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Research Article

Left Ventricular Geometrical Changes Associated with Metabolic Syndrome in People with African Ancestry

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Abstract

Background: Major components of metabolic syndrome (MS) and other underlying biochemical derailments have the tendency to result to cardiac remodeling characterized by increased left ventricular mass index under the influence of renin angiotensin aldosterone system (RAAS). This study investigated the relationship between left ventricular geometry and MS in Black South Africans using the WHO criteria to classify MS.

Methods: The cross-sectional study was conducted among 668 participants of people of African ancestry age 18-70 years. Obesity was assessed using, body mass index (BMI), waist circumference (WC) and waist to-to-hip ratio (WHR), while conventional blood pressure (BP) was assessed using electronic BP monitoring device. Blood sample was taken for biochemical parameters such as lipid profile; triglyceride (TG), high lipid lipoprotein (HDL)), fasting blood glucose. Metabolic syndrome was defined according WHO criteria. All analyses were conducted using SPSS software for Windows, version 11.0J (SPSS, Chicago, USA) and STATA.

Results: When participants were classified according to gender, there was significant difference between men and women in the incidence of BMI. WC and MS were significantly higher in women compared to men. When the participants were classified according to MS status, LVMI was significantly higher in people with MS compared to those without MS while E/A ratio (marker of the function of the left ventricle of the heart) was significantly lower in participants with MS compared to those without MS.

Conclusion: Left ventricular hypertrophy and diastolic dysfunction in Africans with MS is strongly associated with RAAS and IR.

Keywords: Metabolic Syndrome; Insulin Resistance; Left Ventricular Hypertrophy; Diastolic Dysfunction; Renin Angiotensin Aldosterone System (RAAS)

Abbreviations

Aldo: Aldosterone; ARR: Aldosterone Renin Ratio; BMI: Body Mass Index; E/A: Ratio- Marker of the Function of the Left Ventricle of the Heart; EF: Ejection Fraction; FS: Fractional Shortening; ESV: End Systolic Volume; EDV: End Diastolic Volume; HDL: High Lipid Lipoprotein; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance; IR: Insulin Resistance; LDL: Low Lipid Density Lipoprotein; LVEDD; Left Ventricular End Diastolic Diameter; LVESD; Left Ventricular End Systolic Diameter; LVMI: Left Ventricular Mass Index; RAAS: Renin Angiotensin Aldosterone System; ROS: Reactive Oxygen Species; TG: Triglyceride; WC: Waist Circumference; WHR: Waist Hip Ratio

Introduction

The constellation of various components of MS such as obesity, hypertension and other biochemical derangement are associated

with higher left ventricular mass index (LVMI) and prevalence of left ventricular hypertrophy (LVH) which may result to heart failure [1,2]. Insulin resistance (IR) coupled signalling mechanism were believed to underlie the cardiac dysfunction [3]. It also determines the hyperactivation of other systems such as renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, with or without hemodynamic (Figure 1) [3,4]. A study by Ceravolo and colleagues demonstrated that there was a strong association between increased RAAS activation, circulating insulin levels and diastolic dysfunction [5,6].

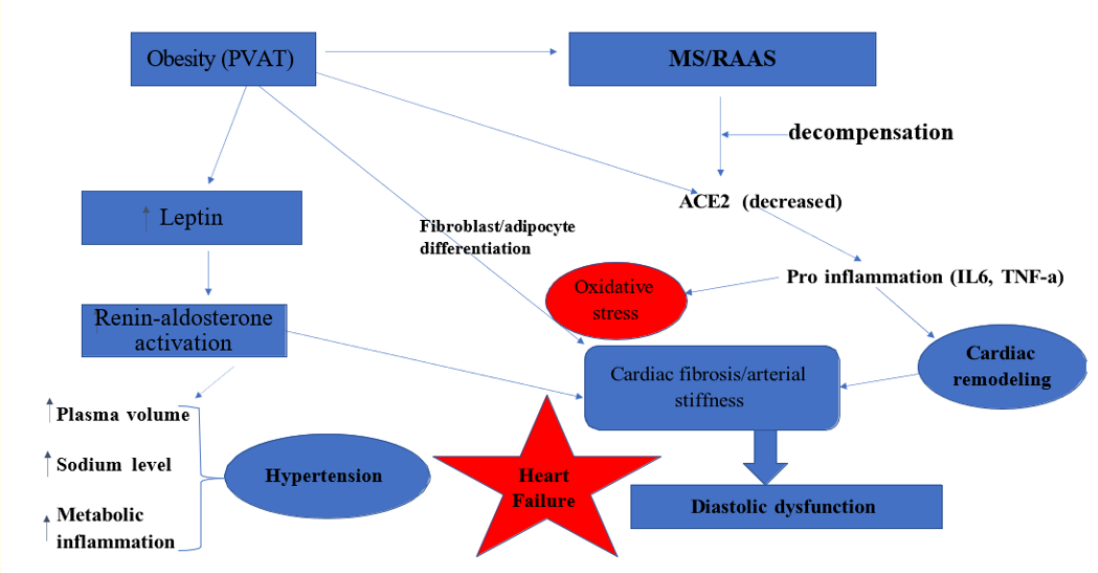

Figure 1: Integrative relationship between obesity, metabolic syndrome and renin-angiotensin aldosterone system (RAAS).

Homeostasis model assessment of insulin resistance (HOMA-IR) is an index used to evaluate IR (fasting serum insulin (μU/ml) × fasting plasma glucose (mmol l-1)/22.5) [7]. A study reported byGayoso-Diz., *et al*. (2013) suggested the possible effects of two absolute factors of MS (age and gender) on HOMA-IR and their association with cardio- metabolic risk [8]. However, the following echocardiographic parameters; end systolic volume (ESV), end diastolic volume (EDV),stroke volume (SV), left ventricular end systolic diameter (LVESD), left ventricular end diastolicdiameter (LVEDD), ejection fraction (EF), E/A ratio (the marker of the function of the left ventricle of the heart) and fractional shortening (FS) have been featured as the reliable prognosticindicator left ventricular dysfunction [9,10]. However, leptin is involved in numerous physiological and pathological processes some of which inflammation and fibrosis, are pivotal contributing to pathophysiological mechanisms in the development and progression cardiac abnormalities due to arterial stiffness and diastolic dysfunction [11]. Hence, this study evaluated the impact of MS on the left ventricular geometry in people of African ancestry.

Methods

Study design and population

The cross-sectional study was conducted among 668 indigenes of Soweto and Johannesburg in South Africa. The minimum age of the participants was 18 years and there was to upper age limit.Ethical approval was obtained from the University of Witwatersrand, Human Research Ethics Committee [Medical (Reference number: M190472)]. Participants were provided with informationsheets detailing the purpose and process of the study. Each participant was given written, informedconsent for his/her voluntary participation in the study.

Measurements and Biochemical analysis Anthropometric measurement

Anthropometric measurement was used to assess the size, shape and body composition of adipose tissue. Weight measurements were recorded using an electronic scale (Healthometer Professional). Height was measured using a stadiometer (Seca por-

table stadiometer) to. Body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Participants were considered to be underweight if BMI is < 18.5 kg/m^2, normal if BMI is between 18.5 and 24.9kg/m^2, overweight if their BMI is greater than or equal to 25kg/m^2 and obese if their BMI is greaterthan or equal to 30kg/m^2. Waist circumference (WC) was determined. Normal WC was taken as ≤ 102 cm in men and ≤ 88 cm in women. Hip circumference was measured at the level of the greatest posterior protuberance, perpendicular to the long axis of the trunk. Normal waist- hip ratio was taken as >0.9 in men and > 0.85 in women [12].

Blood pressure assessment

Blood pressure was accurately measured using automated sphygmomanometer (Omron, Kyoto, Japan) after 10 min of rest in the seated position. Five consecutive BP readings were obtained. Theaverage of the five readings were taken as the BP. Hypertension was defined as the mean value ofBP ≥140/90 mmHg (WHO standard for MS) [12].

Biochemical analysis

Before breakfast, 5ml of venous blood sample was collected from the cubital fossa using aseptic procedure. Lipid profiles [Triglyceride (TG), low lipid density lipoprotein (LDL), High lipid lipoprotein (HDL)] and fasting blood sugar were analysed at the Contact Laboratory Services(CLS) seven days after blood collection.

Echocardiograph

Participants were placed in left lateral decubitus position. Echocardiographic measurements wereassessed to determine cardiac structure (including heart chamber dimensions and wall thickness),as well as left ventricular mass. Two-dimensional targeted M-mode echocardiography (SonoSite R Inc., Bothell, WA, USA) in parasternal long axis view was used to determine left ventricular dimensions, following the method described by Nunez., *et al*. (2005) [13]. The M-mode variables was analysed according to the American Society of Echocardiography convention. All readings were recorded on videotape and analysed by an experienced echocardiographer who was part of the study. The echocardiographer was blinded to the details and clinical data of the subjects.

Diagnosis of metabolic syndrome

- Metabolic syndrome was defined according to WHO criteria; that is; insulin resistance defined astype 2 diabetes mellitus (DM) or impaired fasting glucose (IFG) (> 100 mg/dl) or impaired glucosetolerance (IGT), plus two of the followings:
- Abdominal obesity (waist-to-hip ratio > 0.9 in men or > 0.85 in women, or body massindex (BMI) ≥ 30 kg/m^2.
- Triglycerides 150 mg/dl or greater, and/or high-density lipoprotein (HDL)-cholesterol < 40 mg/dl in men and < 50 mg/dl in women.
- Blood pressure (BP) >140/90 mmHg.
- Microalbuminuria (urinary albumin secretion rate = or> 20 µg/min or albumin-to-creatinine ratio = or > 30 mg/g) [1].

Statistical analysis

Windows version 11.0J (SPSS, Chicago, USA) software was used for grouping and bivariate analysis. A p value of < 0.05 was considered to denote statistical significance. Continuous data will be reported as mean ± SEM. Results from the participants was compared between two groupsusing Student's *t*- test. The χ^2 statistic was used to compare means and proportions. Multivariate analyses using Stata/MP 16.0 (StataCorp, College Station, TX, USA) was used to analyse the association between MS and changes in echocardiograph parameters, biochemical parameters, relative factors and major component of MS among the selected groups. All models were adjustedfor age, sex, alcohol and smoking. Pearson's correlation coefficient was used to determine the association between MS status and measurement of obesity; lipid profile and echocardiograph. P value < 0.05 considered significant.

Results

Table 1 Shows general characteristics of the study population stratified by gender. The prevalenceof MS was higher among women (14.8%) in the study population compared to men (7.4%). The result also showed that BMI and WC were significantly increased in women compared to men, 31.2 ± 7.5 cm and 92.4 ± 16.6 respectively. Metabolic syndrome was defined according to the WHOcriterion; BMI, body mass index etc. *means there was significant p value when compared with MS category, p < 0.05.

	Men	Women	P value
	Mean ± SD	Mean ± SD	
Number	256 (23.8%)	412 (76.2%)	---------
Age	43.3 ± 18.9	44.5 ± 17.6	0.385
BMI	25.1 ± 4.8	31.2 ± 7.5	<0.001*
WC	86 ± 13.3	92.4 ± 16.6	<0.001*
WHR	0.8 ± 0.1	0.8 ± 0.2	0.777
Hypertensive (%)	46.1	45.6	0.936
Diabetic (%)	8.2	10.4	0.207
% Alcohol intake	20.3	18.7	0.615
% smoking	16.4	16.7	1.000
MS (%)	7.4	14.8	0.005*

Table 1: General characteristics of the study population stratified by gender.

Table 2: shows cardiac parameters stratified according to MS status. Those with MS hadsignificant decrease in E/A ratio and ESV ($p = 0.022$ and $p < 0.001$ respectively) compared to thosewithout metabolic syndrome. Moreover, those with metabolic syndrome had significant increase in LVMI ($p < 0.001$). There was no significance in EDV, SV, LVEDD, LVESD, FS and EF. MS defined according to the WHO criterion; ESV, end systolic volume; EDV, end diastolic volume. LVESD; Left Ventricular End Systolic Diameter, LVEDD; Left Ventricular End DiastolicDiameter, EF; Ejection Fraction, E/A ratio- marker of the function of the left ventricle of the heart, FS; Fractional Shortening. Keans corrected for age, gender, hypertension status, diabetes, smoking and alcohol intake. *Means there was significant p value when compared with MS category, $p < 0.05$.

Total population		Without MS Mean ± SD	with MS Mean ± SD	P value
ESV (ml)	661	31.6 ± **13.4**	36.1 ± **16.5**	0.022*
EDV (ml)	661	95.3 ± **28.1**	100.9 ± **28.8**	0.162
SV (ml)	661	63.7 ± **19.5**	64.8 ± **18.6**	0.691
LVEDD (mm)	661	4.7 ± **0.6**	4.8 ± **0.7**	0.071
LVESD (mm)	661	2.8 ± **0.5**	2.9 ± **0.6**	0.117
FS (%)	661	37.7 ± **6.8**	35.9 ± **7.0**	0.660
EF (%)	661	67.2 ± **8.7**	65.9 ± **9.6**	0.326
E/A ratio	661	1.3 ± **0.5**	1.0 ± **0.3**	<0.001*
LVMI (g/m^2)	661	37.9 ± 5.7	53.9 ± 7.0	<0.001*

Table 2: Cardiac parameters stratified by MS status.

Total population		Without MS Mean ± SD	With MS Mean ± SD	P value
Aldo (pg/mL)	653	197.62 ± **171.5**	232.8 ± 176.9	0.091
ARR	652	23.15 ± **36.4**	25.8 ± **85.4**	0.624
Galectin	653	8.9 ± **4.1**	9.6 ± **3.5**	0.201
HOMA IR	631	0.2 ± **0.5**	0.5 ± **0.4**	< 0.001*
Renin (ng/mL)	668	37.5 ± **74.1**	69.0 ± **10.2**	0.003*
Insulin (mmol/l)	631	12.7 ± **15.6**	15.3 ± **19.4**	0.186
Leptin (ng/mL)	631	22.0 ± **24.4**	29.3 ± **19.8**	0.131
Aldo-renin (ng/mL)	631	25.15 ± 36.7	30.0 ± **106**	0.501

Table 3: Biochemical parameters stratified by MS status.

Table 3 Shows association between relative components among those with and without metabolic syndrome. Participants with metabolic syndrome (MS) had significantly increase HOMA-IR concentration (0.5 ± 0.4) compared to participants without MS (0.2 ± 0.5). Furthermore, participants with MS had significantly high renin concentration (69.0 ± 10.2) compared to participants without MS (37.5 ± 10.2). MS defined according to the WHO criterion; Aldo: Aldosterone, ARR:Aldosterone renin ratio, HOMA-IR = Homeostatic Model Assessment-Insulin Resistance, *meansthere was significant p value when compared with metabolic syndrome category, p < 0.05. Keanscorrected for age, gender, hypertension status, diabetes, smoking and alcohol intake.

	AUC	CI	P value
Aldo (pg/mL)	0.645	0.512 to 0.777	0.017*
ARR	0.446	0.322 to 0.570	0.374
Galectin	0.522	0.405 to 0.638	0.722
HOMA IR	0.705	0.617 to 0.793	0.001*
Renin (ng/mL)	0.623	0.510 to 0.735	0.043*
Insulin (mmol/l)	0.608	0.518 to 0.699	0.075
Leptin (ng/mL)	0.636	0.536 to 0.735	0.025*
Aldo-renin	0.447	0.323 to 0.571	0.381

Table 4: ROC curve analysis of the relationship between MS and biochemical parameters.

Table 4 Shows ROC curve analysis of the relationship between MS and cardiac parameters. Therewas significant difference in HOMA-IR, Aldo, leptin and renin, aldosterone, concentrations (p = 0.001, p = 0.017, 0.025 and p = 0.043 respectively) in those with metabolic syndrome. The predictive value (AUC) of HOMA-IR, Aldo, leptin and renin, aldosterone in metabolic syndromewere 0.705, 0.645, 0.636, and 0.623 respectively. AUC, area under the curve; CI, confidence intervals etc. Corrected for age, gender, hypertension status, diabetes, smoking and alcohol intake, *means there was significant p value when compared with metabolic syndrome category, p < 0.05.ESV = End Systolic Volume, EDV = End Diastolic Volume, SV = Stroke Volume, LVESD = Left Ventricular End Systolic Diameter, LVEDD = Left Ventricular End Diastolic Diameter, EF; Ejection Fraction, E/A ratio- marker of the function of the left ventricle of the heart, FS; FractionalShortening. Keans corrected for age, gender, hypertension status, diabetes, smoking and alcohol intake. *Means there was significant p value when compared with metabolic syndrome category, p < 0.05.

	AUC	CI	P value
ESV (ml)	0.676	0.488 to 0.664	0.066
EDV (ml)	0.566	0.483 to 0.648	0.111
SV (ml)	0.519	0.410 to 0.596	0.653
LVEDD (mm)	0.517	0.483 to 0.658	0.086
LVESD (mm)	0.554	0.466 to 0.642	0.0190
FS (%)	0.417	0.333 to 0.501	0.044*
EF (%)	0.461	0.375 to 0.548	0.350
E/A ratio	0.272	0.204 to 0.340	< 0.001*
LVMI	0.683	0.512 to 0.777	< 0.001*

Table 5: ROC curve analysis of the relationship between MS and cardiac parameters.

AUC, area under the curve; CI, confidence intervals etc. Corrected for age, gender, hypertension status, diabetes, smoking and alcohol intake volume. LVESD; Left Ventricular End Systolic Diameter, LVEDD; Left Ventricular End Diastolic Diameter, EF; Ejection Fraction, E/A ratio- marker of the function of the left ventricle of the heart, FS; Fractional Shortening. Keans correctedfor age, gender, hypertension status, diabetes, smoking and alcohol intake. *Means there was significant p value when compared with metabolic syndrome category, p < 0.05.

Discussion

Body mass index and WC are major risk factors for the diagnosis of MS. In this study population,larger percentage of those with MS were women. In addition, there was significant increase in BMI and WC of women compared to men (table 1). This is a pointer to adiposity as a contributorymechanism underlying the development of MS and its complications. Waist circumference and BMI are measure of obesity positively associated with LVMI [14]. There is increasing evidence that adiposity is strongly linked with cardio-metabolic risk and cardiac changes. This may be dueto hypertrophied adipocytes as a result of dysregulated adipokine secretion, increased recruitmentof inflammatory cells and impaired metabolic homeostasis that eventually results in the development of systemic I [15]. There is also production of Nitric oxide synthase (NOS) which functions to maintain vascular and adipocyte homeostasis. Other reactive oxygen species (ROS) are hydrogen peroxide (H_2O_2), superoxide (O_2^-), hydroxyl radical (OH), high levels of nitric oxide (NO) and peroxynitrite ($ONOO^-$). These ROS are products of numerous enzymatic reactions thatlead to subcellular damage in the

heart, kidney and vasculature [16,17]. Moreover, leptin has ability to induce oxidative stress, SNS activation, release of endothelin 1 and reduced NO- bioavailability [11,18]. This infers that, elevated serum leptin levels evident in this study population are likely associated with impaired vasodilation. Also, leptin increases proliferation and migration of vascular smooth muscle cells through its ability to stimulate phosphorylation andactivate mitogen-activated protein kinases [18]. These changes result to vascular, peripheral resistance and vasoconstriction.

This study also revealed an association between HOMA-IR and MS. There was highest predictivevalue of HOMA-IR in those with MS (Table 3). According to Matthew., *et al*. (1985), IR can be ascertained by a homeostatic model assessment (HOMA) of IR. Index value of HOMA-IR above 1.9 (normal range is 0.5-1.4) indicates IR [7].

The release of renin is under the control of numerous cellular, hormonal and hemodynamic factors,there is increasing interest in exploring inappropriate activation of the renin-angiotensin- aldosterone system (RAAS) as a unifying mechanism between IR and other components of the metabolic syndrome [4]. Some studies have suggested that elevations in plasma aldosterone levels are associated with the insulin resistance independent of other components of angiotensin II (AngII) [4,19]. This relationship has been observed in studies exploring the association between primaryaldosteronism, in which there are low levels of renin activity and Ang II and IR [20]. Our study revealed high predictive value between renin and MS. Similarly, aldosterone had high predictive value for MS (table 4). There is evidence to indicate that renin-aldosterone ratio could be used fora more targeted pharmacological treatment of Africans with essential hypertension. This shows that low renin profile in Africans provides a basis for the greater reduction in blood pressure in response to dietary sodium restriction [21,22].

In this study, we observed that leptin had high predictive value of MS. Insulin resistance is strongly related to obesity, a major component of MS [23]. Fang., *et al*. (2020) documented that peri-renal fat thickness is an independent predictor of kidney dysfunction in people with type 2 diabetes, this may be due to hyperstimulation of paracrine gland; thus, affect renal circulation via pro-inflammatory cytokines. Similar effect applies to cardiovascular diseases [24]. Therefore, metabolic consequences of obesity/overweight have been attributed to biological activity of the adipocytes and adipose tissues unique to the fat distribution such as visceral and subcutaneous adiposity other than hemodynamic of salt and water retention alone.

Unique to this study is the prospective analysis of the interrelationship between the development of metabolic syndrome and preclinical diastolic dysfunctions. The increasing number of MS criteria is associated with cardiac diastolic dysfunction. Our finding showed decrease in E/A ratio and reduced ESD in those with MS (Table 3).

Obesity is an independent risk factor for LVH, but it is also associated with other risk factors, such as hypertension and diabetes [25]; these can amplify the effect of obesity on cardiac remodeling related to combination of RAAS mechanism and inflammatory process as earlier discussed. The consequences of the processes on coronary endothelium may have negative influence on left ventricular diastolic performance [26]. There was increased LVMI among those with metabolic syndrome. Notably, studies have reported increase in LVMI in obese and hypertensive individuals [4,15,27]. This study is in agreement with the study conducted in Hispanics/Latinos with MS, the study revealed increase risk of decreased left ventricular diastolic and MS function among participants with MS [28]. In summary, obesity, hypertension and hyperinsulinemia are independent cardiovascular risk factors that determine LVMI in MS individuals as a result of direct activation of RAAS.

Conclusion

Adipose-related cardiovascular events unique to this study population was investigated. In this study, BMI, WC and WHR were used as indices of obesity to assess the impact of adiposity on left ventricular geometry. This study concluded that cardiac damage in Africans is influenced by obesity, diabetes and hypertension; we further corroborated the importance of leptin, renin, aldosterone and insulin in the assessment of preclinical diastolic dysfunctions in Africans.

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Conflict of Interest

The Authors declared no conflict of interest.

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