Research Article

Influence of C-reactive protein and Metabolic Syndrome on the Prevalence of Subclinical Left Ventricular Diastolic Dysfunction - 🔓

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ABSTRACT

Background: Metabolic Syndrome (MetS) has been associated with subclinical changes in cardiac structures and function, including Left Ventricular Diastolic Dysfunction (LVDD). Subclinical LVDD, is strong risk factors for the future development of clinical Heart Failure (HF). Inflammation has a pivotal role in cardiac remodeling and markers of systemic inflammation such as C-Reactive Protein (CRP) independently predict future Heart Failure (HF).

Objective: We sought to determine the influence of CRP and MetS on the prevalence of subclinical LVDD in the patient with MetS.

Methods: We conducted a multicenter observational cross-sectional study. Recruited were 550 consecutive participants, 450 with MetS (mean age 50 years, 49% women) stratified by presence of subclinical LVDD (179 participants with MetS and subclinical LVDD and 271 participants with MetS and normal LVDF), and 100 controls (no risk factors for MetS (mean 51 years, 57% women), who attended outpatient visits at general cardiology Health Care Clinics in 6 town on western region Republic of Macedonia, during 1 calendar year. Participants underwent echocardiography with tissue Doppler imaging.

Results: The overall prevalence of subclinical LVDD in participants with MetS was (39, 7%; *p* = 0.0005). The prevalence of subclinical LVDD in participants with MetS and CRP levels above 3.0 mg/ L was higher when compared with participants with MetS and CRP levels below 3.0 mg/ L{(117 *vs.* 63 (65% *vs.* 35%) *p* = 0.001)}.

CRP levels, was significantly higher in the group with MetS and subclinical LVDD when compared with MetS and normal diastolic function group. (6.6 ± 1.4 *vs.* 3.7 ± 0.6 *p* = 0.000).

There were significant association of increased levels of CRP and: subclinical LVDD (OR = 2.171; 95% CI 1.869-2.522), increased number of risk factor for MetS (OR = 1.7; OR = 2.3), Body Mass Index (BMI). (OR = 1.5) and presence of Diabetes Mellitus Type 2{(T2DM), (OR = 1.2)}.

Conclusions: Patients with MetS and higher levels of CRP have higher prevalence of subclinical LVDD than patients with MetS and lower levels of CRP. CRP a marker of inflammation, may be a marker of subclinical LVDD in MetS patients, underlining the importance of inflammation in evolution of MetS to subclinical cardiac damage.

Keywords: C-reactive protein; Subclinical left ventricular diastolic dysfunction; Metabolic Syndrome

ABBREVIATIONS

MetS: Metabolic Syndrome; CRP: C-Reactive Protein; BW: Body Weight; BH: Body Height; BMI: Body Mass Index; BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; T2DM: Diabetes Mellitus Type 2; Wci: Waist Circumference; CVD: Cardio-Vascular Disease; CHD: Coronary Heart Disease; LV: Left Ventricular; LVDF: Left Ventricular Diastolic Function; LVDD: Left Ventricular Diastolic Dysfunction; HF: Heart Failure; HF-Nef: Heart Failure With Normal Ejection Fraction; CVHD: Cardio-Vascular Heart Disease; DF: Diastolic Function; DD: Diastolic Dysfunction; HDL-C: Serum High Density Lipoproteins Cholesterol: TG: Serum Triglycerides; TDI: Tissue Doppler Imaging; LVEF: LV Ejection Fraction; LAVI: Left Atrial Volume Index; IVRT: Isovolumetric Relaxation Time; DCT: Deceleration Time; ASE: American Society Of Echocardiography

INTRODUCTION

The Metabolic Syndrome (MetS) is defined as a combination of several risk factors associated with cardiovascular disease and Type 2 Diabetes (T2DM); estimates suggest that this disorder affects approximately 35% of the adult population [1,2]. MetS, has been associated with subclinical changes in cardiac structures and function, including Left Ventricular Diastolic Dysfunction (LVDD) [3]. Previous studies have shown that subclinical LVDD, is strong risk factor for the future development of clinical Heart Failure (HF), and specifically increase the risk of Heart Failure with Preserved Ejection Fraction (HFpEF) [4,5]. The pathways leading to subclinical LVDD are diverse, and mechanisms of progression to HF poorly understood.

Experimental and observational evidence suggests that inflammation may play a central role in the pathogenesis of cardiovascular disease [6]. Inflammation has a pivotal role in cardiac remodeling, and markers of systemic inflammation such as C-Reactive Protein (CRP) independently predict future HF [7]. CRP is associated with all parameters of the MetS [8] and has been acknowledged to be an independent but not causal risk factor for incident cardiovascular disease [9].

In MetS, diastolic dysfunction is usually attributed to the increased hemodynamic [10,11]. Alternatively, diastolic dysfunction may also be secondary to the altered metabolic-inflammatory milieu. Changes in this balance may therefore influence ventricular relaxation and compliance [12]. In the MetS, LV diastolic function appear to worsen in a stepwise fashion with the number of risk factors for MetS [13]. These findings may account in part for the augmented cardiovascular morbidity and mortality that is associated with MetS [14]. Diastolic function evaluation has been used to identify cardiac subclinical changes. Diastolic dysfunction is prevalent in patient with MetS and predict a worse outcome independently of any other co-morbidity [15]. The dramatically increasing prevalence of the MetS, is therefore, an important public health concern [16].

However, there are few data regarding the relationships among CRP and subclinical LVDD assessed by echocardiography in the patient with MetS. We set out to determine the influence of CRP on the prevalence of subclinical LVDD in the patient with MetS. We tested hypothesis: Patients with MetS and high level of CRP have higher prevalence of subclinical LVDD than patients with MS and lower level of CRP. These findings might lend further insight into potential mechanisms by which MetS is associated with eventual development of HF.

OBJECTIVE

We sought to determine the influence of CRP on the prevalence of subclinical LVDD in the patient with MetS.

METHODS

Study design

We conducted a multicenter observational cross-sectional study.

The study included data summarized in our previous paper for Metabolic Syndrome prevalence, using the same data, so the survey methodology has been described elsewhere [17]. Briefly, a total of 550 consecutive participants, 450 with MetS (222 women and 228 men) stratified group of participants with MetS and subclinical LVDD, group of participants with MetS and normal LVDF, and 100 controls without MetS, who attended outpatient visits at general cardiology Health Care Clinics in 6 town on western region Republic of Macedonia, during 1 calendar year (from November 2016 to November 2017).

MetS was defined according to the harmonized definition of the International Diabetes Federation and other organizations [18] that three or more out of five following criteria are considered as MetS: (1) central adiposity {Waist Circumference (WCi) > 102 cm in men and > 88 cm in women}; (2) serum HDL-C < 50 mg/ dL in women or < 40 mg/ dL in men; (3) serum triglyceride levels > 150 mg/ dL; (4) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or use of antihypertensive drugs; (5) the presence of T2DM or use of anti-diabetic drugs. Participants with existing cardiovascular disease {(heart failure, Left Ventricular Ejection Fraction (LVEF) < 50%, coronary artery disease, congenital or acquired valvular heart disease, cardiomyopathies, cardiac wall hypertrophy, cardiac arrhythmias)}, patient with history of stroke, pregnancy, lactation, musculoskeletal dysfunction, inflammatory or chronic liver disease, thyroid dysfunction and/or use of corticosteroids or anorectic drugs were excluded from the study.

All participants underwent a comprehensive medical history and physical examination. Resting ECG, anthropometrics, blood pressure (obtained after 10 min of rest in the sitting position, expressed as the average of 3 consecutive measurements). Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg and/or current anti-hypertensive therapy [19]. Diabetes mellitus was defined as a fasting serum glucose level ≥ 126 mg/ dL and/or current medical therapy with an oral hypoglycemic agent and/or insulin [20]. Body Mass Index (BMI) was calculated as weight (kg) divided by the square of the height (m²) .Weight was measured with weight balance scales, and height with stadiometer. WCi, was reported in cm. An overnight fasting blood sample, was drawn from each patient to determine: blood glucose, lipid profile tests Total Serum Cholesterol (TC), serum High Density Lipoproteins Cholesterol (HDL-C), Serum Triglycerides (TG). The sample analysis was performed using standard biochemical analytical methods. Plasma CRP levels was measured using latex particle-enhanced immunoassay with the mephelometry (Roche Swiss). Consistent with recommendations from Centers for Disease Control and Prevention (a CRP cut point of 3.0mg/L), was used to differentiate high-risk and low-risk group [21].

Echocardiographic measurements: M-mode, two-dimensional and Doppler echocardiography, were performed and/or reviewed by experienced staff cardiologists, compliant with the recommendation of the American Society of Echocardiography (ASE), stored in DICOM format and later reviewed by two experienced echocardiographers [22]. Briefly, the Left Ventricular (LV) linear dimensions were measured from a parasternal long-axis view according the recommendations of the ASE [21]. The LV mass was calculated with a validated formula and indexed for Body Surface Area (BSA) [23]. The LV relative wall thickness was calculated as follows: (2 x posterior wall thickness) divided by end-diastolic diameter [24]. The LV Ejection Fraction (EF), was calculated by biplane modified Simpson's rules. From an apical 4-chamber view, transmitral flow was sampled by

pulsed-wave Doppler at the level of mitral valve leaflet tips. Peak velocities of the early phase (E) and late phase (A), of the mitral inflow were measured, and their ratio (E/A) was calculated. Left ventricular myocardial velocities were evaluated by Tissue Doppler Imaging (TDI). Pulse TDI sample volume was placed at the level of the lateral and septal mitral valve annulus, and peak early diastolic velocities (e') were measured and then averaged. The ratio between E and e' (E/ e') was calculated.

Diastolic function: We used measurements of LA size, tissue Doppler and Doppler of mitral flow as parameters of Diastolic Dysfunction (DD), and the cut-offs were set according to previously published data and international guidelines [25-27]. We defined LA size as normal (< 2.2 cm/ m²), moderately enlarged (2.2–2.79 cm/ m²) and severely enlarged (≥ 2.8 cm/ m²). E/A ratio, the ratio of the E-wave and peak late LV filling (A-wave), was divided into low (< 1.0), normal (1.0–2.0) and high (> 2.0). The early myocardial peak velocity of the mitral annulus, tissue Doppler E' wave (the average of the septal e' and lateral e' measurements), was defined as decreased (< 9 cm/ s) or normal (≥ 9 cm/ s). E/e' the ratio of peak early LV filling (E-wave) and average tissue Doppler e' wave, was stratified into normal (< 8) and increased (≥ 8). We defined DCT, the deceleration time of early filling velocity, into low (< 140 ms), normal (140–220 ms) and high (> 220 ms). Isovolumetric Relaxation Time (IVRT) was either reduced (< 60 ms), normal (60–110 ms), or prolonged (> 110 ms). The ratio of the transmitral early and late filling phases (E/A) was calculated as a measure of diastolic function. The ratio of early filling and early myocardial velocity (E/e') was calculated as a noninvasive index of LV filling pressure.

Definition of diastolic dysfunction was as follows:

- LAVI > 34 mL/ m².

- E/A < 0.8; e' < 8 cm/s; mean E/e' ≥8: impaired relaxation (DD) of grade I.

- E/A ≤ 1.5; e' < 8 cm/s; mean E/e' 9 - 12: pseudo-normalized pattern (DD of grade II).

- E/A > 2; e' < 8 cm/s, and mean E/e' ≥ 13: restrictive patter n (DD of grade III).

- Elevated LV filling pressure was defined as when E/E' ratio exceeded 14.

Throughout all echocardiographic findings, a consensus reading was again applied. The study is in compliance with the Declaration of Helsinki. All patient that participated in this study were written informed, consent was obtained from all participating patients before they were enrolled into the study.

Statistical analysis

Results are expressed as mean and ± SD, or as percentage. A simple descriptive analysis was performed for the general characterization of the sample and distribution of variables. The distribution of variables was tested for normality using the Kolmogorov-Smirnov test, and the heterogeneity of variances was evaluated by Levene's test. To compare baseline characteristics and echocardiographic findings between groups, we used student's unpaired t test for continuous data, Mann-Whitney U-test for continuous data with abnormal distribution, and X^2-test for categorical data. The association between variables were analyzed using logistic regression. Odds Ratio (OR) and 95% Confidence Interval (CI) were estimated by logistic regression. A p value < 0.05 was considered statistically significant for a confidence

interval of 95%.Statistical analyses were performed with the SPSS software package (SPSS 19.0).

RESULTS

Demographics

A total of 550 subjects were enrolled in our study, including 450 subjects with MetS (mean age 50, 6 years, 49% women), and 100 controls without MetS (mean age 50, 1 years, 57% women). Baseline demographic, anthropometric, laboratory and echocardiographic characteristics by group are displayed in table 1. Overall, subjects with MetS had a worse cardiovascular risk factor profile, including higher BMI (25,5 ± 3,2 *vs.* 24,3 ± 0,7 $p = 0.0$), higher BP(135,7 ± 18,4 *vs.* 118, 7 ± 2,2 $p = 0.04$; 87,9 ± 10,5 *vs.* 78,7 ± 3,1 $p = 0.006$), increased WCi (97.5 ± *vs.* 84.7 ± 7.8 $p = 0.00$) and dyslipidemia. (HDL-0,9 ± 0,2 *vs.*1,2 ± 0,6 $p = 0.00$; Tg-1,9 ± 0,4 *vs.* 1,4 ± 0,1 $p = 0.04$). CRP level was significantly higher in the group with MetS when compared with controls without MetS (4.9 ± 1.7 *vs.* 1.5 ± 0.2 $p = 0.000$). Subjects with MetS when compared with controls without MetS had worse measures of diastolic function including: higher LAVI (39,7% *vs.* 6% $p = 0.00$), lower E/A ratio (39,7% *vs.* 6% $p = 0.00$) and lower mean e'(8.1 ± 0.5 *vs.* 8.5 ± 0.3), higher E/e' ratio (39,7% *vs.* 6% $p = 0.00$), increased DCT (199,7 ± 1.2 *vs.* 183.3 ± 20.14 $p = 0.000$) and IVRT (101.9 ± 22.1 *vs.* 89.5 ± 10.12), increased LVMI (59.5 ± 1.9 *vs.* 32.1 ± 7.5 $p = 0.00$).

Baseline demographic, anthropometric, laboratory and echocardiographic characteristics of participants with MetS stratified into the group of participants with subclinical LVDD and group of participants with normal LVDF are displayed in table 2. The overall frequency of subclinical LVDD in participants with MetS, was 39,7%;

$p = 0.0005$). Participants with subclinical LVDD had higher CRP levels 6.6 ± 1.4 *vs.* 3.7 ± 0.6, $p = 0.000$. Overall, participants with subclinical LVDD had a worse cardiovascular risk factor profile including: increased WCi (99,1 ± 8,8 *vs.* 94,9 ± 8,0 $p = 0.001$); higher BMI (26,9 ± 3,1 *vs.* 24,6 ± 3,0 $p = 0.001$; higher BP (SBP 138,3 ± 18,0 *vs.* 134,0 ± 18,5 $p = 0,000$; DBP 89,7 ± 10,2 *vs.* 86,8 ± 10,6; HDL-0,85 ± 0,1 *vs.* 1,0 ± 0,2 $p = 0.000$; TG-2,1 ± 0,5 *vs.* 1,7 ± 0,4 $p = 0.000$). Participants with subclinical LVDD, have higher number of risk factors for MetS than participants with normal diastolic function (42% *vs.* 23% $p = 0.002$; 23% *vs.* 0,7% $p = 0.001$. Participants with subclinical LVDD had worse measures of diastolic function including higher LAVI (34.6 ± 0.5 *vs.* 25.2 ± 1.3 $p = 0.00$), lower Mitral E peak wave (0,53 ± 0,1 *vs.* 0,76 ± 0,1 $p = 0.00$, higher Mitral A peak wave (0,81 ± 0,13 *vs.* 0,51 ± 0,8 $p = 0.00$), lower E/A ration < 0.8 (39,7% *vs.* 6% $p = 0.00$, lower mean e' (8,1 ± 0,5 *vs.* 8,5 ± 0,3 $p = 0.01$); E/ e' ratio ≥ 8 (39,7% *vs.* 6% $p = 0.00$), increased DT (m/s) > 200 (218,5 ± 24,1 *vs.* 187,4 ± 16,9 $p = 0.00$); increased IVRT (m/s) > 100. (124,9 ± 15,6 *vs.* 86,7 ± 8,38 $p = 0.00$).

Frequency of subclinical LVDD among group with MetS and subclinical LVDD stratified by levels of CRP are displayed in table 3 and figure 1. The frequency of subclinical LVDD in participants with MetS and CRP levels above 3.0 mg/ L was higher when compared with participants with MetS and CRP levels below 3.0 mg/ L{(117 *vs.* 63 (65% *vs.* 35%) Chi-square 10.9; $p = 0.001$)}.

Association between subclinical LV diastolic dysfunction, inflammation and metabolic syndrome. In a logistic regression (Table 4), we investigated the independent association of CRP levels with: subclinical LVDD, number of risk factor for MetS, T2DM and BMI. There were significant association of increased levels of CRP and subclinical LVDD (OR = OR = 2.171;

Table 1: Basic demographic, anthropometric, laboratory and echocardiographic characteristics of study population.

Variables		MetS (N.450)			Controls (N.100)			*p*-value
		N. (%)	Mean	± SD	N. (%)	Mean	± SD	
Gender	Females	222 (49.3)			57 (57%)			0.43
	Males	228 (50.7)			43 (43%)			0.41
Age (year)			50.6	± 3.9		50.1	± 3.7	0.18
BMI(kg / m²)			25.5	± 3.2		24.3	± 0.7	0.01*
SBP(mm Hg)			135.7	± 18.4		118.7	± 2.2	0.04*
DBP(mm Hg)			87.9	± 10.5		78.7	± 3.1	0.006*
T2DM		324 (72)			0 (0)			
WCi (cm)		381 (84)	97.5	± 8.7	0 (0)	84.7	± 7.8	0.00*
HDL-chol (mmol / l)		303 (67)	0.9	± 0.2		1.2	± 0.6	0.00*
Triglicer (mmol / l)		251 (56)	1.9	± 0.4	0 (0)	1.4	± 0.1	0.04*
CRP(mg / L)			4.9	± 1.7		1.6	± 0.2	0.000*
Three MetS risk fac.		248 (55)			0 (0)			
Four MetS risk fac.		139 (31)			0 (0)			
Five MetS risk fac.		63 (14)			0 (0)			
LAVI (ml / m²) > 34		179 (39.7)			0 (0)			
E (cm / s.)			0.77	± 2.2		0.87	± 0.12	0.00*
A (cm / s.)			0.63	± 0.8		0.54	± 0.11	0.00*
E/A ratio < 0.8		179 (39.7)			6 (6)			0.00*
e' (cm / s)			8.1	± 0.5		8.5	± 0.3	0.01*
E/ e' ratio ≥ 8		179 (39.7)			6 (6)		0.00*	
DT (m / s) > 200		179 (39.7)	199.7	± 1.2	6 (6)	183.3	± 20.14	0.00*
IVRT (m / s) > 100		179 (39.7)	101.9	± 22.1	6 (6)	89.5	± 10.12	0.00*
LVMI (gr / m²)			59.5	± 1.9		32.1	± 7.5	0.00*

Values are mean ± SD; Y = Year; BMI : Body Mass Index; SBP : Systolic Blood Presure; DBP: Diastolic Blood Pressure; T2DM: Diabetes Mellitus Type 2; Serum HDL-C: High Density Cholesterol; serum Triglicerides; hs-CRP: High Sensitive C-Reative Protein; WCi: Increased Weist Circumference; LVVI: Left Arial Volume Index; Mitral E: Peak Wave; Mitral A peak wave; E/A ratio: Early to late transmitral flow velocity; E/E⁻ratio: Early transmitral flow to average mitral tissue doppler; DT: Deceleration time; IVRT- Isovolumetric Relaxation Time; LVMI: Left Ventricular Mass Index; MetS: Number of risk factor present (three, four, five). Overall, subjects with MetS had a worse cardiovascular risk factor profile, including higher BMI, higher BP, increased WCi and dyslipidemia. $p^* < 0.05$ for between group comparison.

Table 2: Demographic, anthropometric and laboratory characteristics of group with subclinical LVDD (n-180) and group with normal LVDF (n-270) among patients with MetS (n = 450).

Variables		Gr with MetS (N.450)						P - value
		Gr with subclinical LVDD (n-180)			Gr with normal LVDF (n-270)			
		N (%)	Mean	± SD	N. (%)	Mean	± SD	
Gender	Females	122 (68)			100 (37%)			0.001*
	Males	57 (32)			171 (63%)			0.004*
Age (year)			51.5	± 3.5		50.1	± 3.8	0.68
BMI (kg / m²)			26.9	± 3.1		24.6	± 3.0	0.001*
SBP (mm Hg)		114 (64)	138.3	± 18.0	201 (74)	134.0	± 18.5	0,000*
DBP (mm Hg)			89.7	± 10.2		86.8	± 10.6	0.003*
T2DM		129 (72)			195 (71)			0.96
WCi (cm.)		149 (83)	99.1	± 8.8	232 (85)	94.9	± 8.0	0.001*
HDL-chlol (mmol / l)		168 (93)	0.85	± 0.1	135 (49)	1,0	± 0.2	0.000*
TG (mmol / l).		136 (76)	2.1	± 0.5	115 (42)	1,7	± 0.4	0.000*
CRP (mg / dL)			6.6	± 1.4		3.7	± 0.6	0.000*
Three MetS risk fac.		62 (35)			186 (68)			0.001*
Four MetS risk fac.		76 (42)			63 (23)			0.002*
Five MetS risk fac.		42 (23)			21 (0.7)			0.001*

Values are mean ± SD; Y = Year; BMI: Body Mass Index; SBP: Systolic Blood Presure; DBP: Diastolic Blood Presure; T2DM: Diabetes Mellitus Type 2; Serum HDL-C: High Density Cholesterol; serum Triglicerides; WCi: Weist Circumference; MetS. Number of risk factor present (three, four, five).

Overall, participants with subclinical LVDD, had a worse cardiovascular risk factor profile, including higher BMI, higher BP, increased WCi, dyslipidemia, high number of risk factors. p^* < 0.05 for between group comparation.

Table 3: Frequency of subclinical LVDD among patients of the group with MetS and subclinical LVDD stratified by levels of CRP (n-180).

Chi-square: 10.91; p^*= 0.001			
Study Group: MetS + subclinical LVDD (n-180)			
Participants with CRP > 3.0mg/L		**Participants with CRP < 3.0mg/L**	
Frequency of subclinical LVDD Count (No)	117	63	p^* = 0.001
Percent (%)	65	35	

Overall, frequency of subclinical LVDD in Participants with MetS and levels of CRP > 3.0mg/L was higher than in participants with MetS and levels of CRP < 3.0mg/ L. p^* < 0.05 for between subgroup comparation.
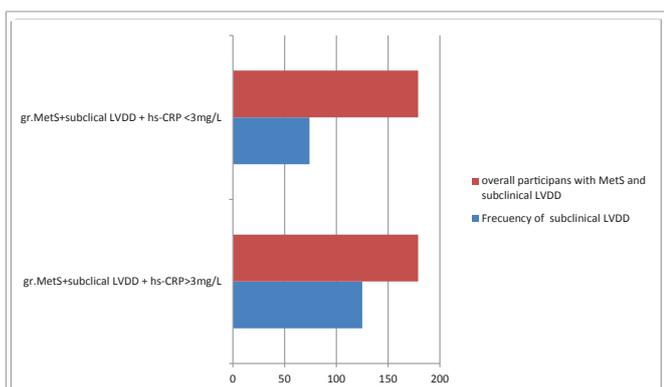

Figure 1: The frequency of subclinical LVDD in participants with MetS and CRP levels (> 3.0 mg/ L and < 3.0 mg/ L).

95% CI 1.869-2.522).There were significant association of increased levels of CRP with increased number of risk factors for MetS. (n-4 risk factors for MetS OR = 1,7,95% CI 1.486-1.934; n-5 risk factors for MetS OR = 2.3, 95% CI 1.934-2.815), also there were significant association of increased levels of CRP with BMI. (OR = 1.5, 95% CI 1.380-1.730) and significant association of increased levels of CRP with presence of T2DM. (OR = 1.2, 95% CI 1.048-1.349).

DISCUSSION

Experimental and observational evidence suggests that inflammation has a pivotal role in cardiac remodeling in patients with MetS[6] also has been associated with subclinical changes in cardiac structures and function, including Left Ventricular Diastolic Dysfunction (LVDD) [28]. The present study confirm this association, because those with MetS and higher levels of CRP had significantly higher prevalence of subclinical LVDD than did those with MetS and lower levels of CRP. Results of the present study confirmed our hypothesis.

The most striking result in our analysis is that increased levels of CRP, reflect subclinical LVDD in patients with MetS, increased CRP a marker of inflammation, may be a marker of subclinical LVDD. Previous studies Anand et al. & Ratnasamy et al. established a strong association between CRP and the severity of symptoms in patients with advanced HF. However, there are no data regarding the associations between CRP and echocardiographic parameters in patients with cardiovascular risk factors but who do not show obvious HF [29]. Our results are consistent with prior studies showing an association of high levels of CRP and LVDD [28].

A number of previous studies have demonstrated that CRP levels correspond with individual components of MetS [28,30]. The

Table 4: Logistic Regression Model: Association of CRP levels (> 3.0mg/ L) with: subclinical LVDD, number of risk factor for MetS, DM and BMI.

	OR*	Significance	95% CI for Exp (B)	
			Lower	Upper
Subclinical LVDDf	2.1	.000	1.869	2.522
MetS-RF n4	1.4	.000	1.485	1.950
MetS-RF n5	2.3	.000	1.934	2.815
BMI	1.5	.000	1.380	1.730
T2DM	1.2	.000	1.048	1.349

Sub clinic LVDD: Left ventricular diastolic dysfunction; Number of risk factor for MetS, n-four: Four risk factors for MetS; n-five: Five risk factors for MetS; DM: Diabetes Mellitus; and BMI: Body mass index OR* > 1.

association between CRP and subclinical LVDD in the present study, may be attributed to the high prevalence of arterial hypertension, diabetes and dyslipidemia in the participants. These findings might lend further insight into potential mechanisms by which MetS is associated with eventual development of HF. The pathophysiological mechanism by which MetS can lead to abnormalities in LV diastolic function is not well understood. In mouse models of diet-induced MetS, increased myocardial oxidative stress has been implicated in the development of diastolic dysfunction, and was associated with both hypertrophy and fibrosis of the myocardium [31]. Animal models of insulin resistance, hypertension, or dyslipidemia have also implicated the development of cardiac fibrosis, abnormal intracellular calcium handling [31,32], cardiomyocyte lipotoxicity, mitochondrial dysfunction, impaired endothelial blood flow, increased vascular stiffness, and inflammation [33]. While mechanistic inferences cannot be drawn from our observational study, these results support the notion that metabolic heart disease can lead to impaired myocardial relaxation. However, the precise metabolic/inflammatory basis of impaired LVDF remain unknown. Further studies are needed to elucidate potential mechanisms and potential therapeutic targets. Both MetS and biomarkers of inflammation are predictive factors for subclinical LVDD, underlining the importance of inflammation in the evolution of MetS to subclinical cardiac damage. Our data suggest that CRP, a marker of inflammation, as an independent determinant of diastolic function, may be clinically useful for detecting subclinical LVDD in patients with MetS.

Several limitations deserve mention. Our study is a cross-sectional observational study, oversimplification of multifactorial mechanisms based upon limited markers, is inhered to this kind of studies and precludes causal inferences. It must also be brought to attention the potential role of newer technologies such as the speckle tracking which could more accurately find these adaptive changes related to the MetS. Healthy controls were selected based on the absence of any MetS criteria. This resulted by design in baseline differences of clinical characteristics between participants with and without MetS. It is therefore possible that residual confounding could in part account for our findings. It was impossible to rule out coronary heart disease as a reason for subclinical LVDD by coronary angiography, because it is difficult to influence asymptomatic patients for an invasive procedure and also from ethical standpoint. This limitation is unavoidable. We do not believe that subtle coronary atherosclerosis would have an influence in the study results at a significant degree, and will not reduce the values of the basic conclusions of the study as well.

CONCLUSIONS

We proved the hypothesis that patients with MetS and high levels of CRP have higher prevalence of subclinical LVDD than patients with MS and lower level of CRP. CRP a marker of inflammation, may be a marker of subclinical LVDD in MetS patients, underlining the importance of inflammation in evolution of MetS to subclinical cardiac damage. These findings might lend further insight into potential mechanisms by which MetS is associated with eventual development of HF.

AUTHORSHIP CONTRIBUTIONS

Concept-Jani Ylber, Design-Pocesta Bekim, Supervision-Rexhepi Atila, Materials-Ferati Fatmir, Lala Dali, Zeqiri Agim, Mirto Arben, Data collection/processing-Xhunga Sotiraq, Serani Artur, Analysis/interpretation-Jani Ylber, Rexhepi Atila, Pocesta Bekim, Literature Search-Lala Dali, Ferati Fatmir, Jani Ylber, Serani Artur, Critical Reviews-Ahmet Kamberi and Rexhepi Atila.

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