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ORIGINAL RESEARCH

Carotid Artery Stiffness in Metabolic Syndrome: Sex Differences

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Introduction: The effect of metabolic syndrome (MS) on carotid stiffness (CS) in the context of gender is under research.

Objective: We examined the relationship between the MS and CS in men (M) and women (W) and investigated if the impact of cardiovascular risk factors on CS is modulated by gender.

Patients and Methods: The study included 419 subjects (mean age 54.3 years): 215 (51%) with MS (109 W and 106 M) and 204 (49%) without MS (98 W and 106 M). Carotid intima-media thickness (IMT) and CS parameters (beta stiffness index (beta), Peterson's elastic modulus (Ep), arterial compliance (AC) and one-point pulse wave velocity (PWV-beta)) were measured with the echo-tracking (eT) system.

Results: ANCOVA demonstrated that MS was associated with elevated CS indices ($p = 0.003$ for beta and 0.025 for PWV-beta), although further sex-specific analysis revealed that this relationship was significant only in W ($p = 0.021$ for beta). Age was associated with CS in both M and W, pulse pressure (PP) and body mass index turned out to be determinants of CS solely in W, while the effect of mean arterial pressure (MAP) and heart rate was more pronounced in M. MANOVA performed in subjects with MS revealed that age and diabetes mellitus type 2 were determinants of CS in both sexes, diastolic blood pressure and MAP – solely in M and systolic blood pressure, PP and waist circumference – solely in W (the relationship between the waist circumference and AC was paradoxical).

Conclusion: The relationship between MS and CS is stronger in W than in M. In subjects with MS, various components of arterial pressure exert different sex-specific effects on CS – with the impact of the pulsative component of arterial pressure (PP) observed in W and the impact of the steady component (MAP) observed in M.

Keywords: carotid artery stiffness, metabolic syndrome, sex differences

Introduction

Metabolic syndrome (MS) may cause endothelial dysfunction and lead to unfavorable remodeling of vascular wall, promoting its greater stiffness and predisposing to atherosclerosis.[1–3] Components of MS were shown to play a role in the pathogenesis of cardiovascular diseases, promoting inflammatory and thrombotic processes. Recently, the problem of different effects of various cardiovascular risk factors on arterial remodeling raises an interest of researchers. The question whether MS has different influence on the arterial tree in women and men is still a matter of debate.[4–6]

The growing interest in the process of arterial remodeling over the lifespan resulted in the concept of "healthy vascular aging" and "early vascular aging" – the

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latter term describing the acceleration of the degenerative processes within the arterial wall beyond the scope expected for a given chronological age.[7,8] Various methods, including arterial stiffness, intima-media thickness (IMT) and calcium score assessment, are used to determine vascular age.[9–11] MS has been shown to accelerate the process of vascular aging and some studies provided evidence for its stronger effect in females.[12] It is also under research if different components of MS exert sex-specific effect on age-dependent arterial remodeling.[13] Identification of subjects with early vascular aging is of crucial importance as it may lead to implementation of preventive strategies that aim at retarding this process.

Arterial stiffening is an inherent component of the aging process and the rate of its progression is influenced by various factors, including cardiovascular risk factors. The pathophysiology of arterial stiffness is complex, comprising many mechanisms within the arterial wall, eg, dysregulation of the balance between elastin and collagen, modification of the vascular smooth muscle cell tone and endothelial dysfunction.[14] There are studies that suggest sex-related differences in the molecular mechanisms involved in the development of arterial stiffness.[15] In the context of arterial remodeling, some sex-related differences also have been established with women showing a tendency for concentric remodeling of the arterial wall.[16,17]

In previous studies, arterial stiffness was determined with various methods, based on regional parameters, such as carotid-femoral pulse wave velocity (cfPWV), which is currently considered a gold standard in arterial stiffness measurement, brachial-ankle pulse wave velocity (baPWV), cardio-ankle vascular index (CAVI), a measure of central and regional stiffness, and local parameters, ie, strain, distensibility, compliance, beta-stiffness index and Young elastic modulus.[5,6,18–21] Moreover, a growing number of researchers have been determining arterial stiffness using echo-tracking (eT), a method suitable for integrated, concomitant registration of local stiffness indices (beta-stiffness index [beta], Peterson's elastic modulus [Ep], one-point pulse wave velocity beta [PWV-beta], arterial compliance [AC]) and IMT.[5,6,18–21] Recently, age- and sex-specific reference values for carotid stiffness (CS) measured with eT system were provided as a result of the study performed on 1847 healthy subjects by the E-tracking International Collaboration Group (ETIC) – a multicenter initiative, in which 14 medical centers in Europe (including our Department of Cardiology) participated. It is noteworthy that in a subgroup of 76 subjects the correlation between CS parameters measured by eT and by applanation tonometry was examined and established as good.[22]

The effect of MS on arterial stiffness is still under research. Many previous studies demonstrated a link between MS or its components and baPWV and CAVI values.[23–25] The results of those studies suggest that MS may contribute significantly to increased arterial stiffness, especially in women. However, only few previous studies analyzed local stiffness determined with the eT method in the context of patient's sex.[26] In some of those studies, the relationship between the number of MS components present in a given patient and the arterial stiffness turned out to be stronger in women than in men.[27]

We hypothesized that functional changes in carotid arteries of women and men with MS are determined by different factors.

The aims of this study were: 1) to verify if MS is a sex-specific determinant of functional changes in the carotid arteries, and 2) to identify factors that determine CS in women and men with MS.

Patients and Methods

The study included 419 consecutive outpatient subjects aged between 18 and 84 years (mean age 54.3 years) with cardiovascular risk factors (at least one of the following: hypertension, type 2 diabetes mellitus, dyslipidemia, obesity, nicotinism, family history of premature cardiovascular disease). The creatinine level was within the normal range. The exclusion criteria of the study were: 1) diagnosis of a cardiovascular disease (ischemic heart disease, history of stroke, peripheral artery disease 2) atherosclerotic plaques in carotid arteries, 3) regional abnormalities of left ventricular contractility, reduced ejection fraction (EF), valvular heart disease or pericardial disease in echocardiography.

The participants were recruited at three centers: Department of Cardiology, T. Marciniak Hospital in Wroclaw (Poland), Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, Division of Anaesthesiology, University of Pisa (Italy), and Division of Cardiology, San Antonio Hospital, San Daniele del Friuli, Udine (Italy). The study group included 215 (51%) patients with MS (109 women and 106 men) and 204 (49%) persons without this condition (98 women and 106 men).

All patients underwent electrocardiography, echocardiography, carotid artery ultrasound and basic blood tests.

MS was defined according to the National Education Cholesterol Program Adult Treatment Panel III (NCEP ATP III) criteria revised in 2005.[28] According to the ATP

III definition MS was diagnosed whenever the patient satisfied any three out of the following five criteria: 1) abdominal obesity (waist circumference ≥88 cm in women and ≥102 cm in men), 2) elevated arterial blood pressure (systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥85 mm Hg or treatment with hypotensive agents), 3) hyperglycemia (fasting blood glucose ≥100 mg/dl or treatment with hypoglycemic agents), 4) hypertriglyceridemia (≥150 mg/dl or pharmacologic treatment of hypertriglyceridemia), and 5) decreased level of high-density lipoprotein (HDL) cholesterol (<40 mg/dl in men and <50 mg/dl in women).

CS parameters were estimated using the eT system integrated with Aloka ProSound Alpha 10 device. During the examination, the patient resembled in a relaxed, supine position, under an ECG monitoring. First, a clear longitudinal image of the right common carotid artery (RCCA) walls was acquired with a linear transducer with >7 MHz frequency. Then, the eT gate for the measurement of arterial diameter changes across the cardiac cycle was positioned at the boundaries between the intima and media of the anterior and posterior wall of the RCCA, 1–2 cm proximal to the bifurcation. Three to five beats were averaged to obtain a representative waveform. Finally, the value of blood pressure (measured on the brachial artery with the certified OMRON sphygmomanometer) was entered into the system.

Intima-media thickness in the RCCA (IMT) was measured in an ultrasonographic B-mode projection using a linear transducer with a frequency >7 MHz.

The following CS parameters were calculated automatically:

- Beta stiffness index (beta), as the ratio of the natural logarithm of SBP/DBP to the relative change in diameter:

beta = ln (SBP/DBP)/[(Ds – Dd)/Dd],

where: ln – the natural logarithm, SBP – systolic blood pressure, DBP – diastolic blood pressure, Ds – systolic arterial diameter, Dd – diastolic arterial diameter,

- Epsilon – Peterson's elastic modulus (Ep), also referred to as the pressure-strain elasticity modulus:

Ep = (SBP – DBP)/[(Ds – Dd)/Dd],

- Arterial compliance (AC), determined from the arterial cross-sectional area and blood pressures:

AC = p(Ds × Ds – Dd × Dd)/[4 × (SBP – DBP)],

- One-point pulse wave velocity (PWV-beta), calculated from the time delay between two adjacent distension waveforms, based on the water hammer equation and using the β- stiffness parameter:

PWV-beta = √(beta x DBP/2 x ρ),

where: ρ – blood density (1.050 kg/m^3).

Echocardiography was performed with an Alpha 10 ALOKA.

Body mass index (BMI) was calculated as a ratio of body weight to squared body height. Pulse pressure (PP) was calculated as a difference between the systolic and diastolic blood pressure. Mean arterial pressure (MAP) was calculated from the formula:

MAP = 2/3 DBP + 1/3 SBP,

where: DBP – diastolic blood pressure, SBP – systolic blood pressure.

All participants completed a survey containing questions about their past and present diseases and hospitalizations. Moreover, body height, body weight, waist and hip circumferences were measured in all study patients.

The protocol of the study complied with the Declaration of Helsinki and was approved by local bioethics committees in all three centers: 1) Ethics Committee of Wroclaw University of Medicine, 2) Ethics Committee of University of Pisa and 3) Ethics Committee of San Antonio Hospital, San Daniele del Friuli, Udine. Written informed consent was sought from all the participants.

Statistical Methods

Normal distributions of the study variables were verified with Kolmogorov–Smirnov test with Lilliefors correction and Shapiro–Wilk test. Clinicodemographic characteristics of the study groups, obtained during the survey and measurements, were presented as arithmetic means and their standard deviations (M±SD) for quantitative variables, and numbers (n) and percentages (%) for qualitative (nominal and ordinal) variables. Depending on the variable type, statistical hypotheses were verified with significance tests (*t*-test, Mann–Whitney *U*-test) or chi-square test of independence. To eliminate a confounding effect of selected cardiovascular risk factors on between-group differences in arterial stiffness indices, the analysis of covariance (ANCOVA) was conducted. Independent determinants of the study variables were identified on multivariate analysis of variance (MANOVA). The results were considered statistically

significant at $p \leq 0.05$. All calculations were carried out with Statistica package, version 12 (StatSoft, Inc.).

Results

The study included 419 persons, 215 with MS (109 women and 106 men) and 204 without MS (98 women and 106 men), aged between 18 and 84 years (mean age 54.3 years). Demographic and clinical characteristics of the study group are presented in Table 1. Patients with MS and without did not differ significantly in terms of their mean age. Individuals with MS significantly more often than persons without this condition presented with type 2 diabetes mellitus and arterial hypertension, had significantly larger waist circumference, higher heart rate, higher concentrations of glucose and triglycerides, lower concentrations of HDL cholesterol, higher SBP and PP. No statistically significant between-group differences were observed in DBP and MAP values.

The demographic and clinical characteristics stratified according to sex of the study participants are shown in Table 2. Women and men, either from the whole study group or from the subgroups with MS and without, did not differ significantly in terms of their mean age. Regardless of their sex, patients with MS significantly more often presented with type 2 diabetes mellitus, had significantly larger waist circumference, higher concentrations of glucose and triglycerides and lower concentrations of HDL cholesterol than persons without MS. Comparative analysis of arterial blood pressure parameters demonstrated that whereas women with MS had significantly higher mean SBP and PP than women without this condition, the SBP and PP values in men with MS and without did not differ significantly. Similarly, women with MS, but not men, presented with significantly higher heart rate than individuals without MS. Regardless of their sex, patients with MS and without did not differ significantly in terms of their mean DBP and MAP values.

CS indices and IMT in patients with MS and without are presented in Table 1 for the whole study group and in Table 2 for women and men separately. Individuals with MS and without, either from the whole study group or from the subgroups of women and men, did not differ significantly in terms of their mean IMT values. Interestingly, however, the IMT values in women from the whole study group and subgroup without MS turned out to be higher than in respective groups of men.

Table 1 Clinicodemographic Characteristics, Echo-Tracking Carotid Stiffness Parameters and IMT of the Whole Study Group

Parameter	Total (N = 419)	Total MS (+) (N = 215)	Total MS (-) (N = 204)	MS (+) vs MS (-) *p*
Women	207 (49%)	109 (51%)	98 (48%)	0.586
Age [years]	54.3 ± 11.1	54.7 ± 11.6	53.8 ± 10.5	0.462
BMI [kg/m^2]	29.6 ± 5.8	31.9 ± 5.2	27.1 ± 5.4	<0.001***
Waist circumference [cm]	97 ± 14	103 ± 13	91 ± 13	<0.001***
Type 2 diabetes mellitus	92 (22%)	77 (36%)	15 (7%)	<0.001***
Hypertension	268 (64%)	150 (70%)	118 (58%)	0.011*
Glucose [mg/dL]	106 ± 28	117 ± 34	95 ± 13	<0.001***
Cholesterol [mg/dL]	201 ± 52	202 ± 57	199 ± 45	0.501
LDL-C [mg/dL]	132 ± 36	133 ± 38	130 ± 34	0.421
HDL-C [mg/dL]	55 ± 23	50 ± 22	60 ± 23	<0.001***
TGL [mg/dL]	139 ± 91	169 ± 91	102 ± 77	<0.001***
HR (bpm)	70 ± 12	72 ± 12	68 ± 11	0.001**
SBP [mm Hg]	138 ± 20	141 ± 20	135 ± 19	0.003**
DBP [mm Hg]	80 ± 12	81 ± 13	80 ± 12	0.275
PP [mm Hg]	58 ± 15	60 ± 15	56 ± 14	0.003**
MAP [mm Hg]	98 ± 17	99 ± 17	96 ± 16	0.052
IMT [mm]	0.65 ± 0.18	0.64 ± 0.16	0.66 ± 0.19	0.335
Beta [-]	8.8 ± 3.4	9.4 ± 3.8	8.1 ± 2.9	<0.001***
Ep [kPa]	127 ± 59	137 ± 67	117 ± 47	<0.001**
AC [mm^2/kPa]	0.72 ± 0.28	0.71 ± 0.29	0.73 ± 0.27	0.445
PWV-beta [m/s]	6.54 ± 1.54	6.78 ± 1.50	6.24 ± 1.54	0.003**

Notes: *$p < 0.001$, **$p < 0.01$, ***$p < 0.001$.

Abbreviations: BMI, body mass index; MS, metabolic syndrome; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TGL, triglycerides; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; IMT, intima-media thickness; beta [-], beta stiffness index; Ep, Peterson's elastic modulus; AC, arterial compliance; PWV-beta, one-point pulse wave velocity.

Compared with individuals free from the MS, patients with MS presented with significantly higher values of beta, Ep and PWV-beta. Higher values of these indices in patients with MS compared with free from MS were also found on separate analyses of women and men (Table 2). Irrespective of sex, no statistically significant differences in AC values were observed between persons with MS and without.

ANCOVA: Effects of Cardiovascular Risk Factors on Carotid Stiffness Indices

ANCOVA analyzing the effects of cardiovascular risk factors on the values of CS indices (Table 3) demonstrated that MS was associated with higher beta and PWV-beta values. Further analysis showed that the effect of MS on beta values was statistically significant in women but not in men. Moreover, no associations between MS and PWV-beta values were observed when the results were analyzed separately for women and men.

Aside from MS, the indices of CS in the whole study group were determined by age (all parameters), male sex (only beta), arterial blood pressure parameters: PP (beta, Ep and AC) and MAP (Ep, PWV-beta and AC), heart rate (PWV-beta and AC) and BMI (only AC). Interestingly, the cardiovascular risk factors exerted different effects on the values of CS indices in women and men. Except age, which determined most stiffness indices regardless patient sex, the effects of other variables, blood pressure parameters, heart rate and BMI, were sex-specific. PP turned out to be a determinant of CS solely in women, whereas the significant effects of MAP on CS indices were observed primarily in men (in women, MAP determined only one parameter of CS, AC). Heart rate exerted a significant effect on some stiffness indices, but only in men, whereas BMI turned out to be a significant determinant of AC values, but solely in women.

MANOVA: Independent Determinants of Carotid Stiffness Indices in Metabolic Syndrome

Subsequently, conventional MANOVA was conducted (Table 4) to verify which factors were associated with the CS indices in MS patients. In the whole group of MS patients, regardless their sex, CS was modulated by age (all indices), SBP (all indices), DBP (AC and PWV-beta), type 2 diabetes

Table 2 Clinicodemographic Characteristics, Echo-Tracking Carotid Stiffness Parameters and IMT Stratified According to Participant Sex

Parameter	Women	Women	Women	Men	Men	Men	Total	Women	Men
	Total	MS (+)	MS (-)	Total	MS (+)	MS (-)	W vs M	MS (+) vs MS (-)	MS (+) vs MS (-)
	(N = 207)	(N = 109)	(N = 98)	(N = 212)	(N = 106)	(N = 106)	*p*	*p*	*p*
Age [years]	55.3 ± 11.1	56.1 ± 12.4	54.4 ± 9.3	53.2 ± 11.0	53.2 ± 10.5	53.3 ± 11.4	0.061	0.288	0.970
BMI [kg/m^2]	30.1 ± 6.5	32.3 ± 5.4	27.7 ± 6.8	29.1 ± 5.0	31.5 ± 5.0	26.6 ± 3.7	0.080	<0.001	<0.001
Waist circum [cm]	95 ± 15	100 ± 11	88 ± 15	99 ± 14	106 ± 13	92 ± 10	<0.001	<0.001	<0.001
Diabetes mellitus	41 (20%)	38 (35%)	3 (3%)	51 (24%)	39 (37%)	12 (11%)	0.293	<0.001	<0.001
Hypertension	122 (59%)	75 (69%)	47 (48%)	146 (69%)	75 (71%)	71 (67%)	0.034	0.003	0.657
Glucose [mg/dl]	103 ± 26	112 ± 31	93 ± 11	109 ± 30	121 ± 36	98 ± 15	0.005	<0.001	<0.001
Cholesterol [mg/dl]	206 ± 52	204 ± 57	209 ± 47	195 ± 51	201 ± 57	189 ± 41	0.030	0.495	0.096
LDL-C [mg/dl]	135 ± 39	131 ± 42	85 ± 35	129 ± 33	135 ± 34	121 ± 31	0.075	0.167	0.004
HDL-C [mg/dl]	61 ± 29	55 ± 28	67 ± 29	49 ± 12	45 ± 11	53 ± 13	<0.001	0.006	<0.001
TGL [mg/dl]	127 ± 72	156 ± 82	92 ± 33	151 ± 106	182 ± 98	113 ± 103	0.007	<0.001	<0.001
HR [bpm]	70 ± 11	73 ± 12	68 ± 12	70 ± 11	71 ± 13	68 ± 10	0.408	0.003	0.103
SBP [mmHg]	137 ±/21	141 ± 20	132 ± 21	139 ± 19	141 ± 20	138 ± 18	0.146	0.002	0.296
DBP [mmHg]	79 ± 11	80 ± 11	78 ± 11	81 ± 13	82 ± 14	81 ± 12	0.081	0.198	0.733
PP [mmHg]	57 ± 18	60 ± 18	54 ± 16	58 ± 11	59 ± 12	57 ± 11	0.449	0.009	0.183
MAP [mmHg]	97 ± 18	98 ± 19	95 ± 16	99 ± 16	101 ± 16	97 ± 16	0.180	0.198	0.141
IMT [mm]	0.67 ± 0.19	0.65 ± 0.18	0.70 ± 0.21	0.63 ± 0.16	0.63 ± 0.15	0.62 ± 0.17	0.015	0.087	0.563
Beta [-]	8.5 ± 3.4	9.2 ± 3.9	7.6 ± 2.6	9.1 ± 3.4	9.6 ± 3.7	8.5 ± 3.0	0.067	0.001	0.025
Ep [kPa]	123 ± 55	133 ± 62	113 ± 45	131 ± 62	141 ± 71	121 ± 49	0.154	0.009	0.022
AC [mm^2/kPa]	0.70 ± 0.29	0.67 ± 0.29	0.72 ± 0.30	0.74 ± 0.27	0.74 ± 0.29	0.73 ± 0.25	0.126	0.192	0.757
PWV-beta [m/s]	6.49 ± 1.39	6.72 ± 1.34	6.21 ± 1.40	6.59 ± 1.67	6.85 ± 1.64	6.28 ± 1.67	0.578	0.032	0.038

Abbreviations: BMI, body mass index; MS, metabolic syndrome; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TGL, triglycerides; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; IMT, intima-media thickness; beta [-], beta stiffness index; Ep, Peterson's elastic modulus; AC, arterial compliance; PWV-beta, one-point pulse wave velocity.

Table 3 Relationships Between Cardiovascular Risk Factors and Carotid Stiffness Parameters in the Whole Study Group and Separate in W and M: The Results of ANCOVA (p value)

	Total				Women				Men			
	(n = 419)				(n = 207)				(n = 212)			
	Beta	Ep	AC	PWV Beta	Beta	Ep	AC	PWV Beta	Beta	Ep	AC	PWV Beta
Age	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.062	<0.001	<0.001	<0.001	<0.001
BMI	0.174	0.250	<0.001	0.729	0.925	0.897	<0.001	0.774	0.051	0.072	0.316	0.195
PP	0.001	<0.001	<0.001	0.065	<0.001	<0.001	0.001	0.013	0.629	0.7	0.101	0.947
MAP	0.723	<0.001	<0.001	0.004	0.415	0.061	0.001	0.556	0.275	0.311	<0.001	0.002
HR	0.455	0.09	0.015	0.001	0.701	0.464	0.335	0.393	0.427	0.543	0.020	<0.001
LDL-C	0.093	0.103	0.134	0.871	0.189	0.169	0.159	0.821	0.272	0.311	0.585	0.887
Sex	0.017	0.086	0.108	0.142	x	x	x	x	x	x	x	x
MS	0.003	0.051	0.256	0.025	0.021	0.251	0.093	0.061	0.119	0.117	0.871	0.228

Abbreviations: BMI, body mass index; MS, metabolic syndrome; LDL-C, LDL cholesterol; HR, heart rate; PP, pulse pressure; MAP, mean arterial pressure; beta [-], beta stiffness index; Ep, Peterson's elastic modulus; AC, arterial compliance; PWV-beta, one-point pulse wave velocity.

Table 4 Relationships Between Cardiovascular Risk Factors and Carotid Stiffness Parameters in Patients with MS: The Results of MANOVA

	Total MS (+) (n = 215)				Women MS (+) (n = 109)				Men MS (+) (n = 106)			
	Beta	Ep	AC	PWV Beta	Beta	Ep	AC	PWV Beta	Beta	Ep	AC	PWV Beta
Age	0.35	0.25	−0.35	0.29	0.32	0.26	−0.27	–	0.39	0.28	−0.34	0.37
Glucose	–	–	–	–	–	–	–	–	–	–	–	–
Cholesterol	–	–	–	–	–	–	–	–	–	–	–	–
HDL-C	–	–	–	–	–	–	–	–	–	–	–	–
LDL-C	–	–	–	–	–	–	–	–	–	–	–	–
TGL	–	–	–	–	–	–	–	–	–	–	–	–
SBP	0.25	0.64	−0.28	0.36	–	0.49	−0.41	0.53	–	–	–	–
DBP	–	–	−0.19	0.23	–	–	–	–	–	0.61	–	0.60
PP	–	–	–	–	0.36	–	–	–	–	–	–	–
MAP	–	–	–	–	–	–	–	–	0.27	–	−0.45	0.58
BMI	–	–	–	–	–	–	–	–	–	–	–	–
Waist	–	–	0.22	–	–	–	0.29	–	–	–	–	–
Women	–	–	–	–	x	x	x	x	x	x	x	x
Diabetes	0.27	0.23	–	–	–	0.18	–	0.31	0.28	0.33	–	–
Hypertension	–	–	–	–	–	–	–	–	–	–	–	–

Abbreviations: BMI, body mass index; MS, metabolic syndrome; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TGL, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; beta [-], beta stiffness index; Ep, Peterson's elastic modulus; AC, arterial compliance; PWV-beta, one-point pulse wave velocity.

mellitus (beta and Ep) and waist circumference (only AC). However, in the case of the latter risk factor, a paradoxical relationship with CS was observed, as larger waist circumference turned out to be associated with higher AC values.

The multivariate analysis conducted separately for women and men with MS provided some interesting findings. In both women and men, CS indices were associated with age and type 2 diabetes mellitus. In women with MS, CS was also determined by the pulsatile components of blood pressure – SBP and PP, as well as by waist circumference (in the case of the latter, the abovementioned paradoxical relationship with AC was observed). Interestingly, none of these associations was found in men with MS, in whom CS was associated with DBP and with the steady component of blood pressure – MAP.

Discussion

The first important finding of this study is the observation that in the examined group, consisting primarily of middle-aged persons (mean age 54.3 years), IMT values in patients

with MS were not significantly greater than in individuals without this condition, whereas the values of all CS indices except AC were significantly higher. This implies that in patients with MS, functional changes manifesting as increased arterial stiffness might precede the structural alterations in form of greater IMT. Presence of such pathophysiological sequence in patients with MS is also supported by the results of a prospective study conducted in young adults (baseline age 36–42 years) from the Netherlands.[1] In this study, patients with MS presented with significantly higher baseline values of CS parameters and greater interadventitial diameters than the controls, whereas no statistically significant between-group differences were found with regards to the IMT. However, during a 6-year follow-up, patients with MS showed significantly greater increase in the IMT and arterial diameters than the controls. Interestingly, also in a substudy of the Hoorn Study, performed in the elderly non-diabetic population, MS was associated significantly with arterial remodeling and stiffness but not with IMT.[29] Concerning the interaction between MS and IMT, it is noteworthy that some authors observed a relationship between MS and increased IMT solely in women.[4,5,27,30]

As the first component of vascular remodeling, increased arterial stiffness deserves particular attention. In our study, MS turned out to be a determinant of 2 out of 4 analyzed CS indices (beta and PWV-beta); however, patients with MS presented with significantly higher values of all CS parameters except AC. The relationship between MS and increased arterial stiffness has been already documented in previous studies.[5,30,31] However, the results of some studies suggest that the association between MS and increased arterial stiffness might be stronger in women than in men.[5,12,13] Also in our present study, the effect of MS on CS turned out to be stronger in women than in men. However, in the MARK study, men with MS presented with higher values of two stiffness indices, CAVI and baPWV.[31] The reason behind the different effect of MS on arterial stiffness in both genders is still not fully understood and one of the possible mechanisms that might be responsible for this phenomenon involves sex hormones. Estrogens have been shown to modulate arterial stiffness over the lifespan: prepubertal females are characterized by higher arterial stiffness than their male counterparts, women of reproductive age have more compliant arteries than men and then – with the onset of menopause – women experience a rapid rise in arterial stiffness.[32,33] Estrogens affect vascular function through various pathways, including nitric oxide-dependent vasodilation, reduction of oxidative stress, reduction of inflammation and regulation of insulin action.[34] In women with MS the positive effects of estrogens, including estrogen – insulin interaction, might be impaired.[35]

Relationship Between Cardiovascular Risk Factors and Carotid Stiffness Parameters in Persons with Metabolic Syndrome

Many previous studies involving large groups of participants with various clinical profiles demonstrated that age was a main independent determinant of arterial stiffness.[36,37] The age-dependent rise in CS measured by eT may show different patterns: with linear increase for PWV-beta and curvilinear (with steeper progress in middle and older age) for beta and Ep.[22,26]

Another potent determinant of arterial stiffness, also in patients with MS, is arterial blood pressure. While the relationship between elevated blood pressure and arterial stiffness has been well documented, the question whether an increase in arterial stiffness predisposes to higher blood pressure or vice versa is still a matter of a debate. With no doubt, these two processes accelerate each other, and recent evidence from experimental and clinical studies suggests that a primary element in this pathophysiological sequence might be increased arterial stiffness, predisposing to arterial hypertension.[38]

In our present study, SBP in patients with MS correlated with all analyzed CS indices. Furthermore, statistically significant relationships were found between DBP, PWV-beta and AC values. In a Spanish study, elevated blood pressure (both SBP and DBP) was identified as the strongest determinant of arterial stiffness of all MS components.[31] Also in other studies, involving MS patients with various ethnic backgrounds (Americans, Koreans), elevated blood pressure was identified as an independent determinant of arterial stiffness.[13,30]

Recently, two components, the so-called "steady" component expressed by MAP and "pulsative" component the measure of which is PP are used to describe the blood pressure characteristics.[39] Interestingly, our present study showed that CS in women and men correlated with different blood pressure components. In women with MS, increased CS was associated with the pulsative component – PP, whereas in men with MS, a significant relationship was found between CS and the steady component – MAP. This confined to women relationship between PP and CS was

described previously in a population of subjects with cardiovascular risk factors.[26] We did not find a significant difference in PP values in women and men, either in the whole study group or in patients with MS. However, women with MS presented with significantly higher PP than healthy controls, whereas no between-group differences in PP were found among men. This implies that MS might exert a stronger effect on PP in women than in men. According to literature, the pulsative component of blood pressure has greater clinical importance in women than in men. In a Korean study, PP was shown to be an independent predictor of an angiographically relevant coronary artery disease in middle-aged women, but not in men, and in the CASTEL study, PP was identified as a predictor of coronary mortality in older Italian women.[40,41] Of noteworthy is that it is the PP, not the steady components of blood pressure, which constitutes the most potent determinant of cardiovascular events.[42]

A question whether type 2 diabetes mellitus has different effect on arterial remodeling in women and men still raises controversies. Moreover, some authors claimed that type 2 diabetes mellitus is a stronger determinant of arterial stiffness in female than in male patients.[43] However, other papers, including our present study, did not show sex-specific differences in the influence of carbohydrate metabolism disorders on arterial stiffness.[44] Those discrepancies justify further research on a link between carbohydrate metabolism and arterial stiffness in women and men.

Although decreased level of HDL cholesterol and elevated concentrations of triglycerides and low-density lipoprotein (LDL) cholesterol are established predictors of cardiovascular mortality, a relationship between the lipid profile of the blood and arterial stiffness is still not fully understood.[45] Similar to our research, many previous studies did not demonstrate a significant association between the lipid profile and arterial stiffness evaluated with various methods.[44] Interestingly, Topouchian et al found that a link between blood lipids and arterial stiffness might depend on the type of analyzed stiffness measure; specifically, they showed that triglyceride and HDL cholesterol concentrations correlated with cfPWV, but not with CAVI.[46] In other studies of MS patients, no significant correlation was found between HDL cholesterol levels and CAVI, and a relationship between HDL concentrations and baPWV turned out to be significant solely in men. Furthermore, an association between triglyceride concentrations and arterial stiffness was observed in some studies, including one in which this relationship was significant solely in men.[25,31] The sex-specific differences in the relationships between various lipid fractions and local measures of CS were also documented in an Italian study, Sapaldia; in this study, CS correlated significantly with triglyceride concentrations in women and LDL cholesterol levels in men.[6] To summarize, published evidence for a link between arterial stiffness and blood lipids is not infrequently inconclusive. The existing discrepancies might result from differences in the methodology of arterial stiffness evaluation and/or different characteristics of examined populations. Hence, still more research is needed to fully understand the effects of blood lipid concentrations on arterial stiffness.

Surprisingly, we found a paradoxical relationship between waist circumference and AC; specifically, an increase in waist circumference was shown to be associated with higher AC values. This association was found both in the whole group of patients with MS and in women with MS. In most previous studies in which arterial stiffness was estimated based on cfPWV, patients with larger waist circumference presented with greater arterial stiffness.[47,48] Interestingly, however, in the study published by Topouchian et al in 2017, waist circumference correlated positively with cfPWV but showed an inverse correlation with CAVI.[46] This implies that patients with larger waist circumference might have presented with lesser arterial stiffness. The relationship was particularly evident in women older than 75 years.[46] An explanation for the paradoxical association between waist circumference and arterial compliance estimated based on CAVI or local AC, likewise in our present study, is yet to be found.

In summary biomarkers of early arterial damage might be helpful in development of preventive and therapeutic strategies (also sex-specific strategies) to avoid cardiovascular episodes in asymptomatic patients.

Strengths

Our study was performed in three centers located in two countries (Italy and Poland). Arterial stiffness was measured with the eT system, which allows for an easy and relatively fast assessment of the local CS, including the assessment of the one-point PWV beta. Furthermore, as the eT measurements are obtained with the ultrasound machine – simultaneous examination of IMT can be performed.

Limitations

The study included solely middle-aged Caucasians, and therefore, the results cannot be generalized onto other populations. The fact that the brachial artery pressure was measured, rather than the central pressure, might

contribute to an overestimation of the stiffness indices, especially in young and middle-aged subjects due to pulse pressure amplification. The influence of medications on CS was not analyzed.

Conclusions

1. In a predominantly middle-aged population, subjects with MS – in comparison to subjects without MS – presented with elevated CS. By contrast, no significant difference in IMT values was found between these two groups.
2. The results of sex-specific analyses imply that in the middle-aged population the relationship between MS and carotid stiffness might be stronger in women than in men.
3. Various components of arterial blood pressure were shown to exert different, sex-specific effects on CS; specifically, CS was associated with the pulsative component in women and the steady component in men.
4. A paradoxical association was found between larger waist circumference and greater AC in women with MS.

Data Sharing Statement

The datasets analysed during the current study are available from the corresponding author on request.

Ethics Approval and Consent to Participate

Our study complied with the Declaration of Helsinki and was approved by the Ethics Committee of: 1) Wroclaw University of Medicine, 2) University of Pisa and 3) San Antonio Hospital, San Daniele del Friuli, Udine. Written informed consent was sought from each participant.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests for this work.

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