ASSOCIATION AND PATTERN OF DIASTOLIC DYSFUNCTION IN PATIENTS OF METABOLIC SYNDROME

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Background: Diastolic dysfunction is important predictor of morbidity and mortality in patients with metabolic syndrome. This prospective study is to evaluate an association and pattern of diastolic dysfunction in patients of metabolic syndrome in our population. This cross-sectional study was performed at Armed Forces Institute of Cardiology Rawalpindi for a period of 6 months from 20th November 2007 to 20th April 2008. **Methods**: One hundred eligible and consenting patients having metabolic syndrome reporting in the OPD were registered. Inclusion criteria included patients of metabolic syndrome with negative ETT and normal systolic function. Exclusion criteria were patients with age above 60 years and valvular heart disease. Data was collected by a structured clinical interview with a physician, ECG and a transthoracic M-mode, 2D and TDI echocardiogram. The metabolic syndrome was defined according to International Diabetes Federation. **Results**: There was a positive association between the degree of the metabolic syndrome–assessed as number of concurrently present components–and parameters of cardiac structure and function, with a consistent and statistically significant trend for all cardiac variables considered($p=0.000$). There was also a positive association between each parameter and the cardiac diastolic dysfunction grading, e.g., systolic blood pressure ($p=0.000$), diastolic blood pressure ($p=0.005$), waist circumference ($p=0.004$), fasting blood sugar ($p=0.008$), triglycerides ($p=0.006$), HDL cholesterol ($p=0.001$). **Conclusion**: Several cardiac functional abnormalities regardless of symptoms increased progressively with increasing degree of metabolic syndrome.

Keywords: Metabolic Syndrome, Echocardiogram, Tissue Doppler Imaging, Diastolic Function

INTRODUCTION

Metabolic syndrome represents a clustering of cardiovascular risk factors affecting approximately 22% of adult population in industrialized countries and over 40% of those aged 50 and older.[1,2] These risk factors have been shown to act synergistically, via mechanisms poorly defined, to increase the risk of adverse cardiovascular events including coronary artery disease (CAD) and congestive heart failure, and are associated with high cardiovascular morbidity and mortality.[2–4] Although studies have shown that hypertension, diabetes mellitus, and obesity adversely affect cardiac structure and function, the extent to which individual and clustering components of the metabolic syndrome predict sub clinical left ventricular (LV) systolic and/or diastolic dysfunction has not been well characterized.[5–9]

The metabolic syndrome is a crucial factor in causation of type 2 diabetes mellitus and coronary heart disease in South Asians. Approximately 20–25% of urban South Asians have evidence of the metabolic syndrome.[10–12] It is important to mention that adiposity is the most important correlate of insulin resistance and the metabolic syndrome. The severity of insulin resistance increases with increasing adiposity. Body composition of South Asians is conducive to development of the metabolic syndrome; South Asians have high percentage of body fat[13,14–17], abdominal obesity[13,16], insulin resistance[18], hyperinsulinaemia[19] and low muscle mass[20]. In particular, abdominal obesity is common in South Asians, and evident even in non-obese people. Further, thick subcutaneous adipose tissue in Asian Indians may be a key correlate of insulin resistance.[21,22]

Although LV hypertrophy (LVH) imparts increased risk of cardiovascular morbidity and mortality, including development of systolic and diastolic dysfunction, and progression to heart failure[23–25] but the effects of the metabolic syndrome and of each of its component criteria on cardiac structure and function has not been well characterized.[26]

It is particularly important to effectively implement and strengthen population-based primary prevention strategies for the prevention of 'epidemic' of obesity and the metabolic syndrome.

The purpose of the study is to assess the association of increasing number of components of metabolic syndrome and the pattern of left ventricular diastolic dysfunction in our population.

MATERIAL AND METHODS

Hundred eligible and consenting patients of metabolic syndrome reporting in the OPD were registered. Patients of either gender having metabolic syndrome were included. Inclusion criteria included patients of metabolic syndrome with negative ETT and normal systolic function. Exclusion criteria were patients with age above 60 years and valvular heart disease. Metabolic syndrome was defined according to International Diabetes Federation is as follows:[27]

Central obesity (defined as waist circumference ≥90 cm for South Asian men and ≥80 cm

for South Asian women, with ethnicity specific values for other groups)

Plus any two of the following four factors:

- Raised TG level: >150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.

History and physical examination were carried out in all patients. After a 12-hour fast, a venous blood sample was collected. Plasma glucose level, serum cholesterol and triglyceride levels were determined using hexokinase and PAP methods done by Hitachi 911 SELECTRA XL machine. Anthropometric evaluation included waist circumference measurement to the nearest centimetre, midway between the lower limit of the rib cage and the iliac crest, with the subject standing using a flexible and non-distensible tape.[28] A structured clinical interview by a physician, a cardiovascular physical examination and a transthoracic echocardiogram with pulsed Doppler evaluation of transmitral inflow and Tissue Doppler Imaging were performed to minimize the errors in assessing the diastolic dysfunction. Hypertension was defined as blood pressure ≥130/85 mmHg or being under anti-hypertensive medication. Blood pressure was measured after a 10-minute rest, with no tight clothes. The mean of two measurements was registered. Diabetes mellitus was considered as self-reported or fasting venous blood glucose ≥100 mg/dl.[29] Participants who were under antihypertensive or antidiabetic medications were considered to have high blood pressure or high glucose levels, regardless of current blood pressure or serum glucose.[1,30]

Echocardiography was performed in iE33 Ultrasound system of PHILLIPS with multifrequency probe. Pulsed-wave Doppler (PWD)-derived transmitral inflow velocities were obtained in the apical 4-chamber view with the sample volume placed at the mitral valve leaflet tips.[28] Measurements included the transmitral early diastolic (E-wave) and atrial (A-wave) velocities to calculate E/A ratio, E-wave deceleration time, and the isovolumic relaxation time.[28] Tissue Doppler imaging (TDI) was used to obtain LV myocardial velocities in the apical 4-chamber view with a 2 mm sample volume placed at the septal and lateral mitral annulus. For Tissue Doppler imaging the normal mitral annulus velocity was obtained from the lateral side of the mitral annulus. The upper limit of E wave in a normal person is up to 20 cm/sec and 10 cm/sec in case of A.[31]

Table-1: standard parameters used for diastolic dysfunction.[32–34]

Parameters	Adults < 41yrs	Adults >41yrs
Peak Mitral flow velocity (E) (cm/sec)	76±3	63±11
Peak Mitral filling rate (A) (cm/sec)	38±8	52±9
Mitral E/A	2.1±0.6	1.3±0.3
Mitral E deceleration time	184±24	--
Isovolumetric relaxation time (m/sec)	74±26	--

Table-2: Grades of diastolic dysfunction[35]

	NORMAL (adult)	Delayed relaxation grade 1	Pseudo-normal filling grade 2	Restrictive filling grade 3 (reversible to grade 2 with valsalva manoeuvre) grade 4 (irreversible to grade 2 with valsalva manoeuvre)
E:A	>1	<1	1-2	>2
E Deceleration time (ms)	220	>220	150–200	<150
IVRT (ms)	<100	>100	60–100	<60
Ea (cm/s), lateral mitral annulus	>8–10	<8	<8	<8

Data analysis was performed through SPSS version 10. Frequency and percentages were computed to present categorical variables like age, gender, height (cm), weight (cm), waist circumference (cm), blood pressure, fasting blood sugar, fasting triglycerides, history of smoking, serum HDL, E velocity, A velocity, E/A Ratio, Mitral E deceleration time, Mitral E Deceleration rate, isovolumetric relaxation time, Doppler tissue imaging E velocity and A velocity . Student's *t*-test and Chi-Square tests were applied to calculate *p* value of quantitative and qualitative data respectively.

RESULTS

The Study was conducted at Armed Forced Institute of Cardiology, Rawalpindi, over a period of six months from 20th November 2007 to 20th April 2008. 100 patients of metabolic syndrome were recruited for the study. Out of the 100 patients, 64 were male and 36 were female. Age ranged from 32 to 59 (49.16±7.54) years.

In the whole study group, the prevalence of the various components of Metabolic syndrome were as follows: blood pressure level ≥130/≥85 mm Hg 100%, glycaemia ≥6.11 mmol L^{-1} (100 mg dL^{-1}) 96%, increased waist circumference in males 90 cm 81% (n=52/64) and in female 80 cm 100%, triglycerides ≥1.7 mmol L^{-1} (150 mg dL^{-1}) 97% and HDL cholesterol <1.04 mmol L^{-1} (40 mg dL^{-1}) in men 53.1% (n=34/64) and <1.30 mmol L^{-1} (50 mg dL^{-1}) in

women 100% . None of the subjects had only one of the clinical traits of the MS. In addition, 8, 10, 36 and 46 patients had two, three, four, or five traits, respectively, and 92 subjects (92%) fulfilled the criteria for the MS. 48% of all the patients of metabolic syndrome were smokers.

Forty-two patients were having no diastolic dysfunction, 42 had grade 1, 12 patients had grade 2, 4 patients had grade 3 and none had grade 4 diastolic dysfunction.

Table-3: Frequency of patients according to gender (n=100)

Gender	Number of patients
Male	64
Female	36

Table-4: Frequency of traits of metabolic syndrome

Number of traits of metabolic syndrome	Number of patients
Two	8
Three	10
Four	36
Five	46

Table-5: Prevalence of various components of metabolic syndrome

components of metabolic syndrome	Percentage
Blood pressure ≥130/85 mm Hg	100%
Glycaemia ≥6.11 mmol/L or 100 mg/dl	96%
Waist circumference In males ≥90 cm In females ≥80 cm	 81% 100%
Triglycerides ≥1.7 mmol/L or 150 mg/dl	97%
HDL cholesterol ≤ 1.04 mmol/L or 40 mg/dl in male ≤ 1.30 mmol/L or 50 mg/dl in female	 53.1% 100 %

Table-6: Positive association between metabolic syndrome parameters and diastolic dysfunction

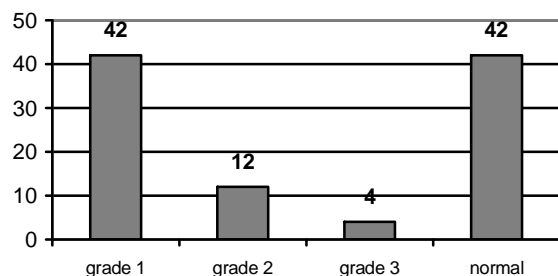| Traits of metabolic syndrome	p-Value
Systolic blood pressure	0.000
Diastolic blood pressure	0.005
Waist circumference	0.004
Fasting blood sugar	0.008
Triglycerides	0.001
HDL Cholesterol	0.006

Figure-1: Distribution of diastolic dysfunction

There was a positive association between the degree of the metabolic syndrome-assessed as number of concurrently present components–and parameters of cardiac structure and function, with a consistent and statistically significant trend for all cardiac variables considered (p=0.000). There was also a positive association between each parameter and the cardiac diastolic dysfunction grading e.g. systolic blood pressure (p=0.000), diastolic blood pressure (p=0.005), waist circumference (p=0.004), fasting blood sugar (p=0.008), triglycerides (p=0.001), HDL cholesterol (p=0.006).

DISCUSSION

South Asians have high rates of diabetes and the highest rates of premature coronary artery disease in the world, both occurring about 10 years earlier than in other populations. The metabolic syndrome (MS), which appears to be the antecedent or 'common soil' for both of these conditions, is also common among South Asians. Because South Asians develop metabolic abnormalities at a lower body mass index and waist circumference than other groups, conventional criteria underestimate the prevalence of MS by 25% to 50%. The proposed South Asian Modified National Cholesterol Education Program criteria that use abdominal obesity as an optional component and the South Asian-specific waist circumference recommended by the International Diabetes Federation appear to be more appropriate in this population. Furthermore, Asian Indians have at least double the risk of coronary artery disease than that of whites, even when adjusted for the presence of diabetes and MS. This increased risk appears to be due to South Asian dyslipidemia, which is characterized by high serum levels of apolipoprotein B, lipoprotein (a), and triglycerides and low levels of apolipoprotein A1 and high-density lipoprotein (HDL) cholesterol. In addition, the HDL particles are small, dense, and dysfunctional. MS needs to be recognized as a looming danger to South Asians and treated with aggressive lifestyle modifications beginning in childhood and at a lower threshold than in other populations.[36]

In our study, we found an association between pattern of diastolic dysfunction in patients with metabolic syndrome, with the frequency and/or the severity of diastolic dysfunction increasing with the number of features of the metabolic syndrome. Importantly, early asymptomatic stages of cardiac dysfunction increased progressively with the severity of the metabolic syndrome, independently of systolic blood pressure.

In a nested case-control study in Swedish elderly men,[37] factors associated with insulin resistance (heart rate, serum proinsulin, a high proportion of dihomogammalinolenic acid in serum cholesterol esters and hypophosphataemia) were

associated with left ventricular systolic dysfunction after 20-year follow-up, independently of ischaemic heart disease, hypertension and medications. In the Strong Heart Study,[5] American Indians with the metabolic syndrome had greater left ventricular dimension, mass, relative wall thickness and left atrial diameter, a higher prevalence of left ventricular hypertrophy, and lower ejection fraction and mitral E/A ratio. In a cross-sectional analysis within the ARIC Study,[38] the degree of metabolic syndrome clustering was strongly related to LV mass and wall thickness in black women and men. This association was not observed for chamber size, suggesting that there was a specific effect on myocardial thickening but not dilation.[39] The statistical association with increasing number of features of metabolic syndrome can be explained by the increasing impact of multiple independent risk factors and does not necessarily mean that there is synergism. Given the tendency of individual factors to aggregate, the prevalence of each component in isolation was high. Therefore, it was possible to estimate the sole effect of each factor, in comparison with the absence of all factors.

From the clinical and public health perspective, it has been questioned whether metabolic syndrome improves cardiovascular risk prediction, beyond previously used tools such as the Diabetes Predicting Model for type 2 diabetes or Framingham risk score for coronary heart disease.[40–45] Some studies have assessed whether the metabolic syndrome predicts the risk of cardiovascular diseases or a surrogate such as subclinical atherosclerosis.[46–48] In the majority of these studies, however, the outcome with which the metabolic syndrome was to be related was atherosclerotic vascular disease, either coronary heart disease alone or stroke. When assessing cardiac structure and function, one must keep in mind that coronary heart disease is not the only determinant of systolic and diastolic dysfunction. When adjusting for Framigham risk score, we are in fact assessing the effect of features of the metabolic syndrome not considered in the score (obesity and triglycerides) as well as abnormalities of carbohydrate metabolism that are not severe enough to establish the diagnosis of diabetes (impaired fasting glucose).

Results of the our study are consistent with those of prior studies that identified hypertension and obesity as independent predictors of impaired LV diastolic function.[48–50] However; few studies have evaluated the relationship between metabolic syndrome and echocardiographically derived measures of LV structure and function.[5,51,52]

Increased LV mass, relative wall thickness (RWT), and deceleration time have been reported in hypertensive subjects with metabolic syndrome compared with a hypertensive cohort without the syndrome.[51] In the Strong Heart Study, those with metabolic syndrome had greater LV mass and RWT and significantly lower E/A ratio; however, LV diastolic function was not characterized in Pre-Metabolic Syndrome.[5] It has been shown that even blood pressure levels within the non-hypertensive range in patients with metabolic syndrome may contribute to the development of sub-clinical LV diastolic dysfunction.

The mechanisms by which hypertension and visceral obesity lead to impaired LV diastolic function remain to be defined. It has been shown that visceral obesity is associated with diastolic dysfunction, an effect that may be mediated by an obesity-related pro-inflammatory state and/or by suppression of adiponectin expression.[48,52–54] Other potential mechanisms whereby metabolic syndrome contribute to impaired LV diastolic function include endothelial dysfunction, abnormalities in myocardial perfusion and/or metabolic substrate utilization, inflammation and oxidative stress, interstitial fibrosis, impaired ventricular–vascular interaction, and others.[55–65]

LIMITATIONS

Insulin resistance may have been found to have a more significant association with LV structure and function if metabolic syndrome was diagnosed according to the World Health Organization criteria. Although insulin and glucose were not obtained in diabetic subjects who were treated with insulin and/or oral hypoglycaemics, the impact of this limitation was minimized by performing regression analyses using impaired fasting glucose as criteria, which includes subjects with diabetes. The main limitation of our study is the relatively small sample, moreover the cross-sectional design is also not the ideal approach.

CONCLUSION

Several cardiac functional abnormalities regardless of symptoms increased progressively with increasing degree of metabolic syndrome. MS imparts a greater risk of target organ damage than each one of its five components. Individuals with the metabolic syndrome and normal LV systolic function frequently show abnormalities in LV diastolic function (i.e., impaired relaxation). These findings are also evident in subjects with only one or two metabolic syndrome criteria (or Pre-Metabolic Syndrome). Blood pressure and increased waist circumference are independently associated with LV diastolic function. These functional abnormalities may partially explain the increased cardiovascular morbidity and mortality associated with metabolic syndrome in our population.

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