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Original Article

The Metabolic Syndrome (MetS) Does not Confer Additional Risk Above and Beyond its Individual Components for Left Ventricular Remodeling

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ABSTRACT

Introduction: The detection of preclinical changes in Left Ventricular (LV) structure in the Metabolic Syndrome (MetS) has not been adequately studied, although MetS is strongly associated with increased cardiovascular risk. The influence of the MetS and its individual components on LV geometry across age groups in a cohort of SA Indians was studied. **Method:** Data on 902 randomly selected participants, a sub-group of the Phoenix Lifestyle project was studied. Detailed methodology has been previously published. The MetS was defined according to the harmonised criteria, hypertension according to the JNC criteria, diabetes according to the American Diabetes Association criteria and echocardiography according to the European Society of Echocardiography guidelines. **Results:** Normal LV geometry was found in 80.8%, eccentric hypertrophy 15.9%, concentric hypertrophy 3.2%, concentric remodelling 0.5%. Logistic regression with MetS as the only independent variable strongly predicted the presence of both concentric (OR = 4.36 CI 1.84, 10.3 p<0.0001) and eccentric hypertrophy (OR = 3.15 CI 2.15, 4.62; p=0.001). When all MetS component risk factors were adjusted for each other, independent predictors for the eccentric hypertrophy were the waist circumference (p=0.002; OR= 2.95 CI 1.49, 5.84), fasting glucose (p= 0.021; OR= 1.7 CI 1.1, 2.7) and Blood Pressure (BP) (p=0.005; OR= 1.78 CI 1.19; 2.71). **Conclusion:** The MetS is not associated with any additional risk for LV remodelling beyond its individual risk factor components. The main determinants of LV remodelling appear to be mediated by the effects of the increased waist circumference, increased blood glucose and BP.

Key words: Metabolic syndrome, Left ventricular modelling, Concentric hypertrophy, Eccentric hypertrophy, Cardiovascular disease.

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INTRODUCTION

The Metabolic Syndrome (MetS) has been strongly associated with increased Cardiovascular (CV) risk.[1] The detection of preclinical changes in Left Ventricular (LV) structure in the MetS has not been adequately studied.[2] Whether structural or functional changes in LV function are due to cardiovascular risk factors or to the MetS as an entity is not clear. The ARIC study[3] showed that the MetS was strongly related to LV mass and its wall thickness, whereas the Strong Heart study[4] reported that of all the MetS components, only high blood pressure was associated with increased LV mass and LV hypertrophy. Although there is evidence to point to the worsening of LV hypertrophy with increasing number of MetS risk factor components,[5] there are conflicting data[6-8] on the effects of the MetS on the geometry of the left ventricle.[9] Furthermore, little is also known about the effects of the MetS on the cardiac structure and function in certain ethnic groups. A study in the Chinese Han population[10] has reported that MetS was associated with an increased risk of concentric and eccentric LV hypertrophy. Gampaoli *et al.*[11] surmised that ethnicity may affect the prognostic impact of the MetS, depending on the distribution of risk factors or the defining criteria used. In South Africa (SA) a high prevalence of the MetS has been recently reported in SA Indians.[12] In this study we determine the influence of the MetS, as well as its individual components, on left ventricular geometry across age groups in a cohort of SA Indians randomly selected from a community setting.

MATERIALS AND METHODS

Method

We reviewed the data on 902 selected participants who were part of the Phoenix Lifestyle Project (PLP), a cross-sectional, community-based study of 1378 subjects, randomly selected from the Phoenix community. The Kish method was used for selection of participants. The detailed methodology has been previously published.[13] Anthropometric measurements, blood pressure and blood sample collection for biochemistry were undertaken in all subjects. Briefly, after an overnight fast blood samples were taken for plasma glucose, total cholesterol, High-density Lipoprotein (HDL) and triglycerides. Low-density Lipoprotein (LDL) was estimated using the Friedewald equation. After blood sampling all participants underwent electrocardiography, anthropometry and two-dimensional (2D) guided echoDoppler studies.

Diagnostic Criteria

The MetS was defined according to the harmonised criteria proposed by the International Diabetes Federation in 2009,[14] which incorporates ethnic-specific cut-points for waist circumference. Participants who presented with a minimum of three of the following five risk factors were diagnosed as having the MetS: increased waist circumference (men: ≥ 90cm; women: ≥ 80cm), raised triglyceride levels (>1.7mmol/L), reduced HDL cholesterol (men: <1.03mmol/L; women: <1.29mmol/L); raised blood pressure (≥130 / ≥85mmHg) and raised fasting plasma glucose (≥6.1mmol/L).

Hypertension was diagnosed in individuals who self-reported previously diagnosed hypertension and/or with average of the three blood pressure

readings ≥140/≥90 mmHg[15] (Joint National Committee VII (JNC VII) criteria) and/or those on current antihypertensive therapy. Diabetes was diagnosed according to the American Diabetes Association criteria[16] if FPG ≥7.0mmol/l or two-hour plasma glucose level during OGTT was > 11.0 mmol/l or if the patient was on treatment for diabetes.

Echocardiographic Measurements

Echocardiographic measurements were performed according to the European Society of Echocardiography guidelines to ensure standardization.[17] Participants who had complete echocardiographic datasets were studied. Each subject underwent transthoracic, 2D- guided m-mode and Doppler echocardiogram with subjects lying in the left lateral decubitus position using a Siemens CV70 imaging system (Siemens, New York).

Ejection Fraction (EF) was measured using the Simpson's method.[18] Left Ventricular Mass (LVM) was estimated by using by the m-mode derived cubed method indexed to height$^{2.7}$ as proposed by Devereaux *et al.*[19] Left ventricular hypertrophy was diagnosed when LV Mass Index (LVMI) was >44 g/m$^{2.7}$ in women, >48 g/m$^{2.7}$ in men. Based on Relative Wall Thickness (RWT), LV hypertrophy was described as concentric (RWT ≥0.42) or eccentric (RWT < 0.42); concentric remodelling was diagnosed when the LV mass was normal (<134 g/m^2 in men; <110 g/m^2 in women) and the RWT ≥ 0.42.[20] Transmitral inflow velocities were obtained using Pulsed-Wave (PW) Doppler in the apical 4-chamber view with the sample volume placed between the tips of the mitral valve leaflets.[21] The transmitral early diastolic (Em) and atrial (Am) velocities were measured and were used to calculate the transmitral E/A ratio. Isovolumic Relaxation Time (IVRT) was measured from the cessation of LV outflow to the onset of LV inflow.

Tissue Doppler Imaging (TDI) was used to obtain Left Ventricular (LV) myocardial velocities in the apical chamber views with a 2 mm sample volume placed at the septal and lateral mitral annulus to record the early (Ea) and late (Aa) diastolic as well as the Systolic (Sa) myocardial velocities as proposed by Dumesnil *et al.* 2002.[22] All echocardiographic measurements were averaged over three consecutive cardiac cycles, measured by a single investigator (DRP) blinded to all other variables. Measurement of intra-observer variability was calculated from samples recorded on the same subject at different intervals. The Coefficient of Variation (CV) for the LA, LVM, EDD, ESD and EF measurements was 4%, 5%, 4%, 4% and 2% respectively. The cv for the transmitral Em, Am and Doppler Ea were 4%, 7% and 5% respectively. All measurements were stored on computer and printed as hard copies. The images were reviewed offline by two experienced observers (DPN and DRP) for analysis.

Ethical Considerations

Ethical approval was granted by the University of KwaZulu-Natal Bioethics committee (Ethics reference: E336/05) and conformed to the principles in the Declaration of Helsinki. Informed consent was acquired from each participant before the collection of this data and all were informed of the results of the examinations undertaken. Subjects in whom risk factors were identified were referred to a health facility for further evaluation and management.

Statistical Analysis

Data were analysed using SPSS software package version 24 (SPSS, Chicago, IL). All data are expressed as mean +/- SD. LV mass was indexed for height$^{2.7}$. For continuous variables, differences between two groups were assessed by independent sample *t*-test to compare clinical, morphometric, biochemical and echocardiographic parameters in subjects with vs those without MetS. The MetS components were correlated with the LVMI and RWT parameters which were used to classsify LV geometric patterns.

Stepwise backward regression models were constructed in order to determine the independent influence of the MetS, as well as that of its individual risk factor components, on LV geometry. Adjusted OR and 95% Confidence Intervals (CIs) for predicting the likelihood of eccentric and concentric hypertrophy were calculated. Values for $p<0.05$ were considered statistically significant. C-statistics were computed by deriving the probability for LV geometry from binary logistic regression, for the construction of a receiver operator curve. The AUC for each model was compared using the MedCalc 2018, MedCalc Software) software programme.

RESULTS

The clinical and echocardiographic data of all participants stratified by gender and age deciles are shown in Table 1. Women had significantly higher BMI (28.5±6.5 vs 24.2±5.4) and waist circumference (94.4±15.4 vs 88.0±14.6) than men ($p<0.001$). All anthropometric and biochemical parameters increased with age (p-trend <0.001). Men had higher levels for all echocardiographic parameters except wall thickness when compared to women (Table 1). There was significant increasing trend across the age groups for LAVI, septal thickness, posterior wall, RWT, LV mass, LVMI as well as transmitral and tissue Doppler indices (p-trend <0.05). Both the LV mass and the LVMI increased with advancing age, with an attenuation of diastolic indices and tissue Doppler indices. Left ventricular geometry was normal in over 90% of participants in the first and second deciles, with a significant decrease in normalcy with increasing age (P=0.001). There was a decrease in the LAVI between the 1st and 2nd deciles ($p<0.001$).

Left ventricular geometry was normal in 80.8% of the participants. Left ventricular hypertrophy was detected in remaining 19.2 % of participants, with the prevalence increasing from 2.7% in the first decile to 29.5% in the oldest decile. The pattern of hypertrophy was eccentric in 15.9% and concentric hypertrophy in 3.2% of the sample. Concentric remodelling was found in 0.5% of participants. Doppler Em and Ea parameters decreased with advancing age, as did the transmitral and tissue Doppler indices ($p<0.05$).

The clinical and metabolic characteristics of participants with and without MetS are shown in Table 2. There was a sharp increase in the prevalence of the MetS from 6.2% in the 15-24-year-old group to 27.2% in the 25-34-year age group which increased more gradually thereafter to a peak of 64.2% in the 55-64 age group ($p<0.001$). As defined by the MetS criteria, significant differences ($p<0.05$) existed for all clinical parameters with the exception of total cholesterol and LDL between participants with and without the MetS. Participants with the MetS had mean BMI levels approaching 30 kg/m^2 and fasting plasma glucose levels in the diabetic range. Of note, in this cohort participants without the MetS also exhibited elevated BMI (25.1±6.4 kg/m^2) and waist circumference levels (86.7±16.1 cm) but did not satisfy the diagnosis of the MetS according to the harmonised criteria.

When compared to subjects without the MetS, participants with the MetS had significantly higher septal (8±2mm versus 7±2mm) and posterior wall thickness (7±2mm versus 6±2mm), as well as higher RWT (0.3±0.09 versus 0.26±0.07). This difference existed in men and women and across all age groups (Table 2). The LV mass and LVMI were also significantly higher. Abnormal left ventricular geometry was more prevalent (13.7% versus 6.0%) in participants with the MetS ($p<0.001$), the prevalence increasing with advancing age. A similar trend was observed with concentric and eccentric hypertrophy ($p<0.0001$). There was a significant association ($p<0.0001$) between increasing number of MetS components when correlated with LVMI (Figure 1) and RWT (Figure 2).

Table 1: Clinical and Echocardiographic Profile of all Participants.

	All (906)	Men (224)	Women (682)	*p**	15-24 (*n*=111)	25-34 (*n*=101)	35-44 (*n*=208)	45-54 (*n*=266)	55-64 (*n*=220)	*p*-trend
BMI (kg/m²)	27.4±6.5	24.2±5.4	28.5±6.5	<0.001	22.3±5.8	27.9±7.5	27.8±6.4	28.6±5.6	28.1±6.2	<0.001
Waist (cm)	92.8±15.4	88.0±14.6	94.4±15.4	<0.001	78.8±13.5	91.6±16.6	93.4±14.5	96.3±14.7	65.7±13.6	<0.001
Hypertension	281(31.0%)	71(31.7%)	210(30.8%)	0.802	4(3.6%)	24(23.8%)	68(32.7%)	103(38.7%)	82(37.2%)	<0.001
Diabetes	289(31.9%)	55(24.6%)	234(34.3%)	0.007	6(5.4%)	15(14.9%)	56(26.9%)	102(38.3%)	110(50.0%)	<0.001
Mean systolic	132.8±23.7	132.3±19.5	132.8±24.9	0.77	116.5±12.1	123.7±16.9	130.7±30.8	137.2±20.9	141.3±20.5	<0.001
Mean diastolic	80.9±12.3	80.3±13.1	81.1±12.2	0.332	70.8±10.2	78.6±11.7	82.3±12.4	83.7±12.0	82.7±11.4	<0.001
FPG	6.4±3.0	6.2±2.6	6.5±3.1	0.115	5.1±2.2	5.4±2.1	6.2±2.8	7.0±3.5	7.1±2.8	<0.001
Se TC	5.5±1.2	5.4±1.2	5.5±1.2	0.19	4.5±1.0	5.0±0.9	5.4±1.1	5.8±1.1	5.8±1.1	<0.001
SeTriglycerides	1.8±2.7	1.8±1.2	1.8±3.1	0.91	1.1±0.9	1.5±0.8	1.6±0.9	2.2±4.8	2.0±1.3	<0.001
Se LDL	3.4±1.0	3.4±1.1	3.4±0.9	0.97	2.7±0.9	3.1±0.9	3.4±1.1	3.6±1.0	3.4±0.9	<0.001
Se HDL	1.3±0.5	1.2±0.3	1.4±0.5	<0.001	1.4±0.4	1.3±0.3	1.3±0.6	1.3±0.5	1.3±0.3	<0.001
LV Edd (mm)	46±5.0	48.0±5.0	46.0±5.0	<0.001	46.0±5.0	47.0±5.0	46.0±5.0	470.±6.0	46.0±6.0	0.69
LV Esd (mm)	28±6	30±7	27±5	<0.001	28±4	28±4	27±5	28±6	28±8	0.556
EF (%)	69.9±9.0	68.0±9.0	70.0±9.0	<0.001	69.0±8.0	69.0±7.0	70.0±7.0	69.0±10.0	69.0±10.0	0.36
LAVI	1.3±0.3	1.4±0.3	1.3±0.3	<0.001	1.5±0.4	1.3±0.3	1.3±0.3	1.3±0.3	1.3±0.4	<0.001
Septum (mm)	7.0±2.0	7.0±2.0	7.0±2.0	0.18	6.0±1.0	6.0±2.0	7.0±2.0	7.0±2.0	8.0±2.0	<0.001
Posterior wall (mm)	6.0±2.0	7.0±2.0	6.0±2.0	0.020	6.0±1.0	6.0±1.0	6.0.±2.0	7.0±2.0	7.0±2.0	<0.001
RWT %	0.3±0.09	0.28±0.09	0.28±0.09	0.914	0.25±0.06	0.27±0.06	0.28±0.08	0.29±0.09	0.3±0.1	<0.001
LV mass (g)	123.0±50.0	139±56.0	118.0±47.0	<0.001	103±33	114±41	118±48.0	128±50	138±57	<0.001
LVMI (g/m$^{2.7}$)	34.4±12.3	33.3±13.1	35.8±14.5	<0.001	27.7±7.4	31.1±10.7	32.9±12.3	37.7±14.8	39.9±16.5	<0.001
Normal geometry	733(80.8%)	193(84.8%)	540(79.2%)	0.064	108(97.3%)	92(91.1%)	178(86.1%)	198(74.8%)	154(70.5%)	<0.001
LVH	173 (19.1%)	31(13.8%)	142(20.8%)	0.038	3(2.7%)	9(8.9%)	29(13.9%)	67(25.2%)	65(29.5%)	<0.001
Eccentric LVH	144(15.9%)	25(11.1%)	119(17.4%)	0.042	3(2.7%)	8(8.5%)	22(10.5%)	58(21.8%)	53(24.1%)	<0.001
Concentric LVH	29(3.2%)	6(2.7%)	23(3.4%)	0.092	0(0.0%)	1(1.0%)	7(3.3%)	9(3.4%)	12(5.5%)	<0.001
C remodelling**	5(0.56%)	2(0.89%)	3(0.44%)	0.784	0(0.0%)	1(1%)	3(1.4%)	1(0.38%)	1(0.45%)	0.586

** C remodelling = concentric remodelling. *significance between men and women, FPG: fasting plasma glucose; TC: total cholesterol, LAVI: left atrial volume index; RWT: relative wall thickness, LVMI: LV mass index; IVRT: isovolumic relaxation time.

Logistic regression models for concentric and eccentric hypertrophy (Table 3) constructed with the MetS as the only independent variable, strongly predicted the presence of both concentric (OR = 4.36 CI 1.84,10.3 p<0.0001) and eccentric (OR = 3.15 CI 2.15, 4.62; p=0.001) hypertrophy when compared to normal LV geometry. In a model with all MetS component risk factors, adjusted for each other, there were no significant predictors of concentric hypertrophy. In contrast, independent predictors for the eccentric hypertrophy were the waist circumference (p=0.002; OR= 2.95 CI 1.49, 5.84), fasting glucose (p= 0.021; OR= 1.7 CI 1.1, 2.7) and the blood pressure (p=0.005; OR= 1.78 CI 1.19; 2.71), negating the predictive power of the MetS as an entity when included in this model. There was no significant difference in the AUC of individual components of the Mets when compared to a model including the MetS parameter (C-statistic = 0.71 for eccentric and 0.63 for concentric hypertrophy).

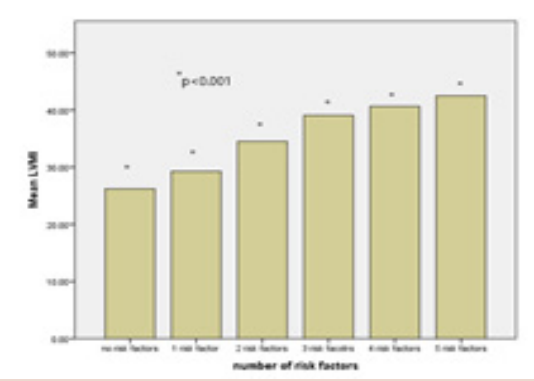

Figure 1: The Relationship between MetS Risk Factor Clustering and LVMI.

Table 2: Comparison of Clinical and Echocardiography Parameters in Participants with and without the MetS.

Parameters	No MetS (*n*=477)	MetS (*n*=429)	*p*
Males	138(61.6%)	86(38.4%)	<0.001
Females	340(49.8%)	342(50.2%)	0.792
Mean age	39±14	49±9	<0.001
15-24	104(93.8)	7(6.2)	<0.001
25-34	73(72.8)	28(27.2)	<0.001
35-44	122(58.3)	86(41.7)	<0.001
45-54	101(37.3)	165(62.7)	<0.001
55-64	78(35.8)	142(64.2)	<0.001
BMI (kg/m^2)	25.1±6.4	29.9±5.6	0.004
Waist (cm)	86.7±16.1	99.6±11.2	<0.001
Mean systolic (mmHg)	123.4±17.1	142.7±25.6	<0.001
Mean diastolic (mmHg)	76.4±11.1	85.9±11.8	<0.001
Fasting plasma glucose	5.3±1.9	7.7±3.9	<0.001
Se TC	5.2±1.1	5.8±1.1	0.845
Se Trig	1.2±0.6	2.4±3.8	<0.001
Se LDL	3.2±1.0	3.6±1.0	0.692
Se HDL	1.4±0.4	1.2±0.5	0.024
Echocardiography			
LVEdd (mm)	46±5	47±5	0.001
LVEsd (mm)	27±6	28±6	0.119
LAVI	1.24±0.3	1.38±0.35	<0.0001
Septum thickness (mm)	7±2	8±2	<0.0001
Posterior wall (mm)	6±2	7±2	<0.0001
RWT (%)	0.26±0.07	0.3±0.09	<0.0001
LV mass (g)	109±40	140±54	<0.0001
LVMI (g/m$^{2.7}$)	30.8±11.7	40.1±15.1	<0.0001
IVRT (msec)	98±23	96±23	0.268
EF (%)	70±8	69±9	0.474
Em	1.37±0.49	1.08±0.46	<0.0001
Am	0.64±0.51	0.78±0.68	<0.0001
Ea	0.25±0.1	0.24±0.12	0.074
Em/Ea	5.97±2.38	5.4±3.13	0.003
LV geometry			
Normal	426(47.01%)	307(33.9%)	<0.0001
Concentric hypertrophy	7(0.77%)	22(2.4%)	<0.0001
Eccentric hypertrophy	44(4.9)	100(11.03%)	<0.0001
Concentric remodelling	3(0.33%)	2(0.22%)	0.109

Table 3: Odds Ratios (95%CI) Derived from Stepwise Backward Logistic Regression of the Metabolic Syndrome Versus the MetS Components Across Normal and Abnormal Ventricular Geometry.

	Concentric Hypertrophy		Eccentric Hypertrophy	
	OR (95%CI)	*p*	OR (95% CI)	*p*
Model 1: MetS only*	4.36 (1.84; 10.3)	<0.0001	3.15 (2.15, 4.62)	0.001
Model 2: MetS + MetS components				
Waist circumference Men: ≥ 90cm Women: ≥ 80cm	1.006(0.29; 3.48)	0.993	2.95(1.49; 5.84)	0.002
Fasting glucose : ≥ 6.1 mmol/L	1.2(0.49; 3.0)	0.671	1.7(1.1; 2.7)	0.021
Triglyceride: ≥ 1.7 mmol/L	0.61(0.25; 1.48)	0.275	1.3(0.82; 2.06)	0.26
Blood pressure: ≥130 and/ ≥85 mmHg	1.87(0.81; 4.3)	0.145	1.78(1.19; 2.71)	0.005
HDL cholesterol Men:<1.03 mmol/L Women: <1.29 mmol/L	0.99(0.42; 2.3)	0.98	0.89(0.59; 1.35)	0.58
MetS	3.75(0.91; 15.5)	0.067	1.35(0.7; 2.6)	0.37
	C-statistic (standard error)			
Model with individual MetS components	AUC = 0.716 (SE 0.043)		AUC =0.675 (SE 0.022)	
Model with MetS parameter plus all MetS components	AUC =0.692 (SE 0.048)		AUC =0.691(SE 0.025)	
Comparison of C-statistics (*p*-value)	0.71		0.63	

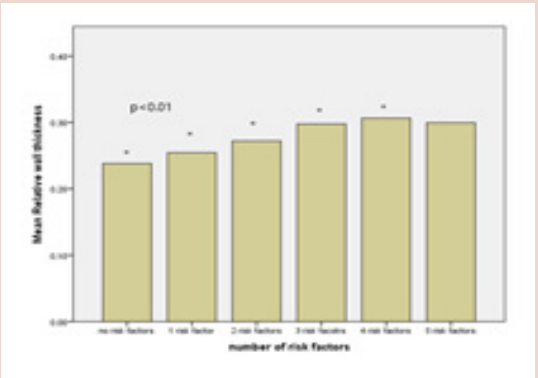

Figure 2: Relationship between increasing number of MetS risk factors and mean relative wall thickness.

DISCUSSION

In this study we report the effects of the MetS on LV geometry in a cohort of SA Indians and show that subjects with the MetS have increased septal and posterior wall thickness, RWT, LV mass and LVMI. Although we found that the MetS was a strong predictor for both concentric and eccentric hypertrophy on univariate analysis; this effect was abolished on multivariate analysis. When the MetS parameter was included with its individual components in a multivariate logistic regression model, after adjusting for all the components, only the waist circumference, fasting glucose and the blood pressure emerged as independent predictors of eccentric LVH.

Although a third of our subjects had diabetes and/or hypertension, concentric hypertrophy was not the dominant adaptive response of the left ventricle.[23] Instead, waist measurement emerged as the strongest predictor of hypertrophy and was associated with a threefold increase in eccentric LVH. This was followed by elevated blood glucose and elevated blood pressure which also significantly predicted hypertrophy albeit to a lesser extent. These findings confirm that obesity is a major driver of hypertrophy in Asian Indians, in keeping with previous reports emphasising the role of obesity in ventricular remodelling in subjects with the MetS.[24,25]

We attribute the higher prevalence of eccentric rather than concentric hypertrophy to the high mean BMI with increased waist measurement in our subjects. Our findings of increased LV dimensions in the MetS are in keeping with other studies[9,24] which have reported increased chamber dimensions and wall thickness in Asian Indians with the MetS.

The finding of eccentric hypertrophy has also been reported by Grandi *et al.*[26] and more recently, by Ratto *et al.*[27] who reported LV dilation in subjects with hypertension and the MetS. In a study similar to ours, Guerra *et al.*[25] reported that obesity accounted for the development of increased LV mass in hypertensive subjects with the MetS. It is thought that excess adipose tissue coupled with increased artery stiffness contribute to increase in afterload leading to eccentric hypertrophy.[28] The haemodynamic mechanisms underlying the development of eccentric obesity in the MetS have been explained in several studies. Recently Seferovic *et al.*[29] emphasised the role of central obesity as a strong contributor to cardiac hypertrophy and remodelling.[30,31] The mild volume-overloaded state that characterises obesity[32] result in increased preload and stroke volume which leads to cardiac remodelling over a prolonged period.[33]

Similarly, the link between increased blood glucose and increased LV mass is well established.[1,34] The deposition of advanced-glycated end-products within the interstitium and elevated serum aldosterone levels contribute to hyperglycemia-induced LV remodelling through metabolic pathways that lead to myocyte growth and changes in the extracellular matrix that result in increased myocardial stiffness. This in turn activate cytokines and angiotensin II that lead to further myocardial fibrosis and increase in LV mass.[35] An important aspect of our study was the association between an increase in the number of MetS components and higher LVM and RWT. Although an association between increased LV mass and the diagnosis of the MetS has been previously described,[9,36] we have shown that this effect falls away when adjusted for other risk factors. The MetS phenotype is thought to produce abnormal loading conditions which increase the LV mass and this is probably mediated through its component risk factors. This could explain why a diminished LV function may also be evident in normal-weight individuals with the MetS.[37] Almost a third of our subjects had hypertension and diabetes, both of which act in concert to affect ventricular remodelling. In addition to the effects of hyperglycaemia described above, patients with hyperglycaemia frequently have coexisting hypertension and together influence LV remodelling leasing to an increase in LV mass.[38] Several mechanisms related to blood pressure have been proposed to explain the relationship between LV remodelling and MetS. Blood pressure is determined by the mechanical stress of pressure overload and by various neurohormonal substances which together determine the hemodynamic workload for the left ventricle.[39] Hypertension increases septal and posterior wall thickness leading to an increase in LV mass measurements.[26]

In conclusion, our study has shown that the MetS in a cohort of South African Indians is not associated with any additional risk for LV remodelling above and beyond that conferred by its individual risk factor components. These findings are supported by those of Patel *et al.* and McNell *et al.*[24,40] Although the MetS was characterised by changes in LV geometry and LV mass, the main determinants of LV remodelling in this population appear to be mediated by the effects of the increased waist circumference, increased blood glucose and blood pressure. The findings of our study support the call for aggressive lifestyle modification in this community to prevent obesity with its accompanying changes in glycaemic levels and blood pressure to delay the development of the MetS and its associated risk for heart failure[41] and LV remodelling.

STRENGTHS AND LIMITATIONS

Some limitations must be considered: participants on treatment for hypertension and diabetes were not excluded from the analysis and this could have introduced some element of confounding, as these drugs are known to affect cardiac remodeling. A very small number of participants in our study exhibited concentric remodelling, which is thought to be a reflection of the adaptive process related to the pathophysiology of glucose and insulin metabolism.

Despite these caveats, our study has some strengths, among them being the characteristics of the cohort studied: the community participants studied are a fairly homogenous group living in one cadastral district in South Africa, although some may argue they were from varying religious sects. In addition, the analysis in this study used routinely measured echocardiography techniques and clinical measurements, thereby increasing the application of the findings of the study to general clinical practice. Another strength that we sought to separate the effects of obesity on LV dimensions and mass by indexing the LV mass to height [2.7].[9] The link between the MetS and obesity[25] is especially relevant to consider in our study of SA Indians, since their smaller body size and body habitus would influence LV dimensions and mass, since when using Asian ethnic-specific cut points ($23 kg/m^2$),[42] since most of these participants were classified as overweight.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

LV: Left Ventricle; **MetS:** Metabolic Syndrome; **SA:** South African; **BMI:** Body Mass Index; **LVMI:** Left Ventricular Mass Index; **RWT:** Relative Wall Thickness; **LA:** Left Atrium; **LAVI:** Left Trial Volume Index; **EDD:** End Diastolic Dimension; **ESD:** End Systolic Dimension; **EF:** Ejection Fraction.

SUMMARY

The detection of preclinical changes in Left Ventricular (LV) structure in the Metabolic Syndrome (MetS) has not been adequately studied, although MetS is strongly associated with increased cardiovascular risk. The influence of the MetS and its individual components on LV geometry across age groups in a cohort of SA Indians was studied.

The study found that MetS as the only independent variable strongly predicted the presence of both concentric and eccentric hypertrophy. When all MetS component risk factors were adjusted for each other, independent predictors for the eccentric hypertrophy were the waist circumference, fasting glucose and Blood Pressure (BP). The MetS is not associated with any additional risk for LV remodelling beyond its individual risk factor components. The main determinants of LV remodelling appear to be mediated by the effects of the increased waist circumference, increased blood glucose and BP.

REFERENCES

1. Liu L, Miura K, Fujiyoshi A, *et al.* Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan. Am J Cardiol. 2014;113(1):84-8.
2. Mogelvang R, Biering-Sørensen T, Jensen JS. Tissue Doppler echocardiography predicts acute myocardial infarction, heart failure and cardiovascular death in the general population. European Heart Journal-Cardiovascular Imaging. 2015;16(12):1331-7. https://doi.org/10.1093/ehjci/
3. Arnett DK, Jones DW, JrTaylor HA. Metabolic syndrome and echocardiographic left ventricular mass in blacks: The Atherosclerosis Risk in Communities Study. Circulation. 2005;112(6):819-27.
4. DeSimone G, Devereux RB, Chinali M,*et al.* Metabolic syndrome and left ventricular hypertrophy in the prediction of cardiovascular events: The Strong Heart Study. Nutrition Metabolism and Cardiovascular Diseases. 2009;19(2):98-104. doi:10.1016/j.numecd.2008.04.001.
5. Delas FL, Brown A, Mathews S. Metabolic syndrome is associated with abnormal left ventricular diastolic function independent of left ventricular mass. European Heart Journal. 2007;28(5):553-9.
6. Mancia G, Bombelli M, Facchetti R, *et al.* Long-term risk of diabetes, hypertension and left ventricular hypertrophy associated with the metabolic syndrome in a general population. Journal of Hypertension. 2008;26(8):1602-11. doi: 10.1097/HJH.0b013e328302f10d
7. Chinali M, Devereux RB, Howard BV, Roman MJ, *et al.* Comparison of cardiac structure and function in American Indians with and without the metabolic syndrome (the Strong Heart Study). Am J Cardiol. 2004;93(1):40-4. [PubMed: 14697463]
8. Nicolini E, Martegani G, Maresca AM, *et al.* Left ventricular remodelling in patients with metabolic syndrome: Influence of gender. Nutr Metab Cardiovasc Dis. 2013;23(8):771-5. [PubMed: 22770750]
9. DeMarco M, DeSimone D, Roman MJ, *et al.* Cardiac Geometry and Function in Diabetic or Prediabetic Adolescents and Young Adults: The Strong Heart Study. Diabetes Care. 2005;34(10):2300-5.
10. Wang S, Xue H, Zou Y, *et al.* Left ventricular hypertrophy, abnormal ventricular geometry and relative wall thickness are associated with increased risk of stroke in hypertensive patients among the Han Chinese. Hypertens Res. 2014;37(9):870-4. [PubMed: 24830536]
11. Giampaoli S, Palmieri L, Mattiello A, Panico S. Definition of high-risk individuals to optimise strategies for primary prevention of cardiovascular diseases. Nutr Metab Cardiovasc Dis. 2005;15(1):79-85.
12. Prakaschandra R, Naidoo DP. Increased waist circumference is the main driver for the development of the metabolic syndrome in South African Asian Indians. Diab Met Syndr: Clin Res Rev. 2017;11S:S81-5. http://dx.doi.org/10.1016/j.dsx.2016.12.011
13. Prakaschandra DR, Esterhuizen T, Motala AA, Gathiram P, Naidoo DP. High prevalence of cardiovascular risk factors in Durban South African Indians: The Phoenix Lifestyle Project. SAMJ. 2016;106(3):284-9.
14. Alberti KGMM, Eckel RH, Grundy SM, *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity. Circulation. 2009;120:1640-5.
15. Chobanian AV, Bakris GL, Black HR, *et al.* Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-52. Available from: http://dx.doi.org/10.1161/01.hyp.0000107251.49515.c2
16. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2006;30:S42-7. Available from: http://dx.doi.org/10.2337/dc07-s042
17. Lang RM, Bierif M, Devereux RB, *et al.* Recommendations for chamber quantification. Eur J Echocardiography. 2006;7(2):79-108.
18. Schiller NB, Acquatella H, Ports TA, *et al.* Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation. 1979;60(3):547-55.
19. Devereux RB. Left ventricular geometry, pathophysiology and prognosis. J Am Coll Cardiol. 1995;25:885-7
20. Foppa M, Duncan BB, Rohde LE. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy?. Cardiovascular Ultrasound. 2005;3(1):17. doi:10.1186/1476-7120-3-17.
21. Quinones MA, Otto CM, Stoddard M, *et al.* Recommendations for quantification of Doppler echocardiography: A report from the Doppler quantification task force of the nomenclature and standards committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;15(2):167-84.
22. Srivastava PM, Burrell LM, Calafiore P. Lateral vs medial mitral annular tissue Doppler in the echocardiographic assessment of diastolic function and filling pressures: which should we use?. European Journal of Echocardiography. 2005;6(2):97-106. https://doi.org/10.1016/j.euje.2004.07.005
23. Gaasch WH, Zile MR. Left ventricular structural remodelling in health and disease: with special emphasis on volume, mass and geometry. J Am Coll Cardiol. 2011;58(17):1733-40
24. Patel DA, Srinivasan SR, Chen W, Berenson GS. Influence of the metabolic syndrome versus the sum of its individual components on left ventricular geometry in young adults. Am J Cardiol. 2009;104(1):69-73. doi: 10.1016/j.amjcard.2009.02.063.
25. Guerra F, Mancinelli L, Angelini L, *et al.* The Association of Left Ventricular Hypertrophy with Metabolic Syndrome is Dependent on Body Mass Index in Hypertensive Overweight or Obese Patients. PLoS One. 2011;6(1):e16630. https://doi.org/10.1371/journal.pone.0016630
26. Grandi AM, Maresca AM, Giudici E, *et al.* Metabolic Syndrome and Morphofunctional Characteristics of the Left Ventricle in Clinically Hypertensive Nondiabetic Subjects. American Journal of Hypertension. 2005;19(2):199-205. https://doi.org/10.1016/j.amjhyper.2005.07.024
27. Ratto E, Viazzi F, Verzola, *et al.* Metabolic syndrome is associated with left ventricular dilatation in primary hypertension. Journal of Human Hypertension. 2016;30(3):158-63. http://dx.doi.org/10.1038/jhh.2015.67
28. Conte L, Fabiani I, Barletta V, *et al.* Early Detection of Left Ventricular Dysfunction in Diabetes Mellitus Patients with Normal Ejection Fraction, Stratified by BMI: A Preliminary Speckle Tracking Echocardiography Study. J Cardiovasc Echogr. 2013;23(3):73-80. doi: 10.4103/2211-4122.123953.
29. Seferovic JP, Tesic M, Seferovic M, *et al.* Increased left ventricular mass index is present in patients with type 2 diabetes without ischemic heart disease. Scientific Reports. 2018;8(1):926. doi:10.1038/s41598-018-19229-w
30. Chumlea WC, Schubert CM, Towne B, *et al.* Leftventricular mass, abdominal circumference and age: The Fels longitudinal study. J Nutr Health Aging. 2009;13(9):821-25.
31. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med. 2005;2(10):536-43.
32. Abel ED, Litwin SE, Sweeney G. Cardiac remodelling in obesity. Physiol Rev. 2008;88(2):389-419.
33. Messerli FH, Christie B, DeCarvalho JG, *et al.* Obesity and essential hypertension. Hemodynamics, intravascular volume, sodium excretion and plasma renin activity. Arch Intern Med. 1981;141(1):81-5.
34. Velagaleti RS, Gona P, Chuang ML, *et al.* Relations of insulin resistance and glycemic abnormalities to cardiovascular magnetic resonance measures of cardiac structure and function: The Framingham Heart Study. Circ Cardiovasc Imaging. 2010;3(3):257-63.
35. Larghat AM, Swoboda PP, Biglands JD, *et al.* The microvascular effects of insulin resistance and diabetes on cardiac structure, function and perfusion: a cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging. 2014;15(12):1368-76.
36. Ayalon N, Gopal DM, Mooney DM, *et al.* Preclinical left ventricular diastolic dysfunction in metabolic syndrome. Am J Cardiol. 2014;114(6):838-42.
37. Burroughs PM, Swett K, Schneiderman N, *et al.* Cardiac structure and function with and without metabolic syndrome: the Echocardiographic Study of Latinos (Echo-SOL). BMJ Open Diabetes Res Care. 2018;6(1):e000484. Published 2018 Aug 13. doi:10.1136/bmjdrc-2017-000484
38. Levelt, E, Mahmoud M, Piechnik SK, *et al.* Relationship between Left Ventricular Structural and Metabolic Remodelling in Type 2 Diabetes. Diabetes. 2016;5(1):44-52.
39. Franklin SS. Hypertension in the metabolic syndrome. Metabolic Syndrome and Related Disorders. 2005;4:287-98.
40. McNell AM, Rosamond WD, Girman CJ, *et al.* The MS and 11-year risk of inci-

dent cardiovascular disease in the Atherosclerosis Risk in Communities Study. Diabetes Care. 2005;28(2):385-90.

41. Voulgari C, Tentolouris N, Dilaveris P, *et al.* Increased Heart Failure Risk in Normal-Weight People with Metabolic Syndrome Compared with metabolically healthy obese individuals. Journal of the American College of Cardiology. 2011;58(13):1343-50.

42. Misra A, Chowbey P, Makkar BM, *et al.* Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. J Assoc Physicians India. 2009;57(2):163-170.

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