reduce cardiovascular disease in this group of patients through greater monitoring and simple treatments.'

The researchers analysed data from 13 000 patients diagnosed with type 2 diabetes with no history of cardiovascular disease. They found that individuals with peripheral neuropathy were more likely to develop cardiovascular disease, noticing that patients who experienced loss of sensation in their feet also tended to have heart and circulatory problems, and so they suggested that the presence of peripheral neuropathy could be used as a simple way to indicate which high-risk patients with diabetes are in need of intensive care and monitoring.

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Once fat was fat and that was that: our changing perspectives on adipose tissue

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Abstract

Past civilisations saw excess body fat as a symbol of wealth and prosperity as the general population struggled with food shortages and famine. Nowadays it is recognised that obesity is associated with co-morbidities such as cardiovascular disease and diabetes. Our views on the role of adipose tissue have also changed, from being solely a passive energy store, to an important endocrine organ that modulates metabolism, immunity and satiety. The relationship between increased visceral adiposity and obesity-related co-morbidities has lead to the recognition that variation in fat distribution contributes to ethnic differences in the prevalence of obesity-related diseases. Our current negative view of adipose tissue may change with the use of pluripotent adipose-derived stromal cells, which may lead to future autologous stem cell therapies for bone, muscle, cardiac and cartilage disorders. Here, we briefly review the concepts that adipose tissue is an endocrine organ, that differences in body fat distribution underline the aetiology of obesity-related co-morbidities, and the use of adipose-derived stem cells for future therapies.

Keywords: adipocytes, obesity, cardiovascular disease, stem cells

A changing view of adiposity through the ages

The incidence of obesity and obesity-related co-morbidities has risen dramatically in the last century. The latest global data shows that in 2004 cardiovascular disease was the primary cause of death, above infectious and parasitic diseases, with the majority of cases attributed to an unhealthy lifestyle. This includes over-nutrition.[1] The increase in obesity has been accompanied by increased interest in fat and an abundance of research investigating the link between excessive adiposity and the associated pathologies. Currently there are over 130 000 research articles on obesity cited on PubMed and these publications show that our perception of the function of fat mass has changed considerably since the first entry cited from 1880. However, our knowledge of adiposity stretches back far beyond the 19th century. Although it is not known whether classical scholars recognised that adipose tissue is our major energy store, they did observe that excessive adiposity has negative health implications.

The Indian physician Sushruta (sixth century BCE) was probably the first to document a relationship between obesity and co-morbidities such as diabetes and heart disease. Not unlike today, he recommended exercise to remedy conditions that had arisen from a sedentary lifestyle and 'pampering the belly'.[2] Later in Europe, Hippocrates (460–377 BC) independently recognized the relationship between body composition, exercise and health, exemplified in his quote: 'If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health'. In a time of scant medical knowledge, his insight extended further, beyond his contemporaries, to include the pathogenicity of obesity, in writing: 'Repletion, carried to extremes, is perilous' and 'Corpulence is not only a disease in itself, but the harbinger of others'. He then subsequently noted that life expectancy was far shorter in the obese compared to lean individuals.[3]

Although the detrimental effects of obesity have therefore long been known, in the intervening millennia since Sushruta and Hippocrates, portliness was generally regarded as a symbol of affluence. This was primarily due to periodic food shortages and famine, which were only brought under control in the Western world in the last century yet still ravish the developing world today. This association between wealth and increased body mass was often reflected in the art of European masters such as Rubens (1577–1640) who depicted women with a full-bodied, hour-glass shape; a shape which was associated with opulence and fertility.[4]

By the 20th century, the use of intensive farming in conjunction with the mechanisation of the food industry helped to eradicate famine in the developed world. The increasing availability of highly palatable, high-energy foods and decreased levels of physical activity has led to an increasing imbalance between energy input and expenditure in the general population. The consequence of this is a burgeoning of portliness and obesity. This rise in the prevalence of obesity is a global phenomenon, occurring in both the developed and the developing worlds. Data from the USA shows that in the period 1988–1994 the prevalence of obesity was 22.5%,[5] and rose to 32.2% in the period 2003–2004.[6] A meta-analysis of studies measuring prevalence of obesity in west African countries showed that the prevalence of obesity in urban areas rose from 7.0% in 1990–1994 to 15.0% by 2000–2004.[7] Data from China demonstrated that the prevalence of overweight and obesity was 14.6% in 1992 and 21.8% in 2002.[8] Similar trends have been reported around the world. The increasing prevalence of obesity in the developing world is compounded by the cultural view of obesity as being a positive attribute, signifying both health and wealth. This is particularly so in African nations,[9] and is in stark contrast to the Western ideal, as portrayed in the mass media, of thin is beautiful!

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Central adiposity, ectopic fat deposition and obesity-related co-morbidities

'Not all fat is created equal' may be the new dogma in obesity research, with many studies reporting that the pathological effects of excessive adiposity are dependent not only on the quantity of fat, but on the distribution of the fat mass. The adipose tissue surrounding the major abdominal organs, the visceral fat, is thought to be the principal adipose depot involved in the aetiology of obesity-related disorders, with the subcutaneous fat depot playing a less prominent role.[10] Closer scrutiny of adipocytes isolated from these two fat depots has corroborated this view and shown fundamental metabolic differences as well as a higher production from visceral adipocytes of adipose tissue-derived cytokines (adipokines), which may play an important role in the aetiology of many obesity-related diseases.[11]

It has been proposed that the rate of lipid uptake is greater in the subcutaneous than the visceral adipose tissue depot until the former site approaches its limit for lipid storage, when triglyceride uptake into the visceral depot predominates.[12,13] Lipid accumulation in obesity promotes both adipocyte hyperplasia and hypertrophy,[14,15] with storage mainly occurring in pre-existing adipocytes. As hypertrophy progresses, the storage capacity of the cells in subcutaneous adipose tissue becomes limiting and lipids that are not readily accumulated are shunted to the visceral stores. Excessive fat accumulation in the visceral stores leads to the secretion of free fatty acids into the portal vein, which, with the secretion of pro-inflammatory adipokines, leads to hepatic insulin resistance and aberrant accumulation of lipids in hepatocytes and the resultant hepatic steatosis.[16]

In obese individuals, the inadequate lipid storage capacity of the body's adipose tissue depots leads to ectopic fat deposition not only in the liver but in other organs such as skeletal muscle and the insulin secreting b-cells of the pancreas. It has been suggested that this ectopic fat deposition may play an important role in the aetiology of both insulin resistance and β-cell failure.[17] Furthermore, in obesity, increased fat deposition has also been noted peri-vascularly and peri-cardially and within myocytes.[18] It has been suggested that this may contribute to vascular stiffness, cardiac dysfunction, hypertension, atherosclerosis and sodium retention, which are all characteristics of the cardiovascular disease observed in obese subjects.[18]

Adipose tissue, a paracrine and endocrine organ

Adipose tissue is no longer just seen as a fat store, but is considered a true secretory tissue, with differences in secretion underpinning the greater pathogenicity of visceral than subcutaneous fat masses. Adipocytes are known to secrete pro-inflammatory cytokines such as TNFα and IL-6, which in conjunction with elevated free fatty acids (FFAs), promote insulin resistance.[11] These cytokines are elevated in obesity and have been proposed to act in an autocrine loop, inhibiting the adipocyte hyperplastic response, which in turn leads to hypertrophy and further secretion of FFAs and pro-inflammatory cytokines.

Adipocytes produce a multitude of secreted peptides other than pro-inflammatory cytokines that have been linked to some of the obesity-related co-morbidities. Many of these molecules, such as plasminogen activation inhibitor 1 (PAI-1), angiotensinogen (AGT), monocyte chemo-attractant protein 1 (MCP-1) and resistin, have effects on vascular function. Plasminogen activation inhibitor 1 inhibits plasminogen activation and leads to fibrinolysis and a pro-thrombotic state.[19,20] PAI-1 is secreted more by visceral than subcutaneous fat[21] and is also a risk factor for coronary artery disease (CAD),[22] whereas angiotensinogen has been implicated in the aetiology of hypertension and is upregulated in obesity,[23,24] with production being higher in visceral fat.[25] Furthermore, angiotensinogen is the precursor of angiotensin II of the vasoconstriction renin–angiotensin system and may be a causal agent for the hypertension seen during obesity.[26]

Monocyte chemo-attractant protein 1 is also secreted predominantly from the visceral depot, is overproduced during obesity and participates in the recruitment of macrophages and monocytes into the arterial cell wall. As this recruitment may lead to atherosclerosis, MCP-1 was measured in patients with or without CAD, and it was found to be elevated in the former group.[27] Adipocytes also secrete resistin, which stimulates inflammatory cytokine production, as well as decreasing endothelial cell adhesion molecule (iCAM-1, vCAM-1, Ccl-2) production, which may promote atherosclerosis.[28] The role of resistin in insulin resistance is still unclear.[29,30]

Adipose tissue also secretes other peptides that have effects peripherally and centrally. The most investigated of these is leptin, a satiety factor which was first characterised in a rodent model of monogenic obesity, the ob/ob mouse.[31] Since the isolation and characterisation of leptin (from the Greek leptos: thin), adipose tissue has been viewed as a true endocrine organ. Leptin is secreted by adipocytes and modulates food intake by suppressing orexigenic peptides (Agouti-related peptide and neuropeptide Y) and upregulates anorexigenic peptides (corticotropin-releasing hormone and α-melanocyte stimulating hormone) in the brain.[32] It also stimulates fatty acid oxidation and prevents lipid accumulation in adipose tissue.[33,34] This forms a negative feedback mechanism, where increased fat mass produces more leptin, which reduces food intake, inhibiting further adipose expansion and limiting leptin expression. It was initially thought that this feedback loop could be used to inhibit food intake in the obese, but clinical trials of leptin analogues had little success, because endogenous leptin has since been found to be elevated in the obese, who often exhibit leptin resistance.[35] The adipokine has since been attributed to being a signal for energy deficiency, rather than a signal to lose weight, as excessive weight loss will result in decreased leptin levels and a consequential increase in food intake.[36,37]

Since the characterisation of leptin, many other adipokines have been discovered, such as apelin, visfatin, chemerin and vaspin, with adiponectin being the most fully studied. Adiponectin is copiously secreted from mature adipocytes,[38-40] with expression negatively correlating with body mass index (BMI).[41,42] Consequently, lean subjects have high levels, whereas obese subjects have low plasma levels. Decreased expression of adiponectin is observed in a number of obesity-related co-morbidities such as type 2 diabetes,[43,44] the metabolic syndrome,[45,46] non-alcoholic steatohepatitis[16] and CAD.[47,48] It has also been found that the protein is anti-diabetic, increasing insulin sensitivity, glucose uptake and fat oxidation, as well as suppressing hepatic glucose output.[49-51] The protein may also alter basal insulin secretion[52] and modulate satiety, increasing food intake and suppressing energy expenditure when fasting, but surprisingly having opposite effects after refeeding.[53] It is also anti-atherogenic[47,54] and anti-inflammatory.[55]

Whereas adiponectin decreases during obesity, there are other glucose-lowering adipokines that correlate positively with BMI.

Circulating apelin increases in obesity[56] and has been show to lower glucose in normal and obese mice.[57] Homozygous apelin knockout mice have severe heart failure in response to pressure overload and diminished heart contractility in aged mice,[58] indicating a role for the adipokine in maintaining cardiac function. Visfatin is an adipokine that is predominantly expressed in visceral adipose tissue and has been attributed to having insulin-like properties,[59] although this has since been disputed,[60,61] and recently visfatin has been shown to have pro-inflammatory effects.[62] Vaspin is a serine protease nhibitor and is reported to reduce expression of leptin, resistin and TNFα and improves insulin sensitivity.[63,64]

The recently discovered adipokine chemerin[65,66] increases insulin sensitivity in 3T3-L1 adipocytes[67] and is essential for normal adipocyte differentiation.[65,66,68] However, it has also been shown to lower glucose tolerance in murine models of obesity/diabetes[69] and to cause insulin resistance in human skeletal muscle cells, where it was also observed to be pro-inflammatory.[70] Consequently adipose tissue secretes both pro- and anti-inflammatory cytokines which modulate metabolism by altering insulin resistance. Generally, pro-inflammatory cytokine production increases and anti-inflammatory expression decreases during insulin resistance and obesity.

Obesity and cardiovascular disease in Africa

Studies have shown that the prevalence of both cardiovascular disease (CVD)[71] and obesity[7] is rising in Africa. Although it is not certain that these two findings are linked, the observation that CVD is more common in obese Africans[72] supports this premise. This recent rise in the prevalence of obesity in Africa is attributed to increased urbanisation and the associated ease of access to a more westernised, calorie-dense diet.[73]

Within Africa, the prevalence of CVD and its risk factors differs across the various resident population groups. Accordingly, mortality due to heart disease is higher in the Asian-Indian and European ethnic groups of South Africa when compared to the indigenous black African population.[74] Fasting serum cholesterol and triglyceride levels are higher in Asian-Indian than African subjects,[75] with type 2 diabetes being more prevalent in the former population group.[76] The reasons for these ethnic differences in disease prevalence rates and cardiovascular risk factors are not fully understood, although it has been suggested that the higher abdominal fat mass observed in Asian-Indian and European compared to African subjects may be involved.[77]

It is, however, of note that African subjects tend to be more insulin resistant than Europeans[78,79] even though they have less visceral adiposity. This would suggest either that visceral fat in African compared to European subjects has a greater ability to reduce insulin sensitivity, or that visceral adiposity is not involved in determining the level of whole-body insulin sensitivity in the African population. The latter hypothesis is unlikely since it has been shown that waist circumference, independently of BMI, is a determinant of insulin sensitivity in this population group.[80] It is also possible that subcutaneous abdominal fat may play a more prominent role in determining whole-body insulin sensitivity in African than European females, as has been observed in a previous study.[79]

Previous investigators have suggested that obesity in African subjects is benign. This hypothesis was based on reports that blood pressure, glucose and lipid levels were not elevated in obese compared to lean African females.[81] However, this hypothesis is challenged by data showing that there is a higher prevalence of CVD in obese compared to non-obese African subjects.[72] Furthermore, it must be noted that these studies[81] did not take into account body fat distribution, which is a major contributing factor to the pathogenesis of obesity-related disorders. It is also of interest to note that the African countries with the highest prevalence of obesity have the highest prevalence of obesity-related disorders, such as type 2 diabetes.[82]

Adiposity and insulin resistance as a biological advantage

Obesity has many negative connotations with regard to health. It is associated with an increased risk of many diseases, ranging from asthma to cancer. However, body fat does have an important physiological role, including the maintenance of body temperature and triglyceride storage. It also acts as an endocrine modulator of insulin sensitivity and appetite. The negative effects of adiposity on insulin sensitivity are often viewed as purely pathological. However, insulin resistance has been proposed to have an important biological role. It is now thought that insulin resistance is a normal physiological response to obesity to slow down triglyceride deposition in adipose tissue.[83] Studies have indeed shown that insulin resistance may protect against weight gain.[84,85] Furthermore, the biological adaptation of insulin resistance has been proposed as advantageous in prehistory, during times of feast and famine. The ability to readily store energy as fat would be beneficial until excessive adiposity would limit the capability of our ancestors to hunt and escape predation. Thus, insulin resistance would act to limit the rate of fat deposition. It is therefore possible that insulin resistance evolved to limit fat deposition in a period of human evolutionary history when excessive caloric intake was not a common occurrence. In modern times however, access to calorie-dense foods is not limited and this homeostatic mechanism for limiting excessive weight gain has been overpowered by new environmental conditions in which famine has been replaced by feast.

Adipose tissue may play an important role in modulating immunity. Adipocytes secrete a wide range of different cytokines that have both pro- and anti-inflammatory properties. Also, lymph nodes are normally found within adipose tissue depots and studies have demonstrated a strong interrelationship between these two tissue types. Therefore, the cells of the lymph node are supplied with specialised free fatty acids by the perinodal adipocytes, and dendritic cells from the lymph nodes are able to modulate lipolysis of the surrounding adipose tissue.[86] Furthermore, the adipokine, leptin has been shown to have effects on immune system functionality. Subjects with a leptin gene mutation have very low serum leptin levels and reduced numbers of CD4+ T cells and low T-cell proliferation rates. All these defects are normalised by administration of exogenous leptin.[87]

Fat as a source of stem cells

Our perception of adiposity has recently changed again. In addition to being an energy store, a major protagonist in the development of insulin resistance and a modulator of satiety, adipose tissue has been found to be an abundant store of stem cells. Adipose tissue may therefore be seen more positively, given that these cells may be used to treat a multitude of diseases.

Originally, Young *et al*.[88] isolated stem cells by digesting the connective tissue in fat and cultured the liberated cells, which they labelled the stromal vascular fraction (SVF). This was an

unpurified population containing stromal cells, endothelial progenitor cells, fibroblasts and haematopoietic stem cells,89 which were used to produce neo-vascular cells. The multipotential mesenchymal precursor cells that are harboured within the SVF may not only be differentiated into adipocytes,[90-92] but also bone-forming osteoblasts,[90,93,94] muscle myoblasts,[93,95] cardiomyocytes[96] and cartilage-forming chondrocytes.[90,93] Consequently, there is considerable interest in these adipose-derived stromal cells (ADSCs)[93,94] for regenerative medicine. This is not only for the replacement of damaged fat,[97] bone,[98-100] muscle[101] and cartilage,[102] for it has been found that ADSCs also secrete cytokines, such as VEGF, HGF and SDF-19,[103,104] which stimulate angiogenesis. These cells may therefore be used to treat ischaemic disease,[105] such as fibrosis and osteoradionecrosis, which are late complications of radiotherapy.[106] It has also been found that the growth factors that ADSCs secrete stimulate fibroblast and keratinocyte growth and therefore ADSCs have been used to aid skin repair.[107] Unlike bone marrow-derived stromal cells (BMSCs), a prominent redeeming feature of ADSCs is their ease of isolation.[108]

ADSCs and fat transplantation have been successfully used after trauma and surgical resection such as mastectomy,[109,110] where ADSCs help to abrogate problems with angiogenesis and the long-term viability of grafts.[111-113] ADSCs have also been used to treat lipodystrophy,[114] which has become common due to side effects of antiretroviral therapies (ART) in HIV-positive patients.[115,116] These ADSCs are expanded in number *in vitro* and differentiated into mature adipocytes using a cocktail including insulin, the cAMP inducer IBMX, a PPARg agonist indomethacin and a low concentration of a glucocorticoid such as dexamethasone.[117,118] The use of different cocktails enables ADSCs to be differentiated into osteoblasts, myocytes or chondrocytes.

Lee *et al*.[119] was the first to demonstrate that ADSCs could be differentiated into bone-forming osteoblasts and these cells were used to heal critically sized calvarial defects in mice. In a direct comparison during this investigation, ADSCs were found to have the same efficacy as BMSCs. It was established, using genetic analysis that 96% of the new bone was from the female donor rather than from the male recipient.[120] As both adults and children over the age of two years are unable to correct large cranial defects due to inadequate ossification, this application has direct relevance in man and was first used to correct a 120-cm^2 defect in a seven-year-old girl with a severe head injury.[121]

The differentiation of ADSCs into myocytes is relatively inefficient and gives a low yield and low reproducibility.[89] Glucocorticoids and 5% horse serum are used to supplement the growth media to stimulate the fusion of cells to form multi-nucleated myotubes which express myocyte markers.[90,93,122]

Although *in vitro* differentiation is far from optimal, these cells have been used to correct defects in the tibialis anterior muscle in a mouse model for Duchennes's muscular dystrophy.

The differentiation of ADSCs into chondrocytes is also inefficient. Insulin, TGFβ1 and ascorbic acid[122,123] are used to stimulate chondogenesis in ADSCs, which takes two weeks, but unfortunately the yield is far less than when using BMSCs.[123] As cartilage repair in vivo is often difficult and slow, the use of ADSCs to treat traumatised and arthritic joints and to aid joint reconstruction still warrants further research[102] and promises to improve therapy for cartilage repair in the future.

Adult mesenchymal stem cells isolated from the adipose tissue of rabbits are able to differentiate into cardiomyocytes when treated with 5-azacytidine.[96] This process has also been observed in human ADSCs cultured in the presence of dimethylsulfoxide.[124] Furthermore, such cells were used to improve cardiac function and increase survival rate in a rodent model of myocardial infarction.[124] Similar results were obtained in experiments in which undifferentiated ADSCs were transplanted into rodent[125,126] and porcine[127] infarcted hearts. These data suggest that at least in non-human models of myocardial infarction, ADSCs may be used to repair damaged cardiac tissue, although their utility in humans is still not known and requires further investigation.

Fat and the future

The future certainly looks secure for fat. The prevalence of obesity in the developing world shows no sign of abating, although recent data from the USA shows evidence of plateauing.[128] The rising levels of obesity in Africa were expected to result in an increase in the prevalence of obesity-related disorders, which seems to be the case.[71,129] Africa is also the centre of an HIV/AIDS epidemic and is therefore suffering a double burden of communicable and non-communicable diseases. Studies have shown that HIV infection and ART can both lead to cardiovascular disease[130] and this will further enhance the current epidemic of obesity-related diseases on the African continent. Consequently, the use of ART has converted our view of HIV infection from a certain death sentence to a chronic disease, and this is leading to the development of health service infrastructures that can be used for HIV diagnosis, ART roll out and patient follow up. Such infrastructure could also be utilised for the diagnosis and monitoring of non-communicable diseases in both HIV-positive and HIV-negative subjects.[131]

There are a number of interesting aspects of obesity in African populations that deserve continued investigation. The more diabetogenic than atherogenic nature of adiposity in African compared to European subjects is not well understood and unravelling the molecular mechanisms involved in such ethnic differences may well uncover new aetiological pathways of obesity-related diseases. The difference in body fat distribution between population groups is also worthy of further study, particularly as African subjects have less visceral fat than BMI-matched Europids, and yet are more insulin resistant.[77-79] The use of high-throughput gene-screening technology, which has yielded important information on the polygenic nature of obesity via genome-wide association studies[132] should therefore be used in African populations to determine the genetic input to adiposity and body fat distribution. It is possible that ethnic differences in insulin sensitivity and the prevalence of obesity-related disorders are due to differences in the secretory output of adipocytes. The comparison of adipocyte secretomes across population groups using the new technologies developed for the analysis of complex mixtures of bioactive molecules[133] may therefore be very worthwhile.

The future of the use of adipose-derived stromal cells (ADSCs) for the treatment of human disease looks very promising. Such cells have already been used to correct cranial defects in humans,[119] and preliminary studies in man to rectify cardiovascular[134,135] and soft tissue[136-138] defects hold hope for the future use of ADSCs in the treatment of muscle and cartilage defects and heart infarcts. However, before this becomes a reality, there are a number of technical problems that need to be overcome. The methods used for the large-scale isolation of ADSCs and their efficient conversion into the correct cell phenotype must be improved and standardised.

Also, the long-term safety of the use of these cells in humans must be explored, initially by the development of the appropriate animal models. Stem-cell therapy is already available for the treatment of haematological malignancies in specialised medical centres within Africa[139] and therefore it is feasible that the therapeutic use of ADSCs may also become a reality for this continent.

Conclusion

Our view of adipose tissue has changed over time. Additional information has led us to confirm that fat is not only a store of energy, but when in excess, it is the instigator of obesity-related co-morbidities. The characterisation of adipokines has led to the realisation that adipose tissue is a true endocrine organ, and the isolation and use of ADSCs has led to hope for future therapeutic treatments of degenerative diseases of fat, bone, muscle and cartilage. Once fat was just fat, but it is now much more than that.

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Epidemiology of ischaemic heart disease in sub-Saharan Africa

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Abstract

Background: **The epidemiology of ischaemic heart disease (IHD) in sub-Saharan Africa (SSA) remains largely enigmatic. Major obstacles to our understanding of the condition include lack of reliable health statistics, particularly cause, specific mortality data, inadequate diagnostic capabilities, shortage of physicians and cardiologists, and misguided opinions.**

Methods: **This review of the epidemiology of ischaemic heart disease in sub-Saharan Africa involved a systematic bibliographic MEDLINE search of published data on IHD in SSA over the past century. Search words included epidemiology, ischaemic (coronary) heart disease, myocardial infarction, cardiovascular risk factors and sub-Saharan Africa. Selected data are presented on the prevalence of cardiovascular risk factors and mortality from ischaemic heart disease from different countries representing the main regions of the continent.**

Results: **Although IHD in SSA remains relatively uncommon, its prevalence is predicted to rise in the next two decades due to the rising prevalence of risk factors, especially hypertension, diabetes, overweight and obesity, physical inactivity, increased tobacco use and dyslipidaemia. It is estimated that age-standardised mortality rates for IHD will rise by 27% in African men and 25% in women by 2015, and by 70 and 74%, respectively by 2030.**

Conclusion: **Ischaemic heart disease remains relatively uncommon in SSA, despite an increasing prevalence of risk factors, but its incidence is rising. The pace and direction of economic development, rates of urbanisation, and changes in life expectancy resulting from the impact of pre-transitional diseases and violence will be major determinants of the IHD epidemic in SSA. The best window of opportunity for prevention of the emerging epidemic of ischaemic heart disease in sub-Saharan Africa is now.**

Keywords: epidemiology, ischaemic heart disease, sub-Saharan Africa

'a riddle wrapped in a mystery inside an enigma'
1 October, 1939
Sir Winston Churchill, British orator, author and Prime Minister (1874–1965)

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Over a century ago, Sir Winston Churchill, a renowned British statesman and leader during the Second World War (WWII), made a celebrated visit to Uganda, where he was so moved as to describe it as 'the Pearl of Africa'. Sir Winston, referring to the quality of intelligence gathered by Western allies during WWII, called Russia a 'riddle wrapped in a mystery inside an enigma'.

While the same phrase could be used today to describe the epidemiology of ischaemic heart disease (IHD) in sub-Saharan Africa (SSA) because of many puzzles and lingering myths, what is enigmatic is the contempt with which the potential threat of IHD has been treated at various levels of health sectors, governments and international agencies. A recent change in posture by World Health Organisation (WHO) Regional Office for Africa, with greater focus on non-communicable disease (NCD), and the United Nations high-level meeting on NCD prevention and control in New York on 19–20 September 2011 are good indicators of the recognition of the importance of NCDs and the rapidly unfolding epidemiological landscape catalysed by the birth of conjoined twins, infectious diseases and non-communicable diseases.

The 30th anniversary of the Pan-African Society of Cardiology (PASCAR) conference along with the Third All-Africa Conference on Heart Disease, Diabetes and Stroke took place at Munyonyo Speke Resort in Kampala on the shores of Lake Victoria in May 2011. The warmth of the land, the gentle tropical rain showers interspersed with bright sunshine, and above all, the friendliness of Ugandans must have pervaded the hearts of most foreign delegates to the conference.

This review article will focus on some of the obstacles to our understanding of IHD in SSA. A synopsis of cardiovascular risk factors and their role in IHD in SSA, and selected mortality data on IHD from various countries across the continent are presented in this article. A plea for urgent and concerted action to avert the impending epidemic of IHD in SSA is made.

Obstacles to our understanding of IHD in SSA

Major obstacles to our understanding of IHD in SSA include lack of reliable statistics on health, life expectancy and disease incidence, and the absence of cause-specific mortality data. This is confounded by lack of diagnostic capabilities in most of SSA, emanating from a shortage of physicians, particularly cardiologists, and lack of appropriate investigations, such as resting 12-lead electrocardiographs (ECGs), exercise ECGs, cardiac biomarkers (troponins, CKMB) and cardiac imaging such as echocardiography, coronary angiography, computed tomography (CT) angiography, intravascular ultrasound scans (IVUS) and radionuclide myocardial perfusion studies.

Resting 12-lead ECGs, although generally more widely available and relatively inexpensive, have limited sensitivity and specificity for the diagnosis of acute coronary syndromes. Furthermore, there are high rates of non-specific ST-segment and T-wave changes suggestive of myocardial ischaemia in up to 10% of asymptomatic African men and 20% of women over the age of 40 years.[1]

Physiologically or pharmacologically induced stress tests are helpful to differentiate cardiac from non-cardiac aetiology of chest pain in patients with inducible ischaemia due to obstructive coronary artery disease. The safe performance of provocative stress testing and IVUS requires appropriate professional competence, careful selection of patients and availability of resuscitation equipment in cases of adverse events during testing. Low autopsy rates often coupled with uncertified deaths outside health facilities exacerbate the situation.

This lack of evidence on IHD in SSA is erroneously reinforced by beliefs that IHD affects only the wealthy and elderly, that it arises from freely acquired risks and that its management is expensive, ineffective and of a lower priority than infectious diseases such as HIV/AIDS, tuberculosis, malaria, and a number of neglected tropical diseases. Moreover, there are strong opinions that IHD in SSA affects mainly small westernised populations and that it is a less serious cause of morbidity and mortality.[2] Some of these authorities are of the opinion that cardiovascular risk factors in groups of older Africans, including obesity, diabetes and metabolic disorders are virtually non-existent and that IHD is bound to be a less serious threat, as there are very few black populations in the older age category.[2]

Others have expressed disbelief of the potential epidemic of IHD in SSA in the next few decades and contend that resources should be appropriated to the current threats, particularly rheumatic heart disease and cardiomyopathies.[3] Additional setbacks accrue from lack of appropriate resources and skills to guide and direct epidemiological studies of ischaemic heart disease; crisis management often focused on acute conditions and infectious diseases; and perpetual uncoordinated approaches to health issues that are often reactionary, leading to neglect of NCDs.

The majority of the 57 countries in the world with critical shortages of health workers are in SSA. The total health workforce density in SSA is the lowest in the world with just 2.3 per 1 000 population, compared to 18.9 and 24.8 per 1 000 population in Europe and the Americas, respectively. In fact, SSA has only 4% of the global number of health workers but 25% of the global burden of disease.[4]

Sadly, some of the myths regarding IHD in SSA are fueled by the notion that the various cardiovascular disease (CVD) risk factors, although prevalent in urban black Africans, appear to exert their influence in a far less noxious manner than is the case in most Western populations. Also that lipid profiles are generally less atherogenic, leading to suggestions of the 'genetic resistance' of black Africans to IHD.

The view that IHD is rare in SSA is rooted in old beliefs arising from earlier authors such as Cook5 and Donnison,6 and needs to be effectively demystified. Firstly, atherothrombotic cardiovascular disease is a global problem that afflicts every community regardless of region, ethnicity or gender. The burden of cardiovascular disease is increasing rapidly in Africa and it is now a public health problem throughout the African region, particularly hypertension, stroke, cardiomyopathies, and not least, ischaemic heart disease. Rheumatic heart disease is still a major concern.

Scarcity of data on IHD and the non-existence of epidemiological surveillance systems for cardiovascular diseases in most of SSA should not be construed to mean rarity of the disorder. INTERHEART, a global case–control study of acute myocardial infarction (AMI) of 28 000 subjects in 52 countries showed that nine risk factors accounted for 90% of population-attributable risk (PAR) in all regions.[7] These risk factors included hypertension, diabetes, central obesity, dyslipidaemia, physical inactivity, psychological stress, tobacco use, inadequate intake of fruits and vegetables, and inadequate or no alcohol intake.

Although the results of the INTERHEART study have been challenged on account of it being a case–control study rather than a prospective study, the major contributing individual risk factors for acute myocardial infarction are generally consistent across the globe and reminiscent of the conclusions of the original Framingham Heart study several decades ago, as well as its 30-year follow-up study.[8,9] Some have questioned the reliability of information on some of the cardiovascular risk factors used in the INTERHEART study, for example history of hypertension and diabetes mellitus, and have raised concerns about recall bias regarding diet and psychosocial factors in the setting of devastating effects of index acute myocardial infarction on a person's mental state. In some parts of SSA, haemoglobinopathies such as haemoglobin S or haemoglobin C might contribute to ischaemic heart disease due to vasoocclussive crises.

Secondly, despite variations in genetic susceptibilities to IHD in different ethnic groups, the common environmental and traditional coronary heart disease risk factors pathogenetically play their roles through a common final pathway in the development of clinical atherosclerotic heart disease in all ethnic groups. Marked regional differences in the impact of CVDs merely reflect a myriad of factors, among them the level of care, quality of health statistics, and differences in stages of socio-economic, nutritional and epidemiological transition between countries, communities and even between individuals.

Thirdly, as societies undergo 'urbanisation', risk-factor levels for CVDs including IHD increase. For instance, only about 5% of Africans were urbanised by 1900. At the start of independence in the 1950s, 14.7% of inhabitants of Africa were urban. In 2000, the urbanisation rate had risen to 37.2%, and by 2015 the rate is expected to hit 45.3% with continually high rates of rural–urban migrations across Africa.[10]

The burden of cardiovascular risk factors in SSA

Hypertension

Systemic arterial hypertension poses a special challenge in SSA, with immense socio-economic implications because of its high prevalence, especially in urban dwellers. Hypertension is arguably the most powerful cardiovascular risk factor in the African context and has been declared by the African Union as one of the greatest health challenges to the continent other than HIV/AIDS. The problem is compounded by lack of awareness, frequent under-diagnosis, low levels of control and the severity of its complications.[11-13]

Despite the dearth of data and marked variation between and within studies, hypertension is estimated to affect 10 to 30% of Africans, virtually one in six people. In West Africa, hypertension affects 30 to 40% of people aged 65 years or older in rural areas, and approximately 50% of semi-urban dwellers. In the mixed population (Coloureds) of South Africa, 50 to 60% of people over the age of 65 years have hypertension. These figures approximate the 60 to 70% prevalence of hypertension in African-Americans over 65 years of age.[14] An estimated 75 to 80 million Africans, more than twice the global estimate of people with HIV/AIDS, had hypertension in 2000. The number of Africans with hypertension will escalate to 150 million by 2025.[15]

The rising prevalence of hypertension in rural settings is of great concern and probably relates to the rapid 'urbanisation' of rural dwellers.[15,16] About 40% of Africans with hypertension are undiagnosed, less than 30% of those who are diagnosed with hypertension are on treatment, and less than 20% of those on treatment have optimal blood pressure control (< 140/< 90 mmHg).[13,17-21]

Diabetes mellitus and impaired glucose tolerance

In 2010, an estimated 12.1 million people with diabetes mellitus (4.2% of the global estimate of 285 million) were in sub-Saharan Africa.[22] The following year, diabetes prevalence rose to 14.7 million (4.02% of the global 366 million). By the year 2030, there will be a 90% projected increase in diabetes prevalence in SSA, bringing the number of Africans with diabetes to 28 million.[23]

Nearly 78% of people with diabetes in sub-Saharan Africa are undiagnosed. Heavily populated countries such as Nigeria have three million diabetics, followed by South Africa with 1.9 million.

Fuelling the diabetes epidemic is a large pool of people with impaired glucose tolerance (IGT), totalling an estimated 26.9 million in 2010, and expected to rise to 47.3 million by 2030. Diabetes is associated with a pro-coagulant state, compounding the commonly accompanying insulin resistance and hyperinsulinaemia, and thus contributing to accelerated atherogenesis.

Although diabetes mellitus and pre-diabetes are important cardiovascular risk factors globally, their roles in populations undergoing rapid epidemiological transition are unclear. Atherosclerotic complications of diabetes are likely determined by the pace and degree of affluence, genetic factors, phenotypic heterogeneity of type 2 diabetes, changes in life expectancy, and burden, duration and contribution of other cardiovascular risk factors such as hypertension, dyslipidaemia and tobacco use. In many parts of SSA, micro-angiopathies are the dominant chronic complications of diabetes,[24-30] unlike in the Western world, where macrovascular complications (MAC) predominate.

Overweight and obesity

Estimates of the prevalence of overweight and obesity vary widely across SSA, but it is generally higher in females than in males and particularly in southern Africa, Mauritius and Seychelles, compared to the rest of the continent. In East and Central Africa the prevalence of overweight (body mass index from > 25 to < 30 kg/m^2) in women is two to three times higher than in men (Table 1). In Ghana, males appear to be more overweight than women. However, in much of West Africa, southern Africa and in the islands off the east coast of Africa, the prevalence of overweight in men is approximating that of females. This trend towards parity indicates that overweight is now a widespread continental problem in populations of SSA above the age of 15 years.

However obesity still has relatively low prevalence rates throughout SSA, ranging between 1.1 and 43.2% in females and 0.1 and 21.3% in males. Populations of southern Africa and the islands of Mauritius and Seychelles exhibit a greater prevalence of obesity, particularly among the women.

Physical inactivity

There are scant data on the prevalence of physical inactivity in SSA. A WHO report of national surveys in both urban and rural settings in five African countries (Ethiopia, Republic of Congo, Ghana, South Africa and Zimbabwe) in 2003, involving a total of 14 725 individuals aged 18 to 69 years revealed a mean prevalence of physical inactivity in 19.6% of men and 22.9% of women.[31]

Physical inactivity was defined using the International Physical Activity Questionnaire (IPAQ). IPAQ inactive is defined as not meeting any of the following three criteria: three or more days of vigorous activity of at least 20 minutes per day, accumulating at least 1 500 MET-min per week, OR five or more days of moderate-intensity activity or walking of at least 30 minutes per day, OR five or more days of any combination of walking, moderate-intensity or vigorous-intensity activities, achieving a minimum of at least 600 MET-min per week.

Across the continent, low levels of physical activity are reported in women compared to men. According to the WHO survey, a greater number of lazy people are found in southern Africa, Mauritius and Seychelles, while those in the Horn of Africa and in West Africa are relatively more physically active (Table 2, Fig. 1). This observation closely mirrors the reported prevalence of overweight and obesity. There are no consistent national (rural and urban) surveys for similar years or later from other SSA countries.

The Seychelles Heart study of 2004, reported by Bovet and colleagues in 2007, revealed a disparate prevalence of physical inactivity, ranging from 28 to 58.6% in both genders aged 25 to 64 years, because of variable and subjective operational definitions of physical inactivity using a modification of the WHO STEPS survey questionnaire, which was not identical to the IPAQ.[32] More surveys are therefore required in many SSA countries using standard questionnaires to provide better insight of the emergence of this cardiovascular risk factor in the continent. There are likely to be wide variations of the levels of physical activities, determined by culture, gender, age, occupation, socio-economic status and levels of education.

Table 1. Prevalence of overweight and obesity in females and males aged 15 years and older in selected african countries by region, 2011.

	Overweight (BMI > 25 kg/m^2, < 30 kg/m^2)		Obesity (BMI > 30 kg/m^2)	
Region/country	**Females (%)**	**Males (%)**	**Females (%)**	**Males (%)**
Eastern Africa		8.2		0.1
Uganda	23.9		1.9	
UR Tanzania	28.7	16.8	3.6	0.8
Central Africa		5.7		0.1
DR Congo	15.8		1.1	
Rwanda	20.7	8.1	1.6	0.1
Western Africa		26.0		3.0
Nigeria	36.8		8.1	
Ghana	32.5	35.6	5.9	4.8
Southern Africa		41.6		6.9
Botswana	53.5		17.7	
South Africa	68.5	41.3	36.8	7.6
Islands		44.8		8.0
Mauritius	56.8		22.3	
Seychelles	73.8	63.8	43.2	21.3

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.
World Health Organisation: WHO Global Infobase: https://apps.who.int/infobase/Comparisons.aspx (Accessed 28 December 2011). Database updated 20/01/2011. Accessed 28 December 2011.

TABLE 2. Prevalence of physical inactivity in selected SSA countries, WHO 2003.

Country N/U/R (18–69 years)	Males (%) [95% CI]	Females (%) [95% CI]	Both genders (%) [95% CI]
Congo (*n* = 1 335) M:F = 623:712	23.5 [16.5–30.5]	30.2 [21.8–38.51]	27.2 [20.5–33.9]
Ethiopia (*n* = 4 430) M:F = 2 171:2 259	9.4 [7.1–11.8]	16.0 [13.9–18.2]	12.7 [11.0–14.4]
Ghana (*n* = 3 362) M:F = 1 532:1 830	7.9 [5.9–9.8]	15.1 [12.7–17.5]	11.5 [9.7–13.3]
South Africa (*n* = 2 028) M:F = 957:1071	43.0 [37.4–48.6]	46.6 [41.4–51.9]	44.9 [40.4–49.4]
Zimbabwe (*n* = 3 570) M:F = 1 296:2 274	14.1 [11.6–16.6]	22.0 [19.6–24.5]	18.1 [16.4–19.8]

N/U/R = National Urban and Rural Survey.
Source: http://infobase.who.int. A

Tobacco use in SSA

Most estimates of tobacco use in SSA vary in their operational definitions. For instance, some surveys have used different age ranges for men and women and between countries. Also, while some surveys considered current tobacco use including smoked and non-smoked tobacco, others have used only daily cigarette smoking. Moreover, these studies were performed in different years, making comparison of prevalence of tobacco use across most African countries problematic.

According to WHO-Afro,[33] tobacco-smoking rates were considerably lower (< 10%) in countries such as Democratic Republic of Congo, Congo, Ethiopia, Nigeria, Ghana, Swaziland and Lesotho. Countries in Central, West and East Africa had smoking prevalence rates ranging between 10 and 19%. High rates of tobacco use (> 20%) were found mainly in southern Africa, Guinea, Guinea Bissau, Niger, Seychelles and Mauritius. There were no data from certain countries such as Angola, Central African Republic, Gabon and Equatorial Guinea.

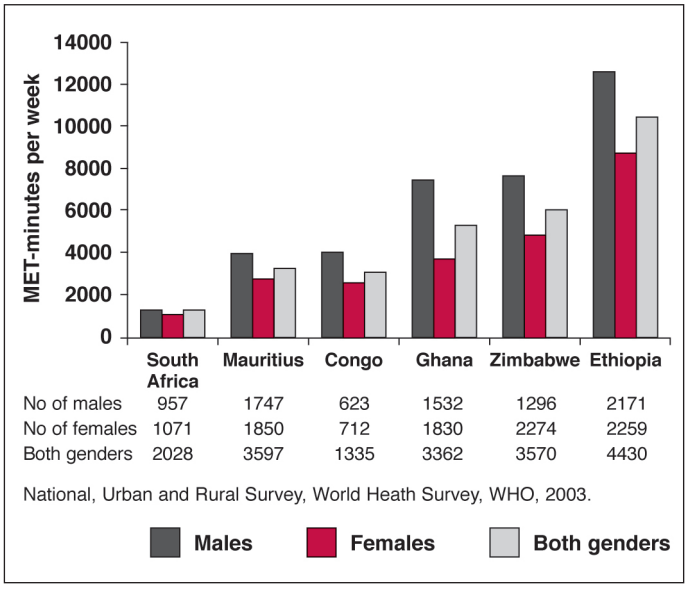

Fig. 1. Physical activity in men and women aged 18 to 69 years in selected countries.

It is widely known that some countries on the continent are major tobacco growers. For instance, tobacco accounts for 61 and 23% of export earnings in Malawi and Zimbabwe, respectively. South Africa, Tanzania, Kenya and Nigeria rank closely behind Malawi and Zimbabwe. Continual commercial pressures, price incentives and other subsidies provided by transnational cigarette companies to African farmers, coupled with aggressive marketing and advertisements will drive the prevalence of tobacco use in SSA. It is therefore not surprising that very few African countries have been signatories to the Framework Convention on Tobacco Control Ratification, with countries such as Zimbabwe, Malawi and Eritrea declining to sign the convention altogether.

Table 3 shows age-standardised prevalence estimates for current smokers in males and females aged 25 years or older in 2006 in selected countries. In general, smoking prevalence remains quite low among African women, although increased trends are emerging in young urban women. The prevalence of smoking is 20 to 50 times higher in men than in women across Africa, with estimates of below 2% in women in most SSA countries except in South Africa and Namibia, where smoking prevalence among women was 5.5 and 5.9%, respectively.[34]

Various estimates of smoking prevalence in African men between 1976 and 2005 revealed rates below 10% in many African countries. But in Tanzania, Mozambique, South Africa, Mauritius and Seychelles, smoking prevalence rates ranged between 15 and 30%. Smoking prevalence rates in adults increased substantially across SSA by 2009, especially in Mauritius where a third of adults smoked, closely followed by South Africa, Tanzania, Burkina Faso

Table 3. Age-standardised prevalence estimates for tobacco smoking (current users) in males and females aged 15 years and older in selected sub-Saharan African countries by region, 2006.

Region/country	Current smoking prevalence in males aged 15 + years (%)	Current smoking prevalence in females aged 15 + years (%)
Eastern Africa		
Uganda	19.0	2.0
UR Tanzania	24.0	2.0
Central Africa		
DR Congo	13.0	0.6
Malawi	21.0	2.0
Western Africa		
Nigeria	12.0	0.2
Ghana	10.0	0.5
Southern Africa		
Zimbabwe	33.0	2.0
South Africa	29.0	8.0
Islands		
Mauritius	34.0	0.9
Seychelles	32.0	3.0

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.
Source: https://apps.who.int/infobase/Comparisons.aspx Accessed on 31 December 2011.
The figures represent age-standardised prevalence rates, using the standard WHO world population for age, for current tobacco smokers. These figures should be used only to draw comparisons of prevalence between countries and between men and women within a country. These figures are different from the crude data reported in country surveys in Infobase.

Table 4. Estimated mean total cholesterol in selected African countries by region in females and males aged 15 years and older, 2011.

Region/country	Females mean total cholesterol (mmol/l)	Males mean total cholesterol (mmol/l)
Eastern Africa		
Uganda	4.4	4.7
UR Tanzania	5.2	4.4
Central Africa		
DR Congo	4.3	4.3
Rwanda	4.3	4.3
Western Africa		
Nigeria	3.7	3.6
Ghana	5.9	4.4
Southern Africa		
Botswana	4.7	4.7
South Africa	4.4	4.4
Islands		
Mauritius	5.2	5.2
Seychelles	5.9	5.8

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.
Source: https://apps.who.int/infobase/Comparisons.aspx Accessed on 31 December 2011

and Senegal with smoking rates of 27.5, 27.1, 22.0 and 19.8%, respectively. Even in Nigeria and Ghana, where smoking rates were relatively low before 2003, estimated at 6.1% in Nigerian men, 0.1% in Nigerian women, 4.6% in Ghanaian men and 0.2% among Ghanaian women, overall smoking prevalence more than doubled in men to 13 and 10.2% in Nigeria and Ghana, respectively in 2009 but remained quite low in women.

Although deaths from tobacco-related causes probably accounted for only 5 to 7% in African men and 1 to 2% in African women in the year 2000,[34] by 2030, tobacco is expected to be the greatest contributor of deaths in SSA. Most victims will die 20 to 25 years prematurely of various cancers, respiratory diseases, IHD and other circulatory disorders.

Regrettably, most governments in African countries have avoided action to control smoking for fear of harmful economic consequences on their fragile economies. Without effective tobacco-control measures, SSA risks becoming the biggest global ashtray as many transnational tobacco companies shift their targets to middle- and low-income countries.

Dyslipidaemia

There is overwhelming epidemiological evidence implicating cholesterol as a cause of atherosclerosis. Most black Africans reportedly have low levels of total cholesterol associated with high high-density lipoprotein (HDL) cholesterol levels.[35] Higher cholesterol levels however, have been found in diabetic patients from Zimbabwe and Tanzania. The total serum cholesterol was also significantly higher in women than men. Reports from West Africa indicate a worrying trend of dyslipidaemia among patients with either type 1 or type 2 diabetes mellitus.[36] Data from the Transition of Health during Urbanisation of South Africa (THUSA) study indicate that black South Africans may be protected from IHD because of favourable lipid profiles characterised by low total cholesterol and high HDL cholesterol levels.[37]

In Nigeria, IHD contributes very little to mortality rates in middle-aged men and women, partly because of particularly low mean cholesterol levels.[38] Different black African communities may be at different stages of their epidemiological transition, as shown in an epidemiological study of coronary heart disease risk factors in the Orange Free State in South Africa.[39] Table 4 illustrates this point quite vividly. Selected countries representing the different regions of SSA show wide differences in mean total cholesterol levels with a tendency to higher cholesterol levels in females in some countries.

The cardiovascular impact of HIV/AIDS

SSA bears a disproportionate share of the global HIV burden. The interaction between HIV infection, acquired immunodeficiency syndrome (AIDS), its treatment with highly active antiretroviral drugs (HAART), and cardiovascular disorders is complex and incompletely understood.

The transformation of HIV/AIDS into a chronic disorder with the advent of antiretroviral drugs is associated with the emergence of certain characteristic cardiovascular risk factors, and raises apprehension about the potential increase in prevalence of cardiovascular diseases, including IHD, in SSA. In Botswana, for instance, where antiretroviral therapy coverage exceeds 90%, AIDS-related deaths declined by approximately 50% between 2002 and 2009.[40]

The repertoire of immunological responses associated with acute and chronic HIV infection is quite complex and will be only highlighted here. Perturbations of cytokine expression, cellular dysfunctions, redistribution of lymphocyte sub-populations, increased cellular turnover and apoptosis are some of the features of general activation of the host's immune system that characterise chronic HIV infection.[41] Chronic HIV infection, and not its pharmacological treatment, induces changes in markers of endothelial function.[42] Untreated HIV infection is also associated with impaired elasticity of both large and small arteries.[43]

Some authors have suggested that HIV infection accelerates atherosclerosis via a pro-inflammatory effect on the endothelial cells through the effects of various cytokines, especially interleukin-6 and D-dimers.[44,45] Other mechanisms of arteriopathy include the direct toxic effects of HIV-associated g1p20 and tat proteins on vascular or cardiac cells. There is also evidence of a hypercoagulable state, which inversely correlates with CD4 count.[46]

Although traditional risk factors for cardiovascular diseases might overshadow the role of non-traditional risk factors, there is increasing evidence that young, asymptomatic, HIV-infected men with long-standing HIV disease demonstrate an increased prevalence and degree of coronary atherosclerosis compared with non-HIV-infected patients.[47] Furthermore, HIV-infected patients tend to develop perturbations in lipid metabolism, characterised by decreased HDL cholesterol and low-density lipoprotein (LDL) cholesterol levels, followed by an increase in plasma triglyceride levels pre-HAART and prior to developing AIDS.[48]

Both traditional and non-traditional risk factors therefore appear to contribute to atherosclerotic disease in HIV-infected patients. Those on HAART, particularly protease inhibitors, develop a myriad of class- and non-class-specific metabolic effects on lipid profiles, glucose levels, insulin sensitivity and anthropometric body changes characteristic of lipodystrophy. Untreated HIV infection may also have a paradoxical overall effect on cardiovascular disease and thereby reduce the risk of ischaemic heart disease because of severe and progressive weight loss, wasting syndrome, hypotension resulting

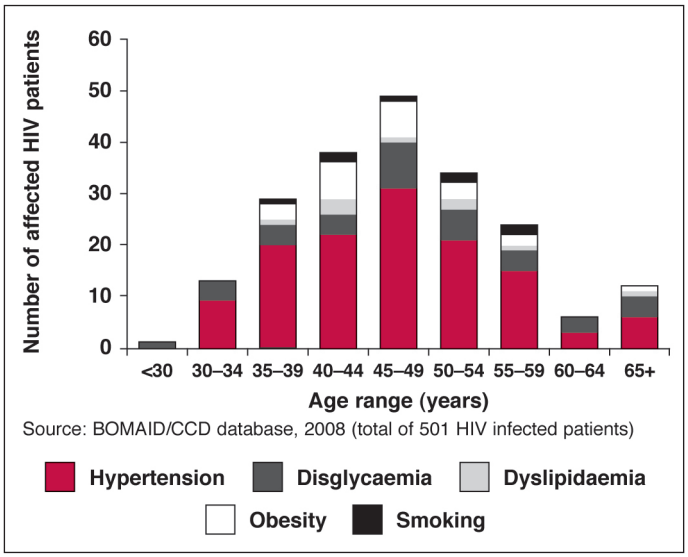

Fig. 2. Cardiovascular disease risk factors in HIV-infected patients in Botswana.

from chronic gastroenteritis, hypoadrenalism and shortened life expectancy associated with advanced AIDS.

Despite the scarcity of data from SSA, there are some indications of overall excess CVD risk factors in HIV-infected patients. Situation analysis in 2008 of 501 HIV-infected patients from Botswana using the database of the Botswana Medical Aid Scheme combined with data from the Centre for Chronic Diseases revealed impressive clustering of hypertension, dyslipidaemia, obesity, dysglycaemia and smoking (Fig. 2). The peak age range for the occurrence of CVD risk factors was about a decade after the peak age for HIV infection in Botswana.

Given the difficulty of determining whether the observed increase in CVD risks were due to HIV itself, treatment with HAART or merely a factor of improved longevity, it would be ideal to perform case–control studies on the prevalence of CVD risk factors and the prevalence of arteriosclerotic cardiovascular endpoints such as IHD, stroke, and peripheral arterial disease in HIV-infected versus age- and gender-matched non-HIV-infected individuals. Also, a comparison of pre-HAART and on-HAART HIV-infected patients would shed light on this grey area. It is important to remember that the enormous impact of HIV/AIDS does not appear to have diminished the impact of chronic cardiovascular diseases on mortality in SSA.[49]

Reports on IHD in SSA

There are a few scattered reports of IHD in SSA. Kengne and colleagues[50] collated a total of 356 cases of SSA patients with coronary heart disease (CHD) from four selected countries (Ghana, Cameroon, Senegal and Kenya). They reported a high prevalence of CHD risk factors, which was not surprising in this selected population of patients with established CHD. Males outnumbered females by ratios ranging from 1.3:1 to 6:1, with hypertension in up to two-thirds of the patients. The report highlighted the fact that IHD was by no means rare in these African populations.

The African arm of the INTERHEART study showed that dyslipidaemia, abdominal obesity and tobacco use accounted for greater population-attributable risk in the overall African population, whereas hypertension and diabetes were less prominent risk factors.[51] However, in black Africans, dyslipidaemia was followed by hypertension, abdominal obesity, diabetes and then tobacco use.

The INTERHEART African study cast doubt on the notion of protective lipid profiles in blacks, as one reason for implicitly low IHD prevalence in Africa. High HDL cholesterol levels in black Africans might be dysfunctional and less protective than generally believed. However, the findings of the INTERHEART African study were at slight variance with reports by Ezzati and colleagues who showed that hypertension, low intake of fruits and vegetables and physical inactivity accounted for population-attributable fractions for ischaemic heart disease mortality of 43, 25 and 20%, respectively, in the Africa region. These were all above the population-attributable fraction of 15% for high cholesterol.[52]

Limitations in diagnostic evaluation of patients with possible IHD might explain, at least in part, the apparent rarity of IHD in SSA. This is illustrated by the study on black South Africans by Joubert and colleagues using data from the Medical University of South Africa (MEDUNSA) stroke data bank. The study showed increased prevalence of CHD with improved diagnostic tools.[53]

History of angina pectoris or myocardial infarction using the Rose questionnaire yielded a prevalence of only 0.7% in 741 black patients with stroke, 71% of whom had cerebral infarction. Resting 12-lead electrocardiography was analysed for the presence of poor R-wave progression in the precordial leads, the presence of pathological Q waves and ST–T wave changes using the Minnesota

Table 5. Top 10 causes of morality in South African men and women > 60 years in 2000.

Cause of death	Percentage (%) in males aged > 60 years [*n* = 71 641]	Cause of death	Percentage (%) in females aged > 60 years [*n* = 73 474]
Ischaemic heart disease	17.2	Stroke	17.7
Stroke	12.2	Ischaemic heart disease	16.0
COPD	8.0	Hypertensive heart disease	9.8
Tuberculosis	6.4	Diabetes mellitus	7.3
Lower respiratory tract infection	5.1	Lower respiratory tract infection	5.3
Hypertensive heart disease	4.2	COPD	4.4
Cancer of airways	4.1	Nephritis	2.8
Diabetes mellitus	4.0	Tuberculosis	2.7
Cancer of prostate	3.1	Asthma	2.4
Cancer of oesophagus	2.8	Cancer of the breast	1.9

COPD = chronic obstructive pulmonary disease.

Table 6. Age-standardised mortality rates for ischaemic heart disease in the WHO Africa region, by selected countries and gender, 2002.

Region/country	Estimated population (millions)	Age-standardised mortality rates for IHD (per 100 000)	
		Males	Females
Eastern Africa			
Uganda	25.00	150	120
Tanzania	36.28	147	128
Ethiopia	6.90	149	127
Central Africa			
DR Congo	51.20	166	132
Rwanda	8.27	149	122
Malawi	11.87	152	125
Southern Africa			
Botswana	1.77	142	102
South Africa	44.76	159	99
Mozambique	18.54	124	107
Western Africa			
Nigeria	120.91	160	127
Ghana	20.47	143	114
Cameroon	15.73	154	124
Islands			
Mauritius	1.21	277	161
Seychelles	0.80	151	49

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania.

code in 555 stroke patients, 72% of whom had cerebral infarctions confirmed on computed tomography. Ninety-three of the 555 patients (16.8%) had evidence of coronary artery disease, of whom 81 had features of myocardial ischaemia, eight had pathological Q waves and four patients had features of acute myocardial infarction. There has been longstanding controversy regarding ECG diagnosis of myocardial ischaemia in black Africans.[53-57]

Ignoring ECG features of 'ischaemia' and ascribing such changes to 'normal variation' poses the potential danger of under-diagnosis or misdiagnosis of myocardial ischaemia in black Africans. Rather, future work should attempt to unravel the genetic mechanisms behind abnormal ECG patterns in black Africans.

The combination of clinical assessment, chest radiograph, resting electrocardiography, transthoracic echocardiography and MUGA scanning showed features of CHD in 18 patients (17.6%) in the MEDUNSA study. Scintigraphy with or without dipyridamole infusion in 60 stroke patients in this study revealed features of coronary heart disease in 45% of the patients. Macroscopic and microscopic pathological examinations of the heart and coronary arteries for evidence of infarction in 23 stroke patients in the study revealed the highest rate of myocardial infarction (17.4%).

Observed differential mortality rates in different ethnic groups in multiracial African communities such as South Africans have been at least partly ascribed to different stages of the epidemiological transition. For instance, Norman and colleagues58 found that black Africans had approximately 60, 70 and 82% less CHD mortality rates compared to South African Coloureds, whites and Asians, respectively.

Part of the reason for relatively high IHD mortality rates in South African Asians is due to their high prevalence of diabetes mellitus.[59-61] By contrast, mortality from stroke in black Africans exceeds the rates for Coloureds, whites and Asians by 2, 96 and 19%, respectively. However, mortality from hypertensive heart disease in black South Africans was 2.5, nine and three times higher than rates in Coloureds, whites and Asians, respectively.

Bradshaw and colleagues[62] demonstrated that IHD was the leading cause of death among 71 641 South African men over 60 years, while it was the second most common cause of death among the top causes of deaths in 73 474 women in the year 2000 (Table 5). In South African men aged 15 to 45 years in the same study, IHD was ninth among the top 10 causes of death (1.1%), although it did not feature among the top 10 causes of death in women. HIV/AIDS was the predominant cause of mortality in younger age groups, accounting for 40.7% of deaths in men and 64.4% in women.

In 2005, the WHO estimated 188 000 and 173 000 deaths from IHD in men and women, respectively in SSA.63 These age-standardised mortality rates (ASMR) will rise by 27 and 25% in men and women, respectively by the year 2015, and by 70 and 74%, respectively by the year 2030.

Table 6 represents ASMR from IHD in selected countries from the main regions of SSA. Despite higher ASMR in men in mainland Africa, rates in females were close to those in men (Table 6). In Seychelles, ASMR in men was three-fold higher than rates in women, while Mauritius shows the highest ASMR for IHD in both genders, with a male preponderance.

Some caveats against current and future projections of mortality data for IHD in SSA include the use of approximations that often embrace substantial uncertainties, especially in the estimation of cause-specific deaths. This huge degree of uncertainty has been attributed to a meagre database on IHD as a specific cause of death in Africa and to the overall low coverage of vital registration.

Despite the heavy toll inflicted by HIV/AIDS in SSA, comparative ASMR across the continent indicate that mortality from IHD matches

Table 7. Comparison of age-standardised mortality rates for ischaemic heart disease and HIV/AIDS in the WHO Africa region in selected countries in 2002.

Region/country	Estimated population (millions)	ASMR (per 100 000)		ASMR HIV/AIDS: IHD ratio
		IHD	HIV/AIDS	
Eastern Africa				
Uganda	25.00	270	555.6	2.06
UR Tanzania	36.28	275	593.2	2.16
Central Africa				
DR Congo	51.20	298	277.7	0.93
Malawi	8.27	271	345.4	1.27
Western Africa				
Nigeria	120.91	287	316.8	1.10
Ghana	20.47	257	174.6	0.66
Southern Africa				
Botswana	1.77	244	2,243.1	9.19
South Africa	44.76	258	840.3	3.26
Islands				
Mauritius	1.21	438	1.6	0.004
Seychelles	0.80	200	5.5	0.03

DR Congo = Democratic Republic of Congo, UR Tanzania = United Republic of Tanzania, ASMR = age-standardised mortality rates.
Sources: WHO Global InfoBase http://infobase.who.int; WHO Statistical Information System http://www.who.int/whosis ; Mackay J, Mensah GA. The atlas of heart disease and stroke. Geneva: World Health Organization. 2004. http://www.who.int/cardiovascular_diseases/resources/atlas/en.

and already exceeds those from HIV/AIDS in some regions of SSA,[48,64-65] except in southern Africa, the epicentre of the HIV/AIDS epidemic (Table 7). In Botswana and South Africa, respectively, there were nine- and three-fold more deaths from HIV/AIDS compared to deaths from IHD. In Mauritius, ASMR for IHD was 274-fold higher than rates from HIV/AIDS, and in Seychelles, the difference was 36-fold. In Ghana, ASMR for IHD was 1.5 times that of HIV/AIDS between 2002 and 2004.

Conclusion

Nearly 40 years ago, Bradlow and colleagues[66] stated that Africa provided a vast natural laboratory for the study of the aetiology and epidemiology of heart disease. Little appears to have changed in terms of the epidemiology of IHD in SSA. The scarcity of cause-specific data makes a mockery of the case for agitating for greater action plans to combat IHD in SSA amidst a storm of infectious diseases such as HIV/AIDS, tuberculosis and malaria.

We need epidemiological data to make IHD less tentative and unconvincing to sceptics, healthcare providers and policy makers. An important starting point is the establishment of cardiac registries in multiple centres across the continent. Various tertiary centres of excellence already exist in parts of sub-Saharan Africa for care of acute coronary syndromes and cardiac rehabilitations. However, these facilities are few and far between and are not within the reach or affordability of all of those who need them. As with HIV/AIDS, the fight against the pandemic of cardiovascular diseases must concentrate on primary prevention. Novel approaches must be developed that effectively connect community resources with organised healthcare systems and must integrate both behavioural and biomedical approaches.

IHD remains relatively uncommon in SSA despite an increasing prevalence of risk factors but its incidence is rising. The pace and direction of economic development, rates of urbanisation and changes in life expectancy resulting from the impact of pre-transitional diseases and violence will be major determinants of the IHD epidemic in SSA. The best window of opportunity for concerted action to tackle the emerging epidemic of IHD in SSA is currently shrouded by the lingering burden of infectious diseases.

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SASCI/SCTSSA joint consensus statement and guidelines on transcatheter aortic valve implantation (TAVI) in South Africa

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The South African Heart Association (SA Heart) together with two of its special-interest groups, the South African Society of Cardiovascular Intervention (SASCI) and the Society of Cardiothoracic Surgeons in South Africa (SCTSSA), represent the scientific, educational and professional interests of South African cardiac specialists, with a combined membership of over 200 members. These two interest groups exclusively represent practicing cardiologists and cardiothoracic surgeons in South Africa. SASCI and SCTSSA are dedicated to maintaining the highest standards of specialist practice and the highest quality of patient care. As a result, SASCI and SCTSSA seek to serve as a knowledge resource for patients and funders in matters related to new technology used in the cardiac interventional and surgical disciplines.

The introduction of new technology is a constant in modern medicine. While authorities in the United States of America (USA) and European Union, such as the Food and Drug Administration (FDA) and Conformité Européene (CE), provide regulatory clearance on safety and effectiveness, practicing medical practitioners require scientific evidence on net health outcomes before offering new procedures to their patients. In addition, to meet clinical expectations of practicing specialists, new technology must stay consistent with fundamental medical and surgical principles.

Transcatheter aortic valve implantation (TAVI) is considered a feasible technique, which may be used as an alternative to standard surgical aortic valve replacement in selected cases. The procedure is performed on the beating heart without the need for a sternotomy or cardiopulmonary bypass. There are currently two devices available in South Africa that are CE-marked and approved by the FDA. The procedure may be performed via the transfemoral, trans-subclavian and transapical approaches or via a mini-sternotomy (transaortic approach).

SA Heart and the respective boards of the SASCI and SCTSSA by consensus hereby adopt the TAVI procedure for aortic stenosis in line with the principles of evidence-based medicine after considering the most recent published evidence and the various multinational society position statements and guidelines concerning TAVI.

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This consensus guideline considers all the literature reviewed, including the 2014 American Heart Association/American College of Cardiology guideline for the management of patients with valvular heart disease, the 2012 European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines on the management of valvular heart disease, and the updated standardised endpoint definitions for TAVI [as per the Valve Academic Research Consortium-2 (VARC-2) consensus document].[1-3]

Consensus guidelines on transcatheter aortic valve implantation (TAVI)

Members of the SA Heart Association, SASCI and SCTSSA with experience in the technique and knowledge of the TAVI literature have agreed to the following consensus statement:

Requirements and structure of the multidisciplinary heart team

- The performance of TAVI, ab initio, should be restricted to a limited number of high-volume centres, which have both cardiology and cardiac surgery departments on site, with expertise in structural heart disease intervention and high-risk valvular surgery. Interventional cardiologists should be experienced in catheter-based valvular interventions and peripheral access using large devices. Cardiac surgeons should be experienced in valve surgery and the management of complex cases. It is recommended that all TAVI teams aim to perform more than 10 implants per year.
- TAVI should currently be reserved for patients who, after evaluation by a multidisciplinary heart team (MDT) are found to have a risk/benefit ratio favouring TAVI rather than open-heart surgery. The heart team should at least include a cardiologist, cardiac surgeon and imaging specialist. Its composition is however dynamic and can also include a cardiac anaesthetist, geriatrician and neurologist as well as other members as the MDT sees fit.
- Patients should be screened into a TAVI programme by a MDT (as defined above) and not by an individual specialist.
- Formal training of the implanting team should include:
  - o didactic theoretical training
  - o simulator training where available
  - o a visit to an experienced centre to observe TAVI cases
  - o support for the initial cases at any site by a proctor until the proctor has certified the centre to be independent.

Patient selection/mandatory prerequisites

- Proof of severe symptomatic aortic valve stenosis.
- Patient evaluation by a MDT.

Indications for TAVI

- TAVI is recommended in patients who are, according to the MDT heart team, considered to be unsuitable for conventional surgery because of severe co-morbidities. These include:
  - Possible procedure-specific impediment, for example:
    - porcelain aorta or severely atherosclerotic aorta
    - hostile chest
    - patent coronary artery bypass grafts crossing the midline and/or adherent to the posterior table of the sterum

OR

  - Frailty. In the absence of validated frailty scores, this remains the opinion of an experienced physician. We recommend that it is the opinion of at least two physicians of which one should be a cardiac surgeon experienced in aortic valve replacement surgery

OR

  - Major organ compromise of two or more organ systems. Examples include:
    - cardiac: severe left or right ventricular dysfunction, severe pulmonary hypertension
    - pulmonary dysfunction (FEV1 or DLCO2 < 50% predicted)
    - central nervous system dysfunction (dementia, Alzheimer's disease, Parkinson's disease)
    - gastro-intestinal dysfunction (Chron's disease, ulcerative colitis)
    - liver cirrhosis, variceal bleeding.

- TAVI is recommended in patients who are, according to the MDT, considered to be at high risk for conventional surgery. In line with other guidelines, the evaluation of surgical risk should rely on the clinical judgement of an MDT rather than quantitative risk scores as these have not been well validated in this population. These risk scores may be used in addition, with cut-off values of an STS (Society of Thoracic Surgeons) risk score > 4 or a log EuroSCORE > 20 recommended. It must be emphasised that risk scores should not be used in isolation to determine whether a patient qualifies to undergo a TAVI procedure. Growing evidence supports the efficacy of TAVI in 'intermediate-risk group' patients.[4] The final recommendation therefore remains with the MDT.

Contra-indications

- Absence of an MDT heart team and no cardiac surgery on site.
- Patients whose life expectancy is less than one year.
- Clinical improvement in quality of life after TAVI limited by co-morbidities. This may be especially relevant if the indication for TAVI is major organ compromise as outlined above.
- Anatomical factors
  - inadequate annulus size
  - active endocarditis
  - inadequate access site.
- Significant other valve lesions or coronary artery disease that requires additional valve or coronary artery bypass surgery.
- Relative contra-indications
  - left ventricular ejection fraction (LVEF) < 20%
  - haemodynamic instability.

Establishing a TAVI programme

- The centre should be sufficiently equipped to perform transcatheter procedures safely.[1-3]
- Minimum infrastructure requirements include:
  - The ability to set up an MDT (as outlined above).
  - Immediate availability of trans-thoracic and trans-oesophageal echocardiography.
  - Availability of a dedicated cardiac catheterisation laboratory or hybrid theatre [a theatre with mobile fluoroscopy ('C'-arm) screening facilities is generally not appropriate for TAVI procedures].
  - Computed tomography (CT) scanning facilities.
  - Immediate availability of perfusion services in case emergency cardio-pulmonary bypass (extracorporeal circulation) becomes necessary.
  - On-site availability of a surgical recovery area and intensive care with staff experienced in looking after patients following surgical aortic valve replacement.
  - Facilities for immediate renal support if necessary.
  - Immediate access to vascular surgery and interventional radiology to deal with peripheral vascular complications.
  - The above requirements will mean that this procedure should only be performed in a unit currently carrying out surgical aortic valve replacement.

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Diabetes News

Hypertension in Africa: what role can interventional strategies play?

AfricaPCR 2016, the third edition of the continent's premier interventional cardiology meeting, got under way in Johannesburg on 10 March with a plenary session devoted to the topic of hypertension in Africa and, specifically, whether interventional measures, notably renal denervation, have a role to play in its treatment, either as complementary or as an alternative to drug therapy, particularly given the compliance issues often associated with the latter.

Hypertension was a major focus of the meeting further to a needs analysis, which identified the magnitude of the problem in Africa. Prof Mpiko Ntsekhe from the University of Cape Town cited a 1929 study involving 2 000 Kenyan subjects in whom there was a complete absence of hypertension. Nearly a century later, however, the picture has changed dramatically. The bulk of the world's hypertension burden is now in Africa, with an estimated prevalence of more than 60% in adults over 60 years.

There are many reasons for this, including urbanisation, poverty and social deprivation, dietary changes entailing high salt and saturated fat intakes, alcohol abuse and rising obesity. 'Hypertension is the biggest contributor to the risk of myocardial infarction, stroke and heart failure, as well as chronic kidney disease and cardiovascular mortality. It is therefore a major contributor to overall morbidity and mortality across the continent.'

When it comes to addressing the problem – awareness, treatment and control – the figures are 'really dismal'. 'Treatment rates are under 20% and only a little over 5% of patients are controlled, and that's using the old targets. As healthcare professionals we need to change this."

What should the targets be?

Prof Bernard Gersh from the Mayo Clinic, USA, underscored the seriousness of hypertension as a worldwide problem. 'Some one billion people are hypertensive and it's the major reason for office visits. The hurdles to combating it are universal.'

Several trials have shown the benefit of systolic blood pressure control in older patients, although the results were not always consistent. The 2014 JNC-8 guidelines, based on the evidence from randomised, controlled trials, recommend relaxed targets of 150 mmHg in those over 60 years with no other health issues and 140 mmHg in those with diabetes and chronic renal failure. 'These targets were already the subject of contention, but then the game changed with the SPRINT trial', said Prof Gersh.

The study involved an intensively treated arm with a systolic blood pressure target of < 120 mmHg, and another that received standard treatment with a target of < 140 mmHg. Key to the trial was that the intensively treated arm received three drugs per patient as opposed to an average of 1.9 in the standard arm. The study was stopped early owing to the significantly lower rate of the primary composite outcome myocardial infarction, acute coronary syndrome, stroke, chronic heart failure, cardiovascular death and all-cause death – in the intensively treated group.

Prof Gersh believes that the major benefit seen in SPRINT redefines systolic blood pressure targets, '150 mmHg is simply too high. The questions are whether we should extrapolate the SPRINT results to younger patients and diabetics and I think it's something we should consider. However, determining optimal thresholds in these groups will require more randomised trials. In the interim, based on the results of SPRINT, for most patients, lower is better. Intuitively, this makes sense. So why not aim for < 120 mmHg if it is relatively easily achievable and tolerable for the patient?'

Is renal denervation a viable option for treating hypertension?

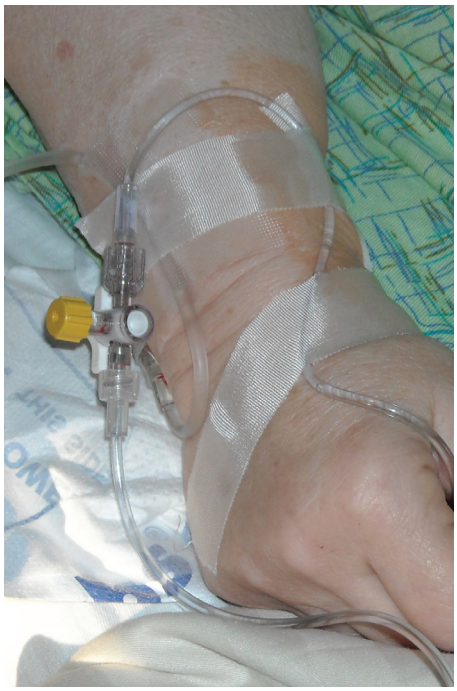
Prof Gersh underscored that sympathetic nervous activation plays a crucial role in cardiovascular disorders. 'Multiple unblinded trials have shown that renal denervation lowers blood pressure by 20–30%. The epidemiological implications of this are enormous. For some patients, a renal denervation procedure every five years might actually be preferable to lifelong multidrug therapy.' That said, he feels current levels of denervation are probably suboptimal.

Contradicting the findings of earlier unblinded trials, however, SYMPLICITY HTN-3, a prospective, single-blind, randomised, sham-controlled study, did not show a significant reduction in systolic blood pressure in patients with resistant hypertension six months after renal artery denervation, compared with the sham control group. 'All good trials raise new questions and both SYMPLICITY HTN-3 and SPRINT have done just that', said Prof Gersh.

Newer trials currently under way are assessing the effectiveness of renal denervation alone and in conjunction with drugs. 'In two years, we'll have the definitive answers to the following questions. Does it work? How does it compare with drugs?'

In the discussions that followed, it was concluded that there is currently a lack of strong scientific evidence to support the wide use of renal denervation, but that if that evidence becomes clear, it will have major implications, given widespread non-compliance with medication. However, even when the evidence becomes available, careful patient selection will still be imperative.

Source: AfricaPCR 2016



Cardiovascular disease market set to grow very slowly to $146.4 billion by 2022, says GBI Research

The cardiovascular disease market, which includes hypertension, dyslipidaemia and thrombotic events, is set to grow from $129.2 billion in 2015 to $146.4 billion by 2022, at a very modest compound annual growth rate of 1.8%, according to business intelligence provider GBI Research.

The company's latest report states that this relative stagnation can be attributed to major product approvals coinciding with key patent expirations. Within cardiovascular disease there are a number of blockbuster products that have recently gone off-patent, and others are expected to in the coming years, many of which belong to significant players.

For example, the current market leader, AstraZeneca's Crestor (rosuvastatin), generated around $7 billion in 2011, with revenues expected to drop sharply following the expiration of its patent on 8 July 2016. Total annual revenues are forecast to be around $1.3 billion in 2022.

Thomas Jarratt, associate analyst for GBI Research, explains: 'Unlike AstraZeneca, some key players will experience revenue growth resulting from the introduction of new products to market. In particular, Sanofi's Praluent (alirocumab) is expected to help mitigate losses associated with falling revenues of its key products Lovenox (enoxaparin) and Plavix (clopidogrel).

'Novartis' heart-failure drug Entresto was introduced to market in July 2015, and GBI Research expects its revenues to increase dramatically during the forecast period. Entresto is a combination drug, which has shown efficacy in clinical trials. Coupled with a high cost, which amounts to over $4 500 annually per patient, the drug contributes to a very high revenue forecast of $5.7 billion by 2022.'

The sheer number of expirations and approvals means the structure of the market will shift significantly. Current market leader AstraZeneca is set to mitigate the damage associated with the introduction of generic Crestor through the rising revenues attributed to its antiplatelet drug Brilinta.

Jarratt continues: 'the market shares of Sanofi and Novartis are expected to increase strongly over the forecast period, leading to Sanofi becoming market leader, and both brands achieving revenues in excess of $7 billion by 2022.'

Risk of cardiac death in diabetic haemodialysis patients increased due to thyroid problems

A prospective study found that diabetic haemodialysis patients' sub-clinical hyperthyroidism and euthyroid sick syndrome may increase the risk of sudden cardiac-related deaths. Dr Christiane Drechsler, of University Hospital Würzburg in Würzburg, Germany, and colleagues conducted a study that included 1 000 patients undergoing haemodialysis for diabetes.

Of those patients, 78.1% had euthyroidism, 13.7% had sub-clinical hyperthyroidism, 1.6% had sub-clinical hypothyroidism and 5.4% had euthyroid sick syndrome. Patients with euthyroidism were compared with those who had sub-clinical hyperthyroidism and euthyroid sick syndrome with regard to which group showed an increased short-term (within a 12-month period) risk of sudden cardiac death.

It showed that patients who had euthyroidism had a 2.0-fold increased short-term risk of sudden cardiac death, and those who had sub-clinical hyperthyroidism and euthyroid sick syndrome had a 2.7-fold increase. The results showed that euthyroid sick syndrome was associated with a three-fold increased risk of short-term mortality, but in the long term (two to four years) it showed no increased risk.

The study revealed that sub-clinical hypothyroidism was not associated with cardiovascular events or all-cause mortality, which indicated that thyroid disorders had no influence on the risks of myocardial infarction and stroke. This study led researchers to conclude, 'Regularly assessing a patient's thyroid status may help estimate the cardiac risk of dialysis patients.'

Reference

http://www.renalandurologynews.com/thyroid-problems-up-cardiac-death-risk-in-diabetic-hd-patients/article/348571/

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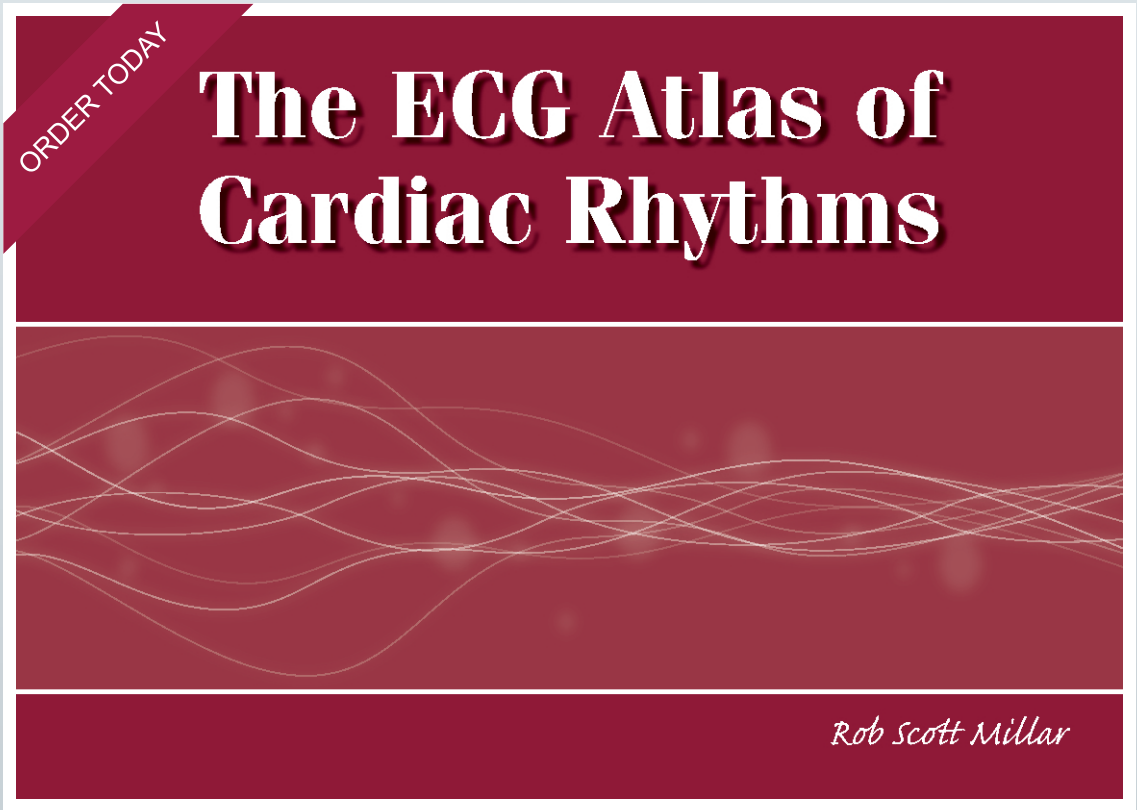

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