The Impact of Metabolic Syndrome on Left Ventricular Performance: As Evaluated by Using Echocardiographic Examination

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***Abstract*- Objective**: there is a possible etiologic link between metabolic syndrome and left ventricular dysfunction. In this regard, this study was conducted to evaluated left ventricular function in patients with metabolic syndrome using ECHO.

Patients and methods: Forty adult patients with metabolic syndrome were recruited from the outpatient department of medicine at Misr University for Science and Technology (MUST) and forty adult serves as control. MS was defined by the presence of 3 or more of ATP-NCEP III criteria. Height, weight and waist circumference will be measured according to a standardized protocol. Body mass index will calculate by dividing weight in kilograms by height in meters squared (kg/m). The waist circumference was measured at its smallest point with the abdomen relaxed. MS subjects were grouped according to the number of criteria they fulfilled: 3 criteria (n=28), more than 3criteria (n=12). All subjects underwent laboratory blood tests, complete echocardiography. Echocardiography was used to assess systolic (LVEF, LVFS) and diastolic function.

Results: left atrium anteroposterior diameter was high in metabolic syndrome cases with more than three risk factors than control (P=0.035). Also, intraventricular septum was higher in group with 3 factors (P=.040) and group with more than 3 factors (P= .012) than control group. By comparing diastolic dysfunction among the three studied groups there was statistically significant difference and by doing multiple comparison the difference was found between control and the group with 3 factors (P=0.001), also there was statistical difference between control and group with more than 3 factors (P=0.003) while there is no significant difference between both metabolic syndrome groups (P = 0.490).

Conclusion: Impaired left ventricular diastolic function and preserved systolic function in metabolic syndrome patients.

***Index Terms*-** metabolic syndrome, diastolic dysfunction, left ventricular performance, hypertension.

I. Introduction

Metabolic syndrome (MS), a highly prevalent condition, characterized by a constellation of fasting hyperglycemia, hypertriglyceridemia, low high density lipoprotein cholesterol (HDL), hypertension, and abdominal obesity (Eckel et al., 2005; Grundy et al., 2005). Metabolic syndrome is considered a common cause of the development of cardiovascular disease (CVD) and type II diabetes mellitus (DM) (Reinhard et al., 2006). At present the MS is already affecting more than a quarter of the world's adult population. Its prevalence is further growing in both adults and children due to a life style characterized by high calorie nutrition combined with low physical activity (Ford et al., 2010; Friend et al., 2013). It is well-known how certain risk factors like hypertension, diabetes or obesity affect the structural and functional changes of the left ventricle (Andersen et al., 2003; Powell et al., 2006). A small number of studies have focused on examining the impact of the metabolic syndrome (Mahmud et al., 2009). Previous studies have shown that preclinical LV diastolic dysfunction and LV hypertrophy are strong risk factors for the future development of heart failure with preserved ejection fraction (Bella et al., 2002; Kane et al., 2011) The mechanisms of progression to heart failure were not understood definitely. In the MS, LV diastolic function and LV hypertrophy appear to worsen with the increasing number of risk factors for MS (Azevedo et al., 2007). These findings may be the cause of cardiovascular morbidity and mortality that is associated with metabolic syndrome. Whether these associations are because of age-related changes, hypertension, or other cardiometabolic effects of MS remains unclear. Further, the true prevalence of preclinical diastolic dysfunction in MS and relation to components of the MS are not well defined. These findings might need further investigations to define mechanisms by which MS is associated with development of heart failure (Ford et al.,2005).

II. Patients and Methods

Forty adult patients with metabolic syndrome were recruited from the outpatient department of medicine at Misr University for Science and Technology (MUST).MS was defined as meeting 3 or more of the following criteria: The diagnosis of MetS was made as per the International Diabetes Federation (IDF) criteria (Alberti et al., 2006). According to this criteria, diagnosis of MetS was performed with waist circumference ⩾90 cm for men or ⩾80 cm for women along with any two of the following: triglyceride (TGL) levels ⩾150 mg/dL or

treatment for elevated TGL, HDL Cholesterol (HDLC) levels ⩾40 mg/dL for men or ⩾50 mg/dL for women; blood pressure ⩾130/85 mmHg or undergoing antihypertensive treatment, and fasting blood glucose levels ⩾100 mg/dL or treatment for DM. The anthropometric measurements (height, weight, waist circumference) were taken from all subjects included in the study in order to calculate body surface (BSA) and body mass index (BMI). Regarding laboratory analyses, we used the level of random blood sugar, low and high-density lipoprotein cholesterol (HDL, LDL) and triglycerides. Arterial blood pressure values were obtained by measuring the average value of 2 consecutive measurements in the sitting position with 5 minutes between measurements in the morning hours, obtained by conventional sphygmomanometer.

The diagnosis of diabetes was based on the criteria of the World Health Organization published in 2006, (WHO Guideline Development Committee., 2006) and arterial hypertension was diagnosed according to recommendations of the European Association for Hypertension in 2007.

Exclusion criteria will include Patients aged above 70 years, significant coronary artery disease, history of myocardial infarction, cardiomyopathy, valvular heart disease, atrial fibrillation, atrioventricular block and Patients with other secondary causes of hyperlipidemia like hypothyroidism and renal insufficiency.

Echocardiographic study

Standard trans-thoracic echocardiographic studies with machine-integrated ECG recording were performed using Vivid S5 machines with an M3S matrix array probe with a frequency range from 1.7 to 3.2 MHz (GE Vingmed, Horten, Norway). All studies were done with patients lying in the left lateral decubitus position and breathing quietly. A comprehensive echocardiographic study following standardized protocols (Lang et al., 2015; Rudski et al., 2010) was performed for all subjects and all recorded studies were revised by an echocardiographer accredited by the European Association of Cardiovascular Imaging. From the parasternal window, parasternal short axis views were obtained by placing the transducer in the left third or fourth intercostal space adjacent to the sternum with the knob pointing toward the right shoulder. The transducer was then angulated superiorly and inferiorly to obtain the papillary muscle level. From the papillary muscle level after confirming a true short axis view that was perpendicular to the center of the true long axis of the left ventricle (LV), measurements for the LV posterior wall thickness at end diastole (PWd), interventricular septum at end diastole (IVSd), LV internal dimensions at end diastole (LVEDD) and end systole (LVESD) were obtained. Measurements were made from the leading edge of the septal endocardium to the leading edge of posterior wall endocardium (Lang et al., 2015).

From the parasternal long axis view, anteroposterior left atrial (LA) diameter was measured perpendicular to the aortic root long axis, at the level of the aortic sinuses by using the leading-edge to leading-edge convention at end systole, just before mitral valve opening representing the maximal LA volume. In addition, aortic root diameter (at the maximal diameter of the sinuses of Valsalva) was obtained from the same view. Sometimes moving the transducer closer to the sternum was done to allow visualization of a longer portion of the ascending aorta and again measurements were made using the leading-edge to leading-edge convention (Lang et al., 2015).

Right ventricular outflow dimension (RVd) was measured in diastole from the parasternal short axis view from the leading edge of anterior wall endocardium to the leading edge of the septal endocardium. Visualization of the RV anterior wall was optimized by placing the transducer in a high left parasternal position as close as possible to the sternal border (Rudski et al., 2010) LV fractional shorting (FS) was assessed, in addition to, LV ejection fraction (LVEF) which was assessed using the Teichholz method. LV mass was calculated using the linear cube method (Lang et al., 2015).

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and the analysis of equal variance (ANOVA) was used to detect differences between groups as they showed normal distribution. Results with $p < 0.05$ were considered to be significant.

III. RESULTS:

Table 1. Comparison of demographic and clinical characteristics.

variables	Control(mean±SD)	Three factors (mean±SD)	More than three factors	P-value
Age	48.13±4.89	54.46±6.70	53.33±5.53	.000*
H(cm)	171.70±9.48	163.88±6.30	161.83±6.15	.000*
Wt(kg)	74.58±11.05	98.33±17.15	89.17±11.43	.000*
BMI	25.13±1.37	36.21±7.53	33.79±5.14	.000*
WC (cm)	84.90±8.21	119.65±14.36	116.92±13.94	.000*
SBP	116.65±7.14	147.13±22.56	149.17±32.32	.000*
DBP	76.63±4.06	88.95±10.73	87.50±13.06	.000*
RBS	85.90±7.90	121.78±68.66	129.17±39.21	.003**
TG	131±17.32	121±68.66	198.42±46.67	.001**
HDL	51.98±5.75	43.68±8.47	39.17±5.24	.000*

MetS: metabolic syndrome; BMI: Body mass index; HDLC: high density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; RBS: random blood sugar; LDL: low density lipoprotein cholesterol; TG: triglyceride.
*Indicates a significant *p*-value ($p < 0.05$). P value by ANOVA (*); P value by Kruskal-Wallis Test (**).

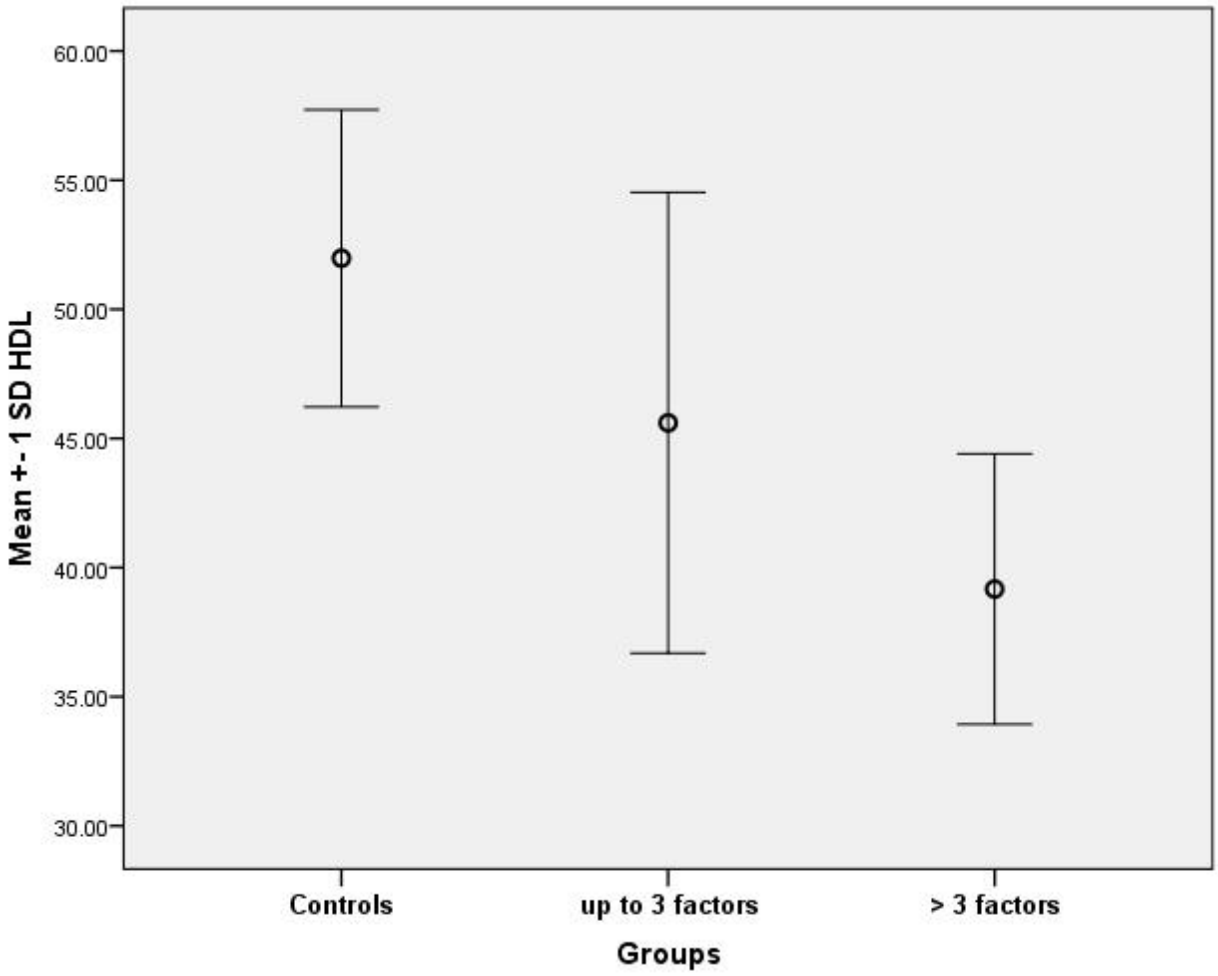

Figure (1): Effect of increase number of metabolic syndrome factors on high density lipoprotein

Table 1 (b): sex distribution among cases and metabolic syndrome sub groups: -

Sex	Control N %	3 factors N %	More than three factors N %	P-value
Female	25 62.5%	14 50.0%	8 66.7%	.490
Male	15 37.5%	14 50.0%	4 33.3%	.490

There was no statistically important difference in sex distribution between MS subgroups and controls (P=0.490). Among subjects with MS, 28 of them (70%) had 3 risk factors, and the remaining 12 patients (30%) had more than three risk factors.

Among the patients with metabolic syndrome, the most common risk factors were high blood pressure (90%), followed by low HDL-C levels (56%), diabetes (47%), hypertriglyceridemia (40%) which were almost equally presented. Comparison of all demographic and clinical characteristics of the study population are summarized in Table 1.

If the subgroups with 3 and more than three risk factors are considered separately, distribution of risk factors is different. In this case, in the subgroup with 3 criteria the most common factor was hypertension (93%), low HDL with 39% was in second place, elevated glucose level was third (36%), and higher level of triglycerides had the lowest prevalence (18%). In the subgroup with more than 3 risk factors, low HDL was in first place (91%), hypertension in second place (83%), higher level of triglycerides was third (75%), elevated glucose level was right behind, and had the lowest frequency (58%). Values of all the

parameters of MS were significantly higher in all MS subgroups compared to controls (Table 1). No statistically significant difference was shown in almost all parameters of the metabolic syndrome subgroups, except for HDL level, which decreases with the increasing number of factors (Fig 1).

Table 2: Comparison of Echocardiographic Parameters between Metabolic Syndrome and Non–Metabolic Syndrome Patients

variables	Control(mean±SD	Case (mean±SD)		P-value
		3 factors	More than 3 factors	
LVED(mm)	46.63±4.88	48.39±5.40	45.67±3.80	.198*
LVES(mm)	28.88±4.44	30.57±5.22	28.33±3.47	.234*
EF%	67.30±5.95	67.79±9.57	70.42±5.04	.433*
FS%	37.37±8.29	36.61±7.71	37.67±4.31	.892*
LA(mm)	33.13±4.35	35.82±4.11	33.50±3.34	.030*
AO(mm)	28.78±4.49	30.75±4.44	27.67±5.45	.099*
IVS	9.52±1.61	10.32±1.59	10.58±1.08	.019**
PW	9.30±2.18	10.00±1.49	9.67±1.23	.550**

P value by ANOVA (*); P value by Kruskal-Wallis Test (**).

LVED: LV end-diastolic diameter; LVESD: LV end-systolic diameter; EF%: ejection fraction; FS: fractional shortening; LA: left atrium; AO: Aortic root dimension, IVS: Interventricular septum; pw: Posterior Wall thickness.

On comparing absolute echocardiographic measurements in subjects it was found that There were no statistical differences in the LVED ($P_{=}$0.198), LVES (P=0.234) between the observed subgroups, nor when compared to the controls (Table 2). LV ejection fraction was 68.58±8.48 versus 67.30±5.95 with no significant difference between metabolic syndrome subgroups and control (p = 0.439). In addition, LV fractional shortening was 36.92±6.83 in cases versus 37.36±8.29 in control with no significant different between observed metabolic syndrome subgroups and control (P= 0.796). Also, there is no significant different between metabolic syndrome patients and control group regarding posterior wall thickness and septal wall thickness.

However, left atrium anteroposterior diameter was high in metabolic syndrome cases with more than three risk factors than control ($P_{=}$0.035). Also, intraventricular septum was higher in group with 3 factors ($P_{=}$.040) and group with more than 3 factors (P= .012) than control group (Figure 2).

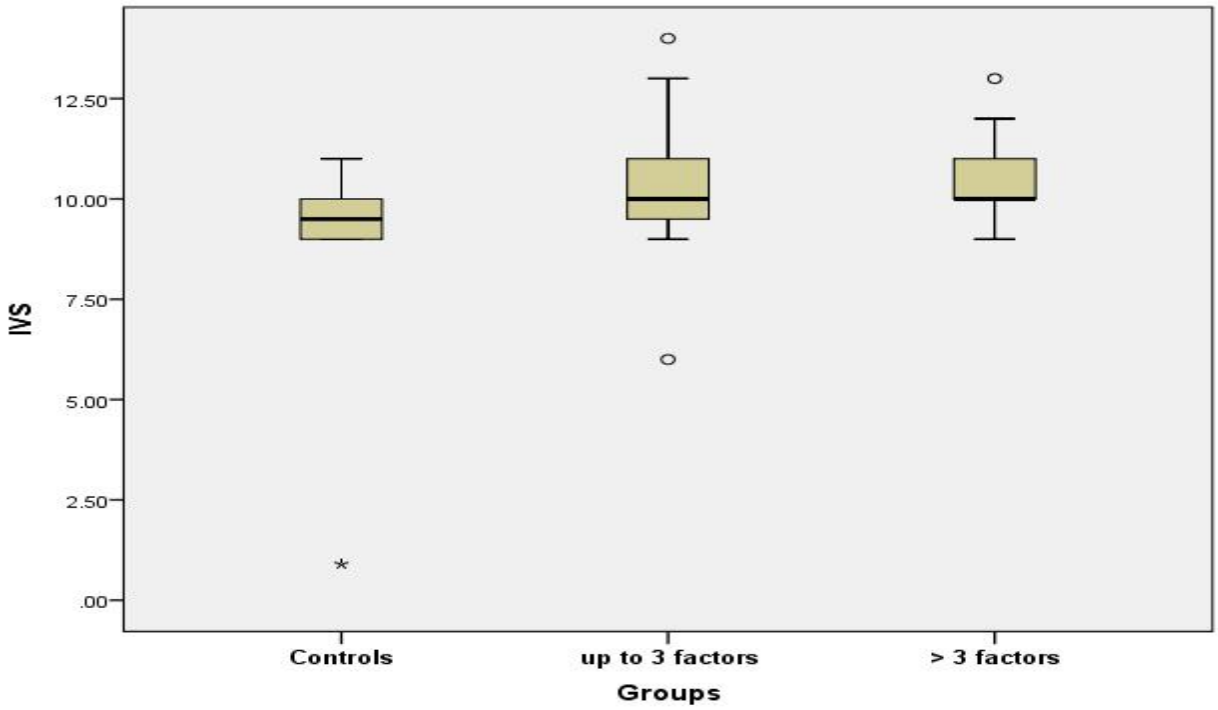

Figure (2): Effect of metabolic syndrome on intraventricular septum.

Table 3 a: Diastolic dysfunction among metabolic syndrome cases and controls.

Diastolic dysfunction	Control		3 factors		More than three factors		P-value
	N	%	N	%	N	%	
present	3	7.5	18	64.3	6	50.0	<0.001
absent	37	92.5	10	35.7	6	50.0	<0.001

By comparing diastolic dysfunction among the three studied groups there was statistically significant difference, however by doing multiple comparison the difference was found between control and the group with 3 factors (P=0.001), also there was statistical difference between control and group with more than 3 factors (P=0.003) while there is no significant difference between both metabolic syndrome groups (P = 0.490) (figure 3).

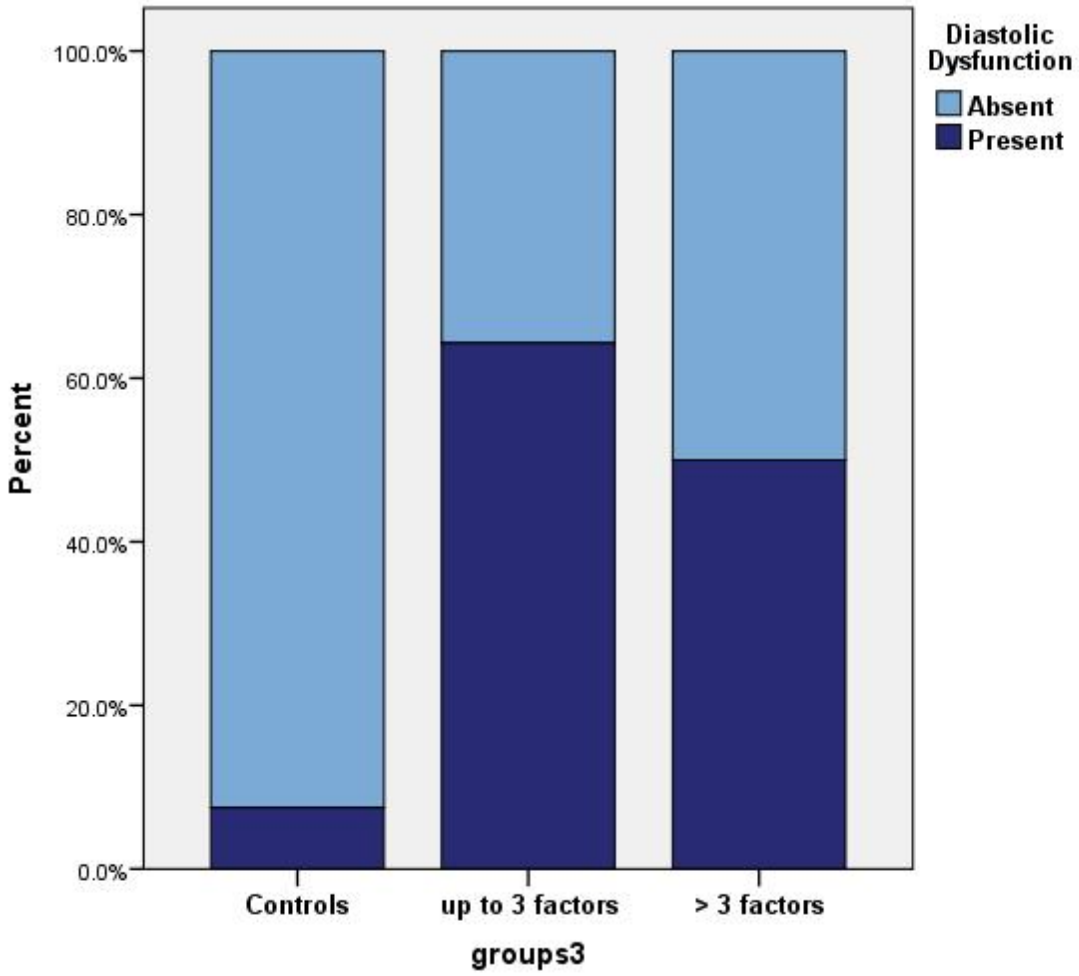

Figure (3); Diastolic dysfunction among metabolic syndrome cases and control

Table 3 b: Mean diastolic blood pressure among patients with and without diastolic dysfunction

	Present (mean±SD)	Absent (mean±SD)	p-value
DBP	(92.0±11.10)	(84.4±8.5)	(P=.026)

Age, sex, clinical and echo parameters were compared among patients with and without diastolic dysfunction within metabolic syndrome sub groups and control and the result was that no significant relations were found except for significantly higher (P=.026) diastolic blood pressure (92.0±11.10) among cases with diastolic dysfunction compared to cases without diastolic dysfunction (84.4±8.5).

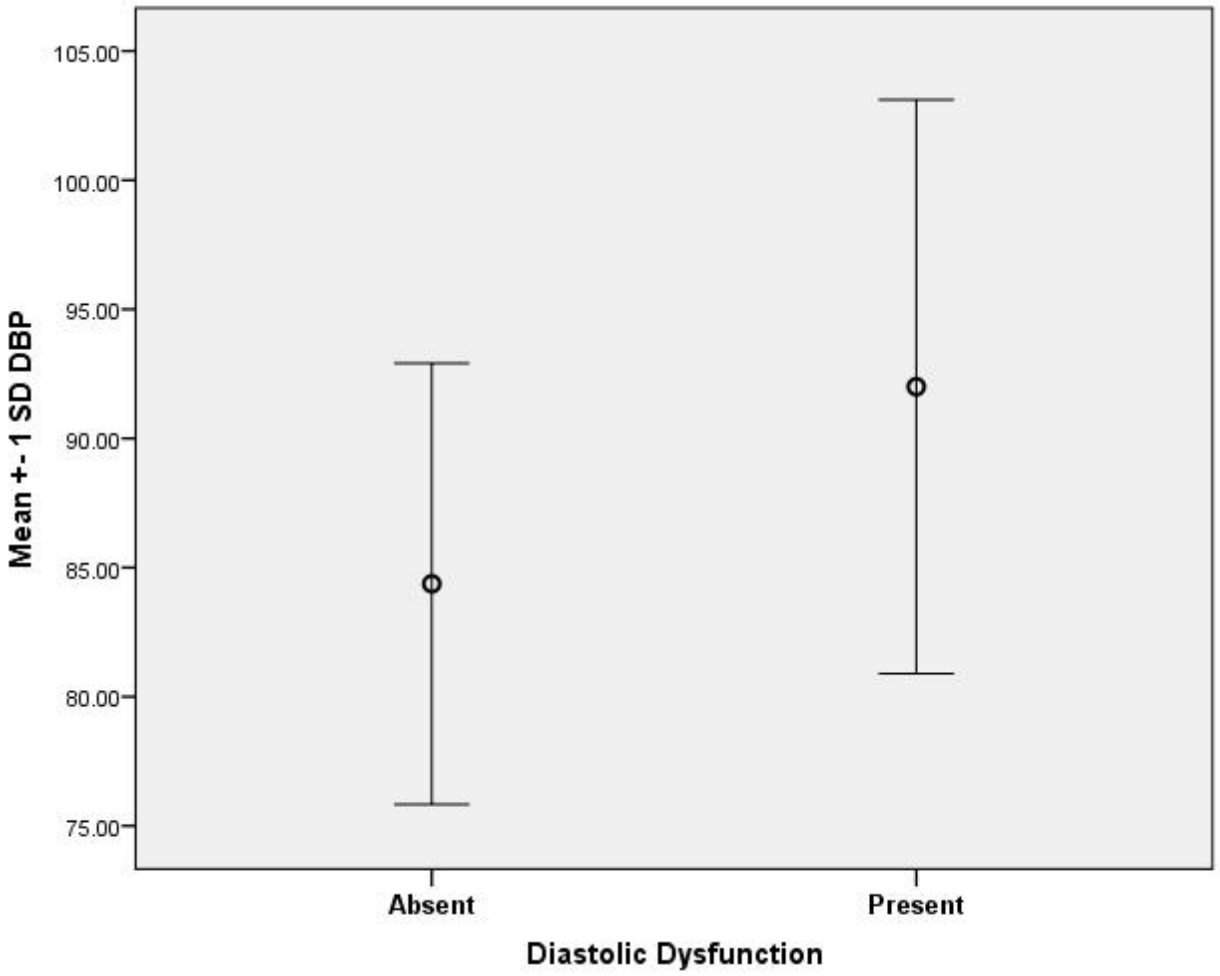

Figure (4); Effect of blood pressure on diastolic dysfunction among metabolic syndrome cases

IV. Discussion

Although the influence of diabetes mellitus on left ventricular function has been studied extensively, there is no available data regarding the impact of metabolic syndrome on left ventricular function. Furthermore, the high prevalence of insulin resistance in patients with idiopathic dilated cardiomyopathy compared with healthy control subjects (Witteles RM et al.,2008), suggesting a possible etiologic link between metabolic syndrome and left ventricular dysfunction. In this regard, this study was conducted to evaluate left ventricular function in patients with metabolic syndrome using ECHO.

In the present study, values of all parameters of MS were significantly higher in persons with MS compared to controls, but there were no significant differences among the 2 MS subgroups. Individual factors of MS in this investigation were not equally distributed in the MS group and its subgroups.

The mean value of BMI was 36.21 ± 7.53 in the study cases, while in the study by Turhan et al., 2009 it was 30 ± 4. In their recent guidelines, the Indian Council of Medical Research (ICMR) lowered the BMI threshold for Indians due to the higher incidence of insulin resistance than their western counterparts (Misra A et al.,2009). According to this classification, BMI of less than 18.4 kg/m2 is underweight, 18.5–22.9 kg/m2 is normal, 23–24.9 kg/m2 is overweight, and more than or equal to 25 kg/m² is considered obese. Using this new classification, 93% of cases and 53% of controls were obese. We also found that both visceral obesity assessed by waist circumference and obesity assessed by BMI is predictive of MetS. This was explained by the fact that among our cases all had abdominal obesity by definition and 93% were obese (BMI > 25 kg/m2). This is in accordance with the finding that increased intra-abdominal fat is associated with worse metabolic profile and elevated pro-inflammatory cytokines, as in the study published by Després and Limieux in Nature in 2006. The same finding was also noted in the study by Voulgari et al.

The analysis of echocardiographic parameters of the left ventricle structure showed that left atrium anteroposterior diameter was high in metabolic syndrome cases with more than three risk factors than control ($P_{=}0.035$) which corresponds to the findings of other authors (Azevedo A et al., 2007). Also, intraventricular septum was higher in group with 3 factors ($P_{=}.040$) and group with more than 3 factors (P= .012) than control group. However, there are studies that have shown that no differences in the left ventricular diameters between the

control group and the 2 subgroups with MS (de las Fuentes L et al., 2007; Adult Treatment Panel III (2001)).

The traditional parameters of systolic left ventricular function (ejection fraction and fractional shortening) were not different among the observed groups. Previous studies have investigated the LV functions in patients with MS, but consensus is still lacking (Masugata et al., 2006; Wong et al., 2005). Grandi et al. (2006) have reported that only LV diastolic function is reduced in metabolic syndrome, although LV systolic function is normal which is consistent with the current study. Masugata et al. also have found that cardiac diastolic function was impaired in patients with metabolic syndrome even if they have neither LV hypertrophy nor systolic dysfunction. In contrast, Wong et al, 2005 have reported that metabolic syndrome is associated with both LV systolic and diastolic dysfunctions in subjects with significant risk factors but no cardiovascular disease.

The prevalence of left ventricular diastolic dysfunction in subgroups of MS

Azavedo et al. found that the prevalence of the left ventricle diastolic dysfunction increases from 20% to 36% starting from the group without risk factors to subjects with 4 or 5 risk factors (Azevedo et al., 2007), while Fuentes et al. revealed that the prevalence of diastolic dysfunction was 7–9% in the control group, 17–18% in the group with pre-metabolic syndrome (1 or 2 criteria), and 29–35% in the group with metabolic syndrome (Fuentes et al., 2007). In the present study, left ventricle diastolic dysfunction was observed in 7.5% of the controls, 64% in the group with 3 factors, 50% in the group with more than 3 risk factors. The slightly higher percentage of left ventricular diastolic dysfunction in this study could be explained by the higher proportion of hypertensive patients and significantly higher values of systolic and diastolic blood pressure compared to the aforementioned studies. The pathophysiological mechanism by which MS can lead to abnormalities in LV diastolic function is not well understood. In mouse models of diet-induced MS, increased myocardial oxidative stress has been implicated in the development of diastolic dysfunction and was associated with both hypertrophy and fibrosis of the myocardium (Kuster, 2010). Animal models of insulin resistance, hypertension, or dyslipidemia have also implicated the development of cardiac fibrosis, abnormal intracellular calcium handling (Kuster, 2010). cardiomyocyte lipotoxicity, mitochondrial dysfunction, impaired endothelial blood flow, increased vascular stiffness, and inflammation (Katz et al., 2006). Although mechanistic inferences cannot be drawn from our observational study, these results support the notion that metabolic heart disease can lead to impaired myocardial relaxation in the absence of LVH. Further studies are needed to elucidate potential mechanisms and potential therapeutic targets. Results for studies of the association of SBP with parameters of LV function have shown that hypertension may have been responsible for the diastolic dysfunction observed in the current study. Hypertension causes increased arterial stiffness and thickness, which may be partly responsible for the myocardial changes because of an abnormal ventriculoarterial interaction (Wong et al., 2005). However, prior studies that identified hypertension and obesity as independent predictors of impaired LV diastolic function (Peterson et al.2004;

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