Research letter

European Journal of Preventive Cardiology

ESC European Society of Cardiology

European Journal of Preventive Cardiology
2020, Vol. 27(19) 2330–2333

DOI: 10.1177/2047487319895400
journals.sagepub.com/home/cpr

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Metabolic syndrome severity score is associated with diastolic dysfunction and low-grade inflammation in a community-based cohort

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Metabolic syndrome (MetS) affects approximately one out of three adults in western countries and it combines a cluster of cardiovascular risk factors.[1] A continuous gender and race/ethnicity-specific MetS severity score was recently described and validated,[2] and is an independent predictor of cardiovascular events, beyond individual MetS components.[3] We aimed to assess if this score was associated with subclinical diastolic dysfunction. Additionally, we searched for a potential relationship between MetS severity score and inflammatory/insulin-resistance markers.

This was a cross-sectional study of a community-based cohort consisting of 925 adults, aged 45 years or older, without any known cardiovascular disease. A detailed description of the cohort assembly is provided elsewhere.[4] All participants underwent clinical, analytical (insulin, adiponectin, leptin and high-sensitivity C-reactive protein (hs-CRP)) and echocardiographic examination (including e' velocities and E/e' ratio). Insulin resistance was estimated according to the homeostatic model assessment (HOMA), as the product of fasting glucose (in milligrams per decilitre) and insulin (in milliunits per litre) divided by a constant of 405.

MetS was defined using the 2005 American Heart Association/National Heart, Lung, and Blood Institute criteria (MetS criteria showing the strongest association with cardiovascular disease in the Portuguese population[5]). A continuous MetS severity z-score was applied to all patients, in theory normally distributed and ranging from theoretical negative to positive infinity with mean = 0 and standard deviation = 1. We used two of the six equations, as described by Gurka et al.[2]: a) non-Hispanic white males: score = $-5.4559 + 0.0125 \times$ waist circumference $- 0.0251 \times$ high-density lipoprotein cholesterol (HDL-C) $+ 0.0047 \times$ systolic blood pressure (SBP) $+ 0.8244 \times \ln$(triglycerides) $+ 0.0106 \times$ glucose; b) non-Hispanic white females: score = $-7.2591 + 0.0254 \times$ waist circumference $- 0.0120 \times$ HDL-C $+ 0.0075 \times$ SBP $+ 0.5800 \times \ln$(triglycerides) $+ 0.0203 \times$ glucose.

Diastolic dysfunction was defined using three criteria: 2009[6] and 2016[7] European Association of Cardiovascular Imaging/American Association of Echocardiography (EACVI/ASE) recommendations and a 2017 clinically oriented algorithm.[8]

Regarding the statistical analyses, continuous variables are reported as mean ± standard deviation or median (interquartile range), according to normality of distribution. Discrete variables are described using frequency and percentage. The HOMA index, hs-CRP, adiponectin and leptin were included in the analyses as a base-2 logarithm due to their skewed distribution (normality was assessed using the Kolmogorov–Smirnov test). One unit variation of the base-2 logarithmic transformation would be equivalent to a doubling of the variable of interest. Bivariate correlations were assessed by Pearson's (r) correlation coefficient (non-normally distributed variables were previously logarithmically transformed). Independent t-test was used to compare MetS severity score in individuals with normal diastolic function and individuals with diastolic dysfunction. Multivariable linear regression analysis

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was used to assess the association between diastolic echocardiographic indices and MetS severity score using two models: a) including age; b) including age and each individual MetS component (dichotomized). In addition, multivariable logistic regression was used to assess if MetS severity score was a predictor of diastolic dysfunction, independently of each individual's MetS component. All statistical analyses were conducted using Stata 14.0 for Mac (StataCorp, College Station, TX, USA).

The final sample included 925 participants with a mean age of 61.5 ± 10.5 years (37% men). The clinical, anthropometric, analytical and echocardiographic characteristics of the study sample are shown in Table 1. The prevalence of MetS was 39.3% (358 individuals), and 10.7% (99 individuals) had type 2 diabetes. The prevalence of diastolic dysfunction was 22% according to the 2009 joint guideline, 1% according to the 2016 joint guideline (with 14.5% categorized as "indeterminate") and 49.2% according to the 2017 algorithm proposed by Mitter et al.[8]

The mean MetS severity score was 0.05 ± 0.83. This score was positively correlated with the HOMA insulin resistance index ($r = 0.57$, $p < 0.001$), hs-CRP ($r = 0.28$, $p > 0.001$) and leptin ($r = 0.36$, $p < 0.001$), and inversely correlated with adiponectin ($r = -0.27$, $p < 0.001$). Higher MetS severity score was associated with a decrease in e' velocity and an increase in E/e' ratio, irrespective of age (Figure 1).

In multiple linear regression analyses, MetS score was a negative predictor of e' velocity (beta-coefficient: -0.62; p-value < 0.001) and a positive predictor of E/e' ratio (beta-coefficient: 0.30; p-value $= 0.042$), even when age and all individual MetS components were included in the model. There was a higher MetS severity score in patients with criteria for diastolic dysfunction according to the 2009 criteria (0.36 ± 0.83 vs -0.03 ± 0.81 in normal diastolic function) and 2017 algorithm (0.25 ± 0.81 vs -0.14 ± 0.80 in normal diastolic function), as well as in patients with positive or indeterminate criteria using the 2016 guideline (0.31 ± 0.79 vs 0.01 ± 0.83 in normal diastolic function). MetS score was an independent predictor of diastolic dysfunction according to the 2017 clinically oriented algorithm, irrespective of age and individual MetS components (odds ratio 1.38, $p = 0.027$), but not using the 2009 (odds ratio 1.26, $p = 0.136$) and 2016 (odds ratio 1.66, $p = 0.410$) EACVI/ASE recommendations.

In this study, we observed that an increasing MetS severity score is associated with higher insulin resistance, increased inflammatory biomarkers and metabolically dysfunctional adipokines profile (high leptin and low adiponectin). These biomarkers might be viewed as surrogates for "metabolic dysfunction",

Table 1. Study participant characteristics.

	Total ($n = 925$)
Age (years)	61.5 ± 10.5
Male sex, *n* (%)	346 (37)
Cardiovascular risk factors	
Total cholesterol, mg/dL	219.9 ± 38.7
LDL-C, mg/dL	132.9 ± 34.4
HDL-C, mg/dL	59.9 ± 13.2
Triglycerides, mg/dL	131.2 ± 76.4
Waist circumference, cm	92.7 ± 11.4
BMI, kg/m^2	27.3 ± 4.6
SBP, mmHg	132.5 ± 19.4
DBP, mmHg	78.4 ± 11.2
Fasting glucose, mg/dL	101.5 ± 24.8
Log2(HOMA-IR)	0.1 ± 1.4
MetS, *n* (%)	358 (39.3)
Increased waist circumference, *n* (% of MetS)	279 (77.9)
Triglycerides $\geq$ 150 mg/dL or receiving fibrates, *n* (% of MetS)	206 (57.5)
Decreased HDL-C or taking niacin, *n* (% of MetS)	210 (58.9)
SBP $\geq$ 130 or DBP $\geq$ 85 mmHg, *n* (%of MetS)	332 (92.7)
IFG or type 2 diabetes, *n* (%of MetS)	254 (70.9)
Type 2 diabetes, *n* (%)	99 (10.7)
Oral antidiabetic medication and/or insulin, *n* (%)	65 (7.0)
Echocardiographic data	
Septum, mm	8.6 ± 1.4
Posterior wall, mm	7.9 ± 1.2
LV mass index, g/m^2	78.3 ± 18.8
LA volume index, mL/m^2	28.2 ± 9.5
LVED volume index, mL/m^2	65.6 ± 15.9
LVES volume index, mL/m^2	26.4 ± 8.8
Ejection fraction, %	60.7 ± 6.1
E wave, cm/s	71.6 ± 15.3
A wave, cm/s	78.2 ± 19.9
E/A ratio	0.96 ± 0.30
Deceleration time, ms	236.3 ± 54.1
IVRT, ms	91.3 ± 15.8

Data are presented as mean $\pm$ standard deviation for continuous variables and count (percentage) for categorical variables.

BMI: body mass index; DBP: diastolic blood pressure; HOMA-IR: homeostatic model assessment of insulin resistance; LV: left ventricle; LA: left atria; LVED: left ventricle end-diastolic; LVES: left ventricle end-systolic; IVRT: isovolumic relaxation time; MetS: metabolic syndrome; SBP: systolic blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; IFG: impaired fasting glucose.

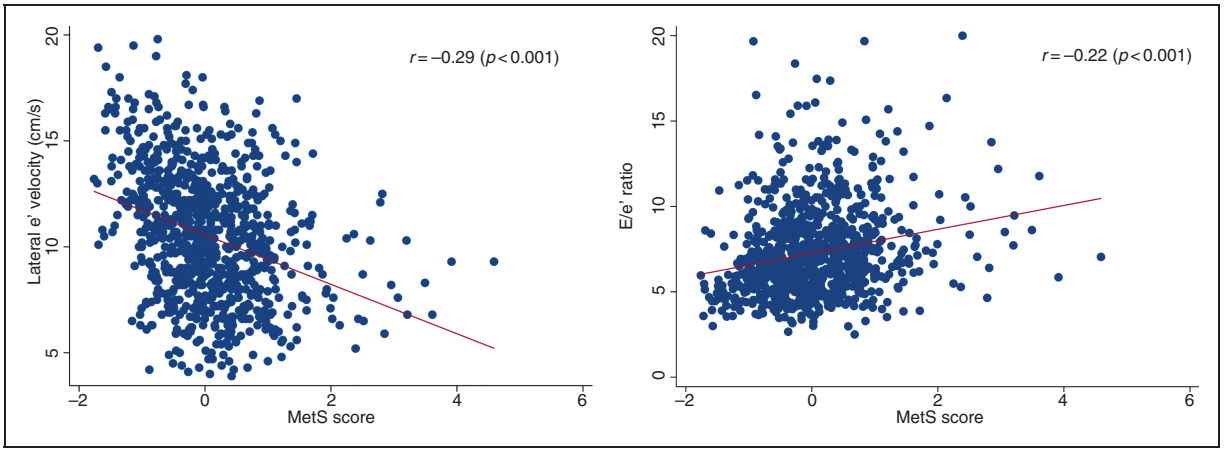

Figure 1. Scatter plots with regression line showing inverse correlation between MetS severity score and lateral e' velocity (surrogate for LV relaxation), and positive correlation with E/e' ratio (surrogate for LV filling pressures).

and all are key players in MetS pathophysiology and important contributors to diastolic dysfunction and heart failure with preserved ejection fraction,[9] as was previously shown for other biomarkers such as amino acids.[10] In addition, higher MetS score was associated with decreased e' velocity (impaired relaxation) and increased E/e' ratio (higher left ventricle (LV) filling pressures). Lastly, patients with diastolic dysfunction showed higher MetS score and the latter was an independent predictor of diastolic dysfunction (defined according to a 2017 clinically oriented algorithm[8]), irrespective of age and individual MetS components, although this was not the case for the definition of diastolic dysfunction according to 2009 and 2016 EACVI/ASE recommendations. There was substantial criticism regarding the updated 2016 diastolic dysfunction definition, due to its higher specificity and the potential for identifying as positive only the most advanced cases of diastolic dysfunction.[11] This might account for the low prevalence of diastolic dysfunction of 1% in our cohort according to this criterion, whereas its prevalence in community-based cohorts according to older criteria is usually around 35%.[12] Further research is needed to assess how using a continuous MetS severity score can improve diastolic dysfunction prediction beyond the dichotomous MetS categorization and its individual components, and even be integrated with other screening models for diastolic dysfunction in the community.[13]

Interestingly, metformin treatment of non-diabetic patients with insulin resistance or pre-diabetes significantly reduced LV mass and oxidative stress.[14] The MET-DIME trial will further explore this topic, by evaluating if the initiation of metformin therapy in non-diabetic patients with MetS and diastolic dysfunction is associated with improvement in diastolic function.[15]

Overall, we showed that a MetS severity score provides an integrated index of metabolic dysfunction, combining insulin resistance, low-grade inflammation and metabolically unfavourable adipokine profile. MetS score is associated with LV relaxation and filling pressures, and is an independent predictor of diastolic dysfunction, beyond MetS individual components.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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