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Arterial stiffness in fertile women with metabolic syndrome

Running title: Arterial stiffness in women with MetS

Original Article

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Abstract

Introduction: Although metabolic syndrome (MetS) is evidently associated with the risk of cardiovascular disease (CVD), recently its use has been questioned. We studied the utility of MetS diagnosis when estimating individual CVD risk.

Methods: We compared 27 fertile women with MetS and 27 counterparts without the syndrome, matched pairwise according to well-known risk factors of CVD. Pulse wave velocity (PWV) and central blood pressure (cBP) were determined noninvasively via a SphygmoCor device. Arterial compliance was measured noninvasively with an HDI/PulseWave^{TM}CR-2000 arterial tonometer.

Results: PWV (7.1 ± 2.5 vs. 6.5 ± 1.1 m/s, P = 0.037), and both systolic (120.9 ± 12.2 vs. 111.5 ± 16.0 mmHg, P = 0.031) and diastolic cBP (81.3 ± 8.5 vs. 74.1 ± 11.2 mmHg, P = 0.035) were higher in the MetS group. Systemic arterial compliance values were lower in both large (15.1 ± 8.0 vs. 16.1 ± 4.4 mL/mmHg×10, P = 0.034) and small arteries (7.1 ± 2.5 vs. 9.3 ± 3.2 mL/mmHg×100, P = 0.010) in women with MetS.

Conclusions: Fertile women with MetS had increased arterial stiffness, as measured by three different methods. Our results highlight the utility of MetS when revealing increased individual CVD risks in fertile-aged women.

Keywords: arterial compliance, arterial stiffness, cardiovascular disease, central blood pressure, gestational diabetes mellitus, metabolic syndrome, pulse wave velocity

Key messages:

- Women with MetS have increased arterial stiffness when measured by different methods.
- MetS is a useful clinical tool to assess increased cardiovascular risk, particularly among fertile-aged women.

Introduction

Metabolic syndrome (MetS) is defined as a group of risk factors related to increased risks of cardiovascular diseases and diabetes (1). Although many diagnostic criteria have been proposed for MetS since the 1980s, hyperglycemia, dyslipidemia, hypertension, and abdominal obesity are recognized as key components (2). In recent decades the prevalence of MetS has increased significantly in parallel with the global epidemic of obesity (3). Although the presence of MetS is associated with an increased risk of CVD (1,4,5), the results of the large INTERHEART study suggested that the use of dichotomous risk factors used in MetS classification may underestimate future CVD risk (6).

Cardiovascular diseases (CVDs) are the leading causes of female mortality, responsible for one third of deaths in women globally (7,8). The appearance of CVD can differ between the sexes, making the identification of CVD in women challenging (9,10). Pregnancy can reveal a woman´s tendency to be at an increased risk of health problems later in life. Growing evidence suggests that women with a history of gestational diabetes mellitus (GDM) are at an increased risk of CVD, type 2 diabetes or MetS later in life (11-14).

Arterial stiffness is an important marker of arteriosclerosis, predicting future CVD events (15-18). With aging, the wall of the artery loses elasticity and becomes rigid (19-21). Measurement of carotid to femoral pulse wave velocity (PWV) as a marker of aortic stiffness has emerged as the gold standard method (18). There are also other ways to measure arterial stiffness noninvasively. Systemic arterial compliance can be determined by using radial artery pulse wave analysis (18,22). Central blood pressure (cBP) registered noninvasively seems to be more relevant than peripheral BP as regards the pathogenesis of CVD (23,24). It also correlates with cardiovascular risk in healthy people (25).

Weighing the possible value of MetS may be related to individual perspectives, i.e. the point of view of an epidemiologist may be different from that of a clinical physician. Hence, the value of assessing MetS *per se* when estimating individual cardiovascular risk has been questioned (6,26-29). We aimed to study this by pairwise matching of fertile-aged women with and without MetS, in relation to well-known risk factors of CVD. Our special interest was to determine whether or not there are differences in pulse wave velocity, central blood pressure and systemic arterial compliance between fertile-aged women with and without MetS.

Material and methods

Study population

This cross-sectional study was performed at Kanta-Häme Central Hospital and Linnan Klinikka, Hämeenlinna, Finland. The complete study protocol has been described in detail previously (14). In brief, we investigated a total of 120 parturients from our area with a history of GDM during the index pregnancy and we compared them with 120 age-matched women with normal glucose metabolism during pregnancy. Index pregnancies and deliveries were 2–6 years before participating in the study. GDM was defined as a pathological value in a 75-g oral glucose tolerance test (OGTT) during pregnancy: venous plasma glucose ≥ 5.3 mmol/L when fasting, ≥ 10.0 mmol/L at 1 hour or ≥ 8.6 mmol/L at 2 hours. The diagnostic criteria of GDM were the same as in current Finnish guidelines (30). MetS was defined according to the National Cholesterol Education Program (NCEP Adult Treatment Panel III), and for women this is the presence of at least three of the following five criteria (2): waist circumference > 88 cm; serum triglycerides ≥ 1.7 mmol/L; serum high-density lipoprotein cholesterol (HDL-C) level < 1.3 mmol/L; blood pressure ≥ 130/85 mmHg; plasma glucose level ≥ 6.1 mmol/L or diabetes mellitus.

We found 2.4-fold increased risk of MetS after previous GDM when compared with normoglycemic pregnancies (14). In the current analysis, we included all 27 women with MetS from a total of 240 participants in our original study. Every woman with MetS was compared with an individually paired counterpart without MetS. To avoid the confounding effects of well-known cardiovascular risk factors, the counterparts without MetS were matched according to age, previous GDM status, and serum concentrations of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) (Table 1). All the participants were of Caucasian origin. Both recruitment and examinations were carried out between January 2013 and July 2014.

We interviewed the participants as regards their medical histories and lifestyle habits. To analyze “yo-yo” dieting, we estimated total lifetime weight loss by adding together the kilograms lost during every previous intentional weight-loss period. Lifetime tobacco exposure was calculated as pack-years by multiplying years of smoking by the average number of packs smoked daily (31). One pack-year is defined as twenty cigarettes smoked every day for one year.

Resting heart rate and brachial blood pressure of the participants was assessed automatically by using CR-2000 equipment (HDI/PulseWave^{TM}CR-2000, Hypertension Diagnostics, Inc., Eagan, Minnesota, USA) during the measurement of arterial compliance. The mean of three measurements was used in the analysis. Weight (kg), height (cm) and waist circumference (cm) were measured according to general recommendations. Waist circumference (WC) was measured midway between the lowest rib and the iliac crest. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (32), and the protocol was approved by the Ethics Committee of Kanta-Häme

Hospital District (reference number 521/2010; date of approval 21.12.2010). Every participant was given both oral and written information on the study before she signed an informed consent document.

Laboratory Methods

Basic blood count and serum levels of creatinine, alanine transaminase (ALAT), fasting glucose and insulin, glycosylated hemoglobin (HbA1c), TC, HDL cholesterol, LDL cholesterol and triglycerides, and the urinary albumin to creatinine ratio, were analyzed according to validated methods as described in detail earlier after at least 12 hours of fasting (14,33). Serum concentrations of high-sensitivity C-reactive protein (hsCRP) were analyzed according to validated immunonephelometric (United Medix Laboratories Ltd., Espoo, Finland) and immunoturbidimetric (VITA Healthcare Services Ltd., Vita Laboratory, Helsinki, Finland) methods (34,35). Plasma concentrations of oxidized low-density lipoprotein (oxLDL) were determined by using a validated ELISA method (Mercodia AB, Uppsala, Sweden). The assay kits include the same monoclonal antibody (4E6) as originally described by Holvoet et al. (36,37).

The homeostasis model assessment of insulin resistance (HOMA-IR) index is based on measurement of plasma glucose and insulin in a single sample and is commonly used as a parameter of the severity of insulin resistance (38). It was calculated in the following way: fasting insulin (mU/L) × fasting blood glucose (mmol/L)/22.5 (39).

Determination of arterial stiffness and compliance

Carotid–femoral PWV was measured by using the foot-to-foot velocity method from carotid and femoral waveforms, using a SphygmoCor device (AtCor Medical, Sydney, Australia). These were obtained transcutaneously at the right common carotid artery and the right femoral artery, with the subject in a supine position, with direct-contact pulse sensors. The

time delay (Dt or transit time) of the two waveforms was registered, and the distance (D) between the carotid and femoral recording sites was obtained by subtracting the distance between the carotid measurement site to the sternal notch from the distance between the sternal notch and the femoral measurement site. PWV was calculated as follows: D/Dt (m/s) (18,25). PWV increases in stiff or less distensible arteries (23,25). Three measurements were performed to obtain average results for every participant. Only measurements that met the automatic quality-control cutoff were used in the final analysis.

Central BP was estimated non-invasively from a radial artery pulse wave (SphygmoCor device; AtCor Medical, Sydney, Australia), which involves use of a radial pulse and a validated generalized transfer function to estimate central pressures from brachial BP and peripheral pulse waves (25). Three consecutive measurements were performed to obtain mean results for every participant. Values of cBP are indirect surrogate measures of arterial stiffness, but they provide additional information concerning pulse wave reflections (18).

Radial artery pulse waves were measured non-invasively with an arterial tonometer (HDI/PulseWave^{TM}CR-2000, Hypertension Diagnostics, Inc., Eagan, Minnesota, USA), which involves use of a modified Windkessel pulse-contour method (40). This technique is based on an assumed model of the circulation which identifies reflections in diastole as a decaying sinusoidal wave (18,41). The equipment automatically records the proximal capacitive compliance of large arteries (C1), including the aorta, and the distal oscillatory compliance, which concerns endothelial function of the microvascular circulation or small arteries (C2) (18,41). During thirty seconds of measurement, values of C1 and C2 were automatically assessed as the mean of the five most similar pulse waves appearing. Three measurements were performed to obtain mean values for every participant. Arterial compliance describes the ability of an artery to expand as a response to pulse pressure.

Compliance can be understood as the inverse of stiffness – in a stiff artery compliance is low (42).

Recordings of PWV, cBP, C1 and C2 were carried out in the morning after at least ten minutes of rest in a semi-sitting position. The participants were asked to refrain from eating, drinking caffeinated drinks, smoking and taking medication for 12 hours, and drinking alcohol for two days prior to measurement. All the measurements were performed by four experienced nurses.

Statistical analysis

Statistical analysis was carried out by using IBM® SPSS® Statistics Version 23 software (copyright 2015). Variables were tested for normality by way of Shapiro–Wilk tests. Data are presented as mean ± standard deviation (SD) if not mentioned otherwise. Differences in continuous variables between MetS participants and paired counterparts were studied by using paired *t* test in cases of normality and by the Wilcoxon test in cases of non-normality. Differences in binomial outcomes between the two paired study groups were tested by using McNemar's test. The Hodges-Lehmann estimate was used for calculating the difference between MetS and their matched controls medians and 95% confidence interval (CI) for the difference. A two-tailed probability value of < 0.05 was considered significant.

Results

Variables of MetS defined according to NCEP Adult Treatment Panel III for women with MetS and their matched counterparts without MetS are shown in Table 2. There were no differences in family history of coronary heart disease, cerebrovascular disease or diabetes mellitus between the study groups (data not shown). In individual pairwise comparisons, no differences were found in diagnosed disorders or permanent medication for any chronic disease (data not shown). Further, there was no difference in current smoking in individual pairwise comparisons (6 vs. 4, $P = 0.728$).

Baseline characteristics and laboratory findings in both groups are shown in Table 3. Body mass index was higher in the women with MetS, but their paired counterparts were also overweight (Table 3). Heart rate was 67.9 (± 8.8) beats per minute (bpm) in the MetS group and 65.7 (± 10.6) bpm among the paired controls (Difference = 2.2; 95% CI: -2.2, 6.6; P = 0.211). There were no differences in the concentrations of white blood cells or platelets between the groups (data not shown), but that of hemoglobin was higher among women with MetS (Table 3). The concentration of HbA1c was 34.6 (± 2.9) mU/L in the MetS group, and 34.7 (± 2.5) mU/L in the paired controls (Difference = -0.1; 95% CI: -1.7, 1.4; P = 1.000). The urinary albumin to creatinine ratio was significantly higher among women with MetS, 0.7 (± 0.4) mg/mmol vs. 0.5 (± 0.3) mg/mmol, Difference = 0.2; 95% CI: 0.0, 0.4 (P = 0.034), respectively.

As measured by three different methods, arterial stiffness values differed significantly between the fertile women with MetS and their matched counterparts without the syndrome. Arterial stiffness was higher among the women with MetS than in their matched counterparts when measured by means of PWV (Figure 1), as were both systolic and diastolic cBP (Figure 2). Values of systemic arterial compliance (both C1 and C2) were significantly lower in the MetS group (Figure 3).

Discussion

Women with MetS had higher PWV values when compared with paired women without the syndrome, suggesting that MetS in fertile-aged women is associated with increased arterial stiffness. Further, women with MetS had increased cBP, as well as decreased C1 and C2 values when compared with their counterparts without MetS, thus providing further support for the finding.

Increased PWV, as a measure of arterial stiffening, is a strong predictor of cardiovascular events and mortality (43). As reviewed by Vlachopoulos et al., an increase in PWV of 1 m/s is related to a 14–15% increase in cardiovascular events, cardiovascular mortality and all-cause mortality (43). There are several plausible reasons for the current finding of increased PWV in women with MetS. Small dense LDL (sdLDL), *i.e.* poor quality of LDL, known to be associated with MetS and hypertriglyceridemia has found to be an important predictor of atherosclerosis (44,45). Like sdLDL, also circulating triglyceride rich lipoproteins may induce endothelial dysfunction (46,47). Chronic hyperglycemia and hyperinsulinemia promote the development of arterial wall hypertrophy by increasing local activity of the renin-angiotensin-aldosterone system (48). Moreover, high blood pressure stimulates excessive collagen production in the arterial wall (48) and insulin resistance promotes the formation of advanced glycation end-products and collagen cross-linking (49). Furthermore, decreased vasodilatory effects of insulin and free fatty acids cause impaired endothelial function (48). MetS can also be considered to be a pro-inflammatory state, which could cause endothelial dysfunction (50). All these changes in arterial wall structure and function have adverse effects on the cushioning capabilities of arteries, thus increasing arterial stiffness.

Carotid–femoral PWV is widely studied and considered as a gold standard in the evaluation of arterial stiffness (17). Arterial stiffness can also be determined by measuring cBP (17) or compliance of large (C1) and small (C2) arteries (40). As discussed in a consensus document by Agabiti-Rosei et al. (25), increased cBP has been shown to correlate with cardiovascular risk in apparently healthy subjects and in patients with atherosclerotic disease. Moreover, decreased values of C1 and C2 have been found to be associated with MetS (51) and increased cardiovascular risk as estimated by using FINRISK and SCORE risk models (52). We found higher cBP, and lower C1 and C2 values among fertile-aged women with MetS when compared with women without the syndrome. This provides further evidence of the

negative effects of MetS on arterial stiffness among fertile-aged women. Between the study groups there was a small but significant difference in microalbuminuria. As a marker of endothelial dysfunction, this finding also highlights the effect of MetS on arterial stiffness. The number of subjects was relatively small, but the number of patients was big enough to show the statistically significant difference between the matched groups. Hence, the confounding factors were used as matching criteria. In this setting, according to all methods used women with MetS had increased arterial stiffness.

Physical activity is known to be crucial in the prevention of CVD. Two recent studies are part of a continuum concerning research into atherosclerotic risk factors among men with MetS and physically active (PhA) men (53,54). Pohjantähti-Maaroos et al. found that PhA men had better C1 values compared with MetS participants, but no difference was found as regards C2 (54). Higher numbers of smokers and greater alcohol intake were more often present among men with MetS compared with PhA subjects (54). Our study has expanded research into MetS in women. In contrast to earlier findings, there were no significant differences in pack-years of smoking or alcohol intake between the paired study groups. The apparent discrepancy of these results may be attributed to variability in selection of controls. In agreement with this, MetS *per se* seems to be an independent predictor of increased arterial stiffness in the present study.

Initially successful weight losses followed by weight regain (weight cycling or so called “yo-yo” dieting) is associated with body-weight excess and abdominal fat accumulation (55). Nonalcoholic fatty liver disease is commonly associated with obesity, insulin resistance, dyslipidemia and type 2 diabetes, and can thus be regarded as the hepatic manifestation of metabolic syndrome (56). We found no difference in lifetime weight loss between the paired study groups. The women in both groups were overweight. In contrast, both BMI and serum

concentrations of ALAT were higher among women with MetS compared with women without the syndrome, reflecting the hepatic manifestation of MetS.

Diagnosis of MetS has been the subject of severe criticism, and it has even been suggested that MetS "should rest in peace" (57,58). The major concerns are the uncertain pathophysiology of the syndrome, the use of discrete thresholds to define abnormalities, the existence of different definitions, the exclusion of other important cardiovascular risk factors (e.g. age, sex, family history, LDL-cholesterol), and the lack of specific treatment for the syndrome (57,58). However, MetS has previously been shown to be associated with an increased risk of CVD (1,3,4,59), and the risk of CVD associated with MetS is even greater than the risk associated with the individual components (5). Moreover, it has been suggested that MetS could be a valuable public-health tool as it can be used to identify high-risk individuals at a young age (60). Our results, showing increased arterial stiffness in fertile-aged women with MetS support the use of MetS in the evaluation of CVD risk.

In conclusion, fertile-aged women with MetS have increased arterial stiffness as measured by three different methods, even when their counterpart are matched according to many other well-known CVD risk factors. The present results strongly support the clinical use of MetS as a tool for cardiovascular risk assessment, particularly among fertile-aged women.

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Disclosure of interest

The authors report no conflicts of interest.

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Figure legends

Figure 1 PWV in the MetS women and their matched controls without the syndrome.

Median (minimum, maximum) PWV among matched control women was 6.3 (5.1, 9.7) m/s, and among women with MetS, 6.9 (5.9, 9.2) m/s (Difference = -0.7; 95% CI: -1.1, -0.0; P = 0.037).

Figure 2 Central systolic (A) and diastolic pressures (B) in the MetS women and their matched controls without the syndrome.
A: Median (minimum, maximum) central systolic pressure among matched control women was 107 (90, 154) mmHg and among women with MetS, 120 (97, 147) mmHg (Difference = -12.5; 95% CI: -20.3, -1.2; P = 0.031).
B: Median (minimum, maximum) central diastolic pressure among matched control women was 73 (56, 106) mmHg and among women with MetS, 81 (65, 94) mmHg (Difference = -9.3; 95% CI: -15.3, -0.7; P = 0.035).

Figure 3 Large- (A) and small-artery (B) compliance index values in the MetS women and their matched controls without the syndrome.

A: The median (minimum, maximum) large-artery compliance index value among matched control women was 15.5 (7.2, 25.7) mL/mmHg×10 and among women with MetS, 13.8 (8.8, 53.3) mL/mmHg×10 (Difference = 2.0; 95% CI: 0.4, 4.2; P = 0.034).

B: The median (minimum, maximum) small-artery compliance index value among matched control women was 9.4 (3.5, 15.3) mL/mmHg×100 and among women with MetS, 7.8 (1.8, 9.7) mL/mmHg×100 (Difference = 2.2; 95% CI: 0.7, 3.5; P = 0.010).

Table legends

Table 1 Parameters matched among MetS participants and their counterparts without MetS.
Table 2 Variables of MetS in the MetS women and their matched controls without the syndrome.
Table 3 Baseline characteristics and laboratory findings in the MetS women and their matched controls without the syndrome.

Table 1. Parameters matched among MetS participants and their counterparts without MetS.

Matching parameter	MetS (n = 27)		Control (n = 27)				P value
	Mean	SD	Mean	SD	Difference	95% CI	
Age, years	36.8	4.7	36.6	4.5	0.2	-2.3, 2.7	0.880
Previous GDM, n (%)	19	70	19	70			1.000
TC, mmol/L	5.1	1.2	5.2	0.9	-0.1	-0.7, 0.5	0.851
LDL-C, mmol/L	3.4	0.9	3.3	0.8	0.1	-0.4, 0.5	0.768

CI: confidence interval; GDM: gestational diabetes mellitus; LDL-C: low-density lipoprotein cholesterol; MetS: metabolic syndrome; TC: total cholesterol

Table 2. Components of MetS in the MetS women and their matched controls without the syndrome.

Determinant of MetS	MetS (n = 27)		Control (n = 27)				P value
	Mean	SD	Mean	SD	Difference	95% CI	
Waist circumference, cm	107.7	11.0	97.8	14.1	9.9	2.6, 17.2	0.010
Systolic BP, mmHg	135.7	13.6	125.9	18.7	9.8	0.2, 19.4	0.021
Diastolic BP, mmHg	78.4	8.1	73.0	12.1	5.4	-0.6 11.4	0.053
Fasting glucose, mmol/L	5.7	0.6	5.4	0.4	0.3	0.0, 0.6	0.029
T2DM, n (%)	1*	4	0	0			1.000
TG, mmol/L	1.7	0.9	1.0	0.3	0.7	0.4, 1.1	< 0.001
HDL-C, mmol/L	1.2	0.2	1.6	0.2	-0.3	-0.5, -0.2	< 0.001

BP: blood pressure; CI: confidence interval; GDM: gestational diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; T2DM: type 2 diabetes mellitus

* T2DM in a woman with previous GDM

Table 3. Baseline characteristics and laboratory findings in the MetS women and their matched controls without the syndrome.

	MetS n = 27		Control n = 27				P value
	Mean	**SD**	**Mean**	**SD**	**Difference**	**95% CI**	
Pack-years of smoking	4.1	8.7	1.9	4.8	2.1	-1.8, 6.0	0.276
Alcohol intake, g/day	1.1	1.4	1.5	1.6	-0.6	-1.4, 0.1	0.242
Lifetime weight loss, kg	30.4	31.4	28.0	35.2	2.4	-18.7, 23.6	0.657
BMI, kg/m^2	33.5	6.2	28.9	5.0	4.6	1.2, 7.9	0.010
Clinical chemistry							
Hemoglobin, g/L	138.2	6.9	130.5	9.1	7.2	2.5, 11.9	0.004
hsCRP, mg/L	3.6	4.1	3.7	5.2	-0.1	-2.7, 2.6	0.516
oxLDL, U/L	48.3	14.6	48.0	17.1	0.3	-8.1, 8.7	0.942
F-insu, mU/L	9.0	5.9	6.4	4.3	2.6	-0.5, 5.7	0.073
ALAT, U/L	32.3	24.1	22.2	20.5	10.3	0.6, 19.5	0.022
Crea, µmol/L	65.3	9.0	64.6	5.4	0.7	-3.8, 5.2	0.748
HOMA-IR	2.3	1.5	1.6	1.1	0.7	-0.1, 1.5	0.046

ALAT: alanine transaminase; BMI: body mass index; CI: confidence interval; Crea: creatinine; F-insu: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; hsCRP: high-sensitivity C-reactive protein; MetS: metabolic syndrome; oxLDL: oxidized low-density lipoprotein (plasma concentration)