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CLINICAL STUDY

Obesity, elevated levels of fasting plasma glucose and type 2 diabetes are associated with aortic stiffness

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ABSTRACT
OBJECTIVES: Obesity and metabolic syndrome (MetS) are associated with structural and functional vascular abnormalities. MetS and its components may increase arterial stiffness and the risk of cardiovascular events. However, the relationship of MetS and its components, including obesity, with arterial stiffness is still not fully understood.
SUBJECTS AND METHODS: In a group of 116 patients undergoing treatment for hypertension, we searched for the relationships between parameters of MetS and aortic stiffness expressed by pulse wave velocity (PWVAo).
PWVAo was measured using an arteriograph working on the oscillometric principle, and pulse wave analysis (PWA) for noninvasive assessment of the parameters of central hemodynamics.
RESULTS: From the cluster of parameters of MetS we found a significant association between body mass index (BMI) and aortic stiffness, and between fasting plasma glucose/type 2 diabetes (FPG/T2DM) and aortic stiffness**.** We did not find significant relationships between other components of MetS (HDL cholesterol and triglycerides) and aortic stiffness, based on the influence of hypolipidemic therapy. Arterial stiffness increased with age and was higher in females.
CONCLUSION: Arterial stiffness was associated with age, sex, and MetS components (BMI and FPG/T2DM). Surprisingly, the parameters of dyslipidemia do not influence stiffness parameters, which can be explained by hypolipidemic therapy. The influence of hypolipidemic therapy should therefore be borne in mind when evaluating arterial tree function *(Tab. 7, Ref. 62)*. Text in PDF *www.elis.sk*_
KEY WORDS: obesity, fasting plasma glucose, type 2 diabetes, aortic stiffness, metabolic syndrome, arterial hypertension, cardiovascular risk.

Introduction

Excessive caloric supply and reductions in physical activity have caused an increase in the number of industrialized countries with a large proportion of obese people (1, 2).

Obesity has become the most common nutritional disorder in many countries. With the advent of modern conveniences promoting increased dietary ingestion and a sedentary lifestyle, it is inevitable that a higher proportion of the population is exposed to a state of energy excess, which contributes to the exponential growth of type 2 diabetes (T2DM) and obesity-related diseases (3, 4). Obesity with visceral fat accumulation (visceral fat obesity) associates closely with T2DM, hyperlipidemia, hypertension, and atherosclerosis (5, 6, 7).

Previously, the adipose tissue was considered a generally passive repository for stored triglycerides (8). Although traditionally regarded as a silent organ that passively stores excess energy, adipose tissue is now considered to be an endocrine organ. With the discovery of adiponectin, it has become clear that the adipose tissue carries out a large number of metabolic, paracrine, and endocrine functions (8, 9). Thus, increasing evidence suggests that adipose tissue, especially visceral fat tissue, participates directly in the pathophysiology of the metabolic syndrome (MetS) and obesity-related cardiovascular diseases (CVD) (5, 10). Adipose tissue inflammation is considered a major contributing factor in the development of obesity-associated insulin resistance and CVD. However, the cause of adipose tissue inflammation has not yet been fully clarified (11, 12).

Cardiovascular diseases represent a serious global health problem. MetS is a complex health condition responsible for the occurrence of several metabolic abnormalities and cardiovascular

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disturbances, despite the lack of a unified definition among health organizations, such as the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III) (13), International Diabetes Federation (IDF), World Health Organization (WHO), American Heart Association and National Heart, Lung and Blood Institute (AHA/NHLBI) (14). MetS comprises glucose metabolism dysregulation due to insulin resistance, central obesity, dyslipidemia, including increased blood triglycerides and decreased high-density lipoprotein cholesterol, and arterial hypertension (15, 16, 17). This combination of risk factors favors adverse outcomes such as T2DM and CVD and increases mortality rates by approximately 50 % (18, 19).

MetS is recognized as a progressive pathophysiological state, being part of the trajectory leading to prediabetes, T2DM, and CVD (20, 21). In fact, MetS is not only a precursor but also a predictor of the development of T2DM (22, 12). MetS has a relationship with CVD and increases the incidence of cardiovascular complications in patients with arterial hypertension (AH). The probable cross-connection between CVD and MetS is the visceral fat, which represents a large endocrine organ that releases into circulation a large number of mediators that negatively affect the arterial system.

Treated AH, or blood pressure values in the high–normal pressure range, is included among the components of MetS (23). In terms of the negative effect of AH on the cardiovascular system, the importance of central systolic pressure, which is directly related to heart load, and exposed in the most important organs such as the brain and kidneys, has been highlighted in recent years (24). The probable link between MetS and CVD is endothelial dysfunction, which, through a cascade of metabolic effects, affects the intima-media complex, leads to the development of atherosclerosis and vascular wall hypertrophy, and is connected to increasing the thickness of the vascular wall (21).

MetS has a relationship with cardiovascular diseases and increases the incidence of cardiovascular complications in patients with arterial hypertension. We know from our own experiences, as well as published studies, that patients with arterial hypertension have MetS at the same time (metabolic syndrome is very often present in patients with hypertension) (25, 26, 27). In routine clinical practice, we encounter treated hypertensive patients, and when monitoring the effect of treatment, we also aimed to monitor the level of central systolic pressure and aortic stiffness in relation to the presence of MetS. In order to clarify the relationship between MetS and aortic stiffness, we examined a group of treated patients with arterial hypertension.

Material and methods

The analyzed group consisted of 116 patients aged 61 ± 11 years, (mean ± SD), 58 men aged 58.0 ± 13 years and 58 women aged 63 ± 10 years with well-controlled arterial hypertension. The patients were analyzed for brachial systolic blood pressure (SBPbrach), brachial diastolic blood pressure (DBPbrach), central systolic blood pressure (SBPAo), heart rate (HR), mean arterial pressure (MAP), pulse pressure (PP), aortic pulse wave velocity (PWVAo), aortic augmentation index (AIx-Aortic), brachial augmentation index (AIx-Brachial), and return time of reflected pressure wave (RT) (Tabs 1, 2, and 3).

Tab. 1. Basic clinical characteristic of the subjects.

Parameter	Males	Females	Total
Number	58	58	116
Age (years)±SD	58±12	63±10	61±11
Height (cm)±SD	179±6	164±6	171±10
Weight (kg)±SD	93±13	74±12	83±16
BMI (kg/m^2)±SD	29±3.5	28±4.5	28±4.1

Tab. 2. Peripheral hemodynamics.

Parameter	Males	Females	Total
Brachial Systolic BP (mmHg)±SD	134±17	129±14	131±16
Brachial Diastolic BP (mmHg)±SD	81±10	77±8	80±10
Heart rate (b/min)±SD	64±10	65±11	65±10
MAP (mmHg)±SD	99±12	94±11	97±12
PP (mmHg)±SD	52±10	52±9.5	52±10

Tab. 3. Central hemodynamics.

Parameter	Males	Females	Total
Central Systolic BP (mmHg)±SD	130±18	130±14	130±17
Aortic Pulse Wave velocity (m/s)±SD	9.3±1.8	10.0±1.8	9.7± 1.8
Return time (m/s)±SD	120.5±22	105.6±18	113±22
AIx Brachial (%)±SD	–13.3±27	9.1±23	–2.1±27
AIx Aortic (%)±SD	27.4±12	36.5±9	32±12

We used the Tensiomed arteriograph Ltd (H-1103 Budapest, Hungary) working on the oscillometric principle using pulse-wave analysis (PWA) for central systolic blood pressure (SBPAo) and related parameters (28).

Each patient underwent standard clinical evaluation, measurement of anthropometric parameters, laboratory tests including lipid profile, and glycaemia. The patients signed an informed consent form after we had explained the nature and aim of this type of noninvasive BP measurement, which was added to our usual set of examinations focused on the identification of preclinical CVD in patients diagnosed with hypertension (29, 30). The association between investigated parameters and PWVAo was assessed.

The diagnosis of MetS in our work was established on the basis of the recommendation of a panel of experts from professional companies, based on the NCEP-ATP III criteria of the National Cholesterol Education Program, Adult Treatment Panel III (ATP III) (13).

National recommendations made by a panel of expert associations have proposed criteria for the diagnosis of MetS in the Slovak Republic: (1) being overweight/obesity (BMI above 25 kg/m^2 and/or waist circumference above 102 cm in men and above 88 cm in women), (2) triglycerides levels above 1.7 mmol/l, (3) a decrease in the level of HDL-C below 1.0 mmol/l in men and 1.3 mmol/l in women, (4) elevation of blood pressure above 130/85 mmHg, (5) fasting plasma glucose level above 5.6 mmol (marginal fasting plasma glucose levels or T2DM), and (6) glycaemia above 7.8 mmol/l 2 hours after an oral glucose toleration test (OGTT) (glucose tolerance disorder or T2DM). If three of the above criteria were met, patients in our study were diagnosed with MetS (31).

The group of all patients was divided into two subgroups – those with and without MetS. The diagnosis of MetS was established according to classification of MetS, when the patients fulfilled the accepted criteria regardless of blood pressure, fasting glycaemia/type 2 diabetes (FPG/T2DM), body mass index (BMI), triglycerides (TAG), and HDL cholesterol (HDL-C).

Patients were also categorized and analyzed according to their metabolic syndrome components clustering and combinations. For both subgroups, with and without MetS, we also assessed the total cholesterol values (T-chol), non-HDL cholesterol (non-HDL-C), and LDL cholesterol (LDL-C).

Statistical methods

We used the mean, standard deviation and median to characterize the evaluated data. For statistical evaluation, we used the independent two-sample t-test, nonparametric paired Wilcoxon test, Pearson chi-squared test of independence and linear regression, one-way analysis of variance (ANOVA), and multiple linear regression analysis.

Results

The basic clinical characteristics of the subjects, peripheral hemodynamics, and central hemodynamics of investigated group are shown in Tables 1, 2 and 3.

The mean PWVAo was 9.66 ± 1.81 m/s and was significantly higher in women (10.04 ± 1.82) than in men (9.31 ± 1.75, p = 0.026) (Tab. 4). One-way analysis of variance (ANOVA) showed that sex was associated with PWVAo (p = 0.039). Multiple linear regression analysis showed that age was associated with PWVAo (p < 0.001). The Pearson correlation between age and PWVAo (r = 0.35) was statistically significant (p < 0.001).

Tab. 4. Influence of sex on PWVAo in investigated group.

Aortic pulse wave velocity (m/s)	Total (mean±SD) (n=116)	Males (mean±SD) (n=58)	Females (mean±SD) (n=58)	p
	9.6±1.8	9.3±1.7	10.04±1.8	p=0.026

Tab. 5a. Influence of abdominal obesity on PWVAo in investigated group.

Aortic pulse wave velocity (m/s)	Total (mean±SD)	Males (mean±SD)	Females (mean±SD)
With abdominal obesity as a component of MetS (n=77)	10.0±1.8	9.6±1.8	10.3±1.8
Without abdominal obesity as a component of MetS (n=39)	9.1±1.7	8.8±1.7	9.4±1.7
p	p=0.011	n.s.	n.s.

Tab. 5b. BMI in investigated group.

BMI	%	n
18.5–25 (normal)	21.6	25
25–30 (overweight)	45.7	53
30–35 (moderate obesity)	25.9	30
> 35 (severe obesity)	6.9	8
Σ	100.0	116
Overweight/obesity	78.5	91

Tab. 5c. BMI in males and females in investigated group.

BMI	Males		Females	
	%	n	%	n
18.5–25 (normal)	12.1	7	31.0	18
25–30 (overweight)	55.2	32	36.2	21
30–35 (moderate obesity)	25.9	15	25.9	15
>35 (severe obesity)	6.9	4	6.9	4
Σ	100.0	58	100.0	58
Overweight/obesity	88.0	51	68.0	40

Tab. 5d. BMI in investigated group of patients with and without MetS.

BMI	MetS		Without MetS	
	%	n	%	n
18.5–25 (normal)	6.9	4	36.2	21
25–30 (overweight)	43.1	25	48.3	28
30–35 (moderate obesity)	39.7	23	12.1	7
>35 (severe obesity)	10.3	6	3.4	2
Σ	100.0	58	100.0	58
Overweight/obesity	93.1	54	63.8	37

The mean PWVAo in the group of patients with abdominal obesity was 10.0 ± 1.8 m/s, i.e., significantly higher than in the group without obesity (9.1 ± 1.7 m/s, p = 0.011) (Tab. 5a). The Pearson correlation between BMI and PWVAo (r = 0.199) was statistically significant (p = 0.033). Multiple linear regression analysis showed that BMI was associated with PWVAo (p = 0.044).

Regardless of other components of MetS (HDL-C and TG), the association of all components of MetS (as a complex group) with PWVAo was not significant.

Regardless of the values of SBPAo, RT, AIx-Brach, and AIx-Aortic, the association of SBPAo with the presence of MetS was not statistically significant.

The entire investigated cohort and the subgroups with and without MetS were analyzed according to the presence of being overweight/obese and according to sex.

In our entire investigated group, more than three-quarters of patients (78.5 % of patients in total, i.e., 91 out of 116 patients) were overweight/obese. Out of these, 6.9 % of patients (8 patients) were severely obese (Tab. 5b).

When dividing the cohort by gender, 88.0 % of men (i.e., 51 of 58 men) and 68 % of women (i.e., 40 of 58 women) were overweight/obese. Overweight/obesity was more common in men (Tab. 5c).

When dividing the cohort into subgroups with and without MetS, 93.1% of patients (i.e., 54 of 58 patients) were overweight/obese in the MetS group, compared to 63.8% of patients (i.e., 37 of 58 patients) without MetS (Tab. 5d).

Thus, a total of 93.1% of patients in the group with MetS were overweight/obese.

When the cohorts with and without MetS were further divided by sex, 100 % of men with MetS (i.e., 30 men) and 85 % of women with MetS (i.e., 24 women) were overweight/obese. In the group of patients without MetS, 75 % of men (i.e., 21 men) and 53.3 %

Tab. 5e. BMI in males and females in investigated group of patients with and without MetS.

BMI	Males				Females			
	MetS		Without MetS		MetS		Without MetS	
	%	n	%	n	%	n	%	n
18.5–25 (normal)	0	0	25.0	7	14.3	4	46.7	14
25–30 (overweight)	46.7	14	64.3	18	39.3	11	33.3	10
30–35 (moderate obesity)	43.3	13	7.1	2	35.7	10	16.7	5
>35 (severe obesity)	10.0	3	3.6	1	10.7	3	3.3	1
∫	100.0	30	100.0	28	100.0	28	100.0	30
Overweight/obesity as risk component of MetS	100.0	30	75.0	21	85.7	24	53.3	16

Tab. 6a. Influence of FPG/T2DM and sex on PWVAo in investigated group.

Aortic Pulse Wave velocity (m/s)	Total (mean±SD) (m/s)	Males (mean±SD) (m/s)	Females (mean±SD (m/s)
With FPG/T2DM component of MetS (n=49)	10.1±1.7	9.7±1.9	10.5 ±1.4
Without FPG/t2dmcomponent of MetS (n=67)	9.41±1.8	9.0±1.6	9.7±2.0
p	p=0.025	n.s.	p=0.03

Tab. 6b. FPG/T2DM in investigated group.

FPG/T2DM	%	n
< 5.6	57.8	67
> 5.6 or T2DM	42.2	49
Σ	100.0	116
FPG/T2DM	42.2	49

Tab. 6c. FPG/T2DM in males and females in the investigated group.

	Males		Females	
FPG/T2DM	%	n	%	n
< 5.6	51.7	30	63.8	37
> 5.6 or T2DM	48.3	28	36.2	21
Σ	100.0	58	100.0	58
FPG/T2DM	48.3	28	36.2	21

Tab. 6d. PGT/T2DM in investigated group of patients with and without MetS.

	MetS		Without MetS	
FPG/T2DM	%	n	%	n
< 5.6	29.3	17	86.2	50
>5.6 or T2DM	70.7	41	13.8	8
Σ	100.0	58	100.0	58
FPG/T2DM	70.7	41	13.8	8

of women (i.e., 16 women) had overweight/obesity as a component of MetS (Tab. 5e).

One of the risk criteria for MetS, namely BMI over 25, occurred in 100 % of men and 85.7 % of women with MetS.

The mean PWVAo in the group of 49 patients with increased FPG/T2DM (10.1±1.7 m/s) was significantly higher than in the group of 67 patients without FPG/T2DM (9.4±1.8 m/s) (p = 0.025), with some differences according to the sex of the patients. In the female subgroup with FPG/T2DM, the value of PWVAo was higher (10.5±1.4) in comparison with the male subgroup (9.7±2.0 m/s, p = 0.03) (Tab. 6a).

Return time of reflected wave (RT) in the female subgroup with FPG/T2DM was shorter (100.4±14.6 m/s) compared to the male subgroup (117.0 ±17.3 m/s, p=0.045).

When adjusted to systolic blood pressure, PWVAo was higher in the subgroup of 35 patients (10.4±1.7 m/s) with more risk factors, namely with a combination of central obesity together with FPG/T2DM, than in the subgroup of 81 patients without this combination (9.3±1.8 m/s, p=0.003).

The entire investigated cohort as well as the subgroups with and without MetS were analyzed according to the presence of FPG/T2DM (Tab. 6b).

When the group was divided according to gender, 48.3 % of men (i.e., 28 of 58 men) and 36.2 % of women (i.e., 21 of 58 women) had FPG/T2DM (Tab. 6c).

When dividing the cohort into subgroups with and without MetS, 70.7 % of patients (i.e., 41 out of 58 patients) had FPG/T2DM in the MetS subgroup, compared to 13.8 % (i.e., 8 patients) without MetS (Tab. 6d).

FPG/DM as one of the components of MetS was thus present in a total of 70.7 % of patients in the MetS group.

When dividing the cohorts with and without MetS by sex, 80 % (i.e., 24 men) with MetS and 60.7 % of women (i.e., 17 women) had FPG/T2DM. In the group of patients without MetS, 14.3 % of men (i.e., 4 men) and 13.3 % of women (i.e., 4 women) had FPG/T2DM present as a component of MetS (Tab. 6e).

PGT/T2DM as one of the risk criteria for MetS occurred in 80 % of men and 60.7 % of women with MetS.

Regardless of other components of MetS (HDL-C and TAG), an association with PWVAo was not present.

The groups with and without MetS were analyzed according to differences in mean values in investigated lipid parameters. There were statistically significant differences in HDL-C (1.2±0.3 vs 1.5±0.3, p<0.001), TAG (1.8±0.9 vs 1.1±0.4, p<0.001), and non-HDL-C (3.9±1.1, vs 3.5±0.8, p=0.031) between both investigated subgroups with and without MetS. There were no statistically significant differences between the two investigated subgroups in either T-Chol (5.1±1.1 vs 5.0±0.9, p=n.s.) or LDL-C (3.4±1.0 vs 3.2±0.8, p=n.s) (Tab. 7).

Discussion

A frequent companion of diabetes mellitus, dyslipidemia, hypertension, and other disorders linked to atherosclerotic cardiovascular disease and death, obesity generates an enormous economic burden which, in addition to its human costs, renders it one of the most urgent issues in medicine today (5).

In our entire investigated group, more than three-quarters of patients (78.5 % of patients in total) were overweight/obese. Of those, 6.9 % of patients were severely obese. When dividing the cohort by gender, 88.0 % of men and 68 % of women were over-

Tab. 6e. FPG/T2DM in males and females in the investigated group of patients with and without MetS.

FPG/T2DM	Males				Females			
	MetS		Without MetS		MetS		Without MetS	
	%	n	%	n	%	n	%	n
<5.6	20.0	6	85.7	24	39.3	11	86.7	26
> 5.6	80.0	24	14.3	4	60.7	17	13.3	4
Σ	100.0	30	100.0	28	100.0	28	100.0	30
FPG/T2DM as risk component of MetS	80.0	24	14.3	4	60.7	17	13.3	4

Tab. 7. Lipid parameters in investigated group of patients with and without MetS.

	T-Chol (mean±SD)	HDL-C (mean±SD)	LDL-C (mean±SD)	Non-HDL-C (mean±SD)	TAG (mean±SD)
MetS	5.1±1.1	1.2±0.3	3.4±1.0	3.9±1.1	1.8±0.9
Without MetS	5.0±0.9	1.5±0.3	3.2±0.8	3.5±0.8	1.1±0.4
p	NS	p<0.001	NS	p=0.031	p<0.001

weight/obese. Being overweight or obese was more common in men. When dividing the cohort into subgroups with and without MetS, 93.1 % of patients were overweight/obese in the MetS group as compared to 63.8 % of patients without MetS. Being overweight/obese was thus present in a total of 93.1 % of patients in the group with MetS. When the cohorts with and without MetS were further divided by sex, 100 % of the men with MetS and 85 % of the women with MetS were overweight/obese. In the group of patients without MetS, 75 % of men and 53.3 % of women had overweight/obesity as a component of MetS. BMI over 25 as one of the risk criteria for MetS occurred in 100 % of men and 85.7 % of women with MetS.

In our study, we found that the mean PWVAo in the group of patients with abdominal obesity (10.0 ± 1.8 m/s) was significantly higher than in the group without abdominal obesity (9.1 ± 1.7 m/s, p=0.011). The Pearson correlation between BMI and PWVAo (r=0.199) was statistically significant (p=0.033). Multiple linear regression analysis showed that BMI was associated with PWVAo (p=0.044).

PWVAo was statistically significantly higher in patients with abdominal obesity as a component of MetS (p=0.011). This suggests higher aortic stiffness in overweight patients as compared to nonobese and non-MetS patients. Thus, we confirmed the relationship of abdominal obesity with PWVAo and aortic stiffness in men and women with arterial hypertension.

In their work, Mzayek et al (2019) assessed the cross-sectional and the longitudinal associations of abdominal obesity with aortic intima–media thickness (aIMT). Waist circumference was associated with wall thickness in all three segments of the aorta (proximal ascending aorta (PA-aIMT), proximal descending aorta (PD-aIMT), and distal aorta (bifurcation) (32).

In another study of patients with and without MetS, ascending aortic pulsatility, an index of arterial stiffness, was significantly higher in the MetS group. The multiple regression analysis revealed a statistically independent relationship between the ascendent AP (aortic pressure) fasting blood glucose, waist circumference, and systolic blood pressure. MetS as a whole was also independently statistically significantly associated with both ascending aortic pulsatility and aortic pulse pressure. The data showed that MetS is independently associated with increased aortic pulse pressure and ascending aortic stiffness in patients with normal coronary arteries, suggesting aortic stiffness as one of the possible mechanisms underlying the excess cardiovascular risk associated with MetS (33).

In our study, there was a statistically significant difference in the mean values of PWVAo between males and females with arterial hypertension and MetS (p=0.026).

The mean PWVAo was 9.66±1.81 m/s and it was significantly higher in women (10.004±1.82) than in men (9.31±1.75, p=0.026). One-way analysis of variance (ANOVA) showed that sex was associated with PWVAo (p=0.039). The multiple linear regression analysis showed that age was associated with PWVAo (p<0.001). The Pearson correlation between age and PWVAo (r=0.35) was statistically significant (p<0.001).

Arterial stiffness is said to be a novel predictor of cardiovascular events (34). A study by Topolska et al (2019) investigated the correlation between arterial stiffness parameters and estimated cardiovascular disease risk (RISK) in a cohort of Polish patients divided by age, sex, and BMI. The cross-sectional study enrolled 295 patients who met the inclusion criteria. Subjects were divided into three age groups, four weight groups, and by gender. The stiffness of the vessels was assessed by stiffness index (SI) and reflection index (RI) measurements. Individual 10-year RISK was calculated for each patient using the American Heart Association's Heart Risk Calculator algorithm. A significant correlation between the SI and estimated RISK was observed. The strongest relationship was present in women, in the age group of 40–54 years, and individuals with normal weight. A significant correlation between RI and calculated RISK was observed, the highest correlation being found in people aged 40–54 years who were also obese. Both SI and RI were correlated with estimated cardiovascular risk, however SI appeared to be more useful than RI to predict the individual risk of future cardiovascular events. Both can be measured using noninvasive techniques, which demonstrates their potential utility in clinical practice (34).

In a study by Lopes-Vicente et al (2017) involving patients with MetS, arterial stiffness was evaluated using pulse wave velocity (PWV) in the carotid–femoral segment. Statistically significantly increased PWV was observed in comparison with controls. In multivariate analysis, the variables that remained as predictors of PWV were age, systolic blood pressure, and TAG (35). When adjusted to systolic blood pressure, PWV was greater in the group with five risk factors as compared to the group with three risk factors and control group. Similarly, the group with four risk factors had higher PWV than the control group. The number of risk factors appears to increase arterial stiffness. Notably, in addition to age and increased systolic blood pressure, alterations in TAG worsened

the stiffness of large vessels, which emphasizes the importance of addressing this risk factor in MetS patients (35).

Obesity is a chronic inflammatory disorder in which leptin, adiponectin, and c-reactive protein (CRP) play an important role (11, 36). In metabolic disorders, the distribution of body fat may be of greater significance than total fat accumulation (5, 17). Obesity is accompanied by adipose tissue remodeling characterized by an increase in the production of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, leptin, and resistin, and by reduction in secretion of adiponectin, which favors inflammation, metabolic disorders, and cardiovascular diseases (20, 3). The clustering of risk factors augments atherosclerotic CVD, even beyond the contribution of the isolated components (5, 37).

Thus, increasing evidence suggests that adipose tissue, especially visceral fat tissue, participates directly in the pathophysiology of MetS and obesity-related CVD (5, 12). The increasing rates of this obesity-related syndrome have spurred the search for greater insight into the mechanisms contributing to the development of MetS, and especially those reflecting a dysfunction of adipose tissue, which is likely to play a major role in its development (38).

Because several clinical definitions of MetS co-exist, its true prevalence is difficult to establish. Despite this, U.S. surveys indicate that one-third of adults (39), including young adults, have MetS (21). Therefore, it is now accepted that MetS represents a global public health concern with a worldwide prevalence ranging from 10 to 84 %, depending on ethnicity, age, and sex (40, 41, 42, 21).

Obesity with visceral fat accumulation (visceral fat obesity) is closely associated with diabetes mellitus, hyperlipidemia, hypertension, and atherosclerosis (5).

Low-grade inflammation in adipose tissue is considered a major contributing factor in the development of obesity-associated insulin resistance and CVD (12). Despite its well-established role in causing insulin resistance, the cause of adipose tissue inflammation is not currently understood (12). The adiponectin gene was found to be the most abundantly expressed gene in adipose tissue (43). It encodes a 244-amino-acid protein with a predicted size of 30 kDa (8).

In our entire investigated group, 42.2 % of patients met the criterion of FPG/T2DM as a component of MetS. When the group was divided by gender, 48.3 % of men and 36.2 % of women had FPG/T2DM. When dividing the cohort into subgroups with and without MetS, 70.7 % of patients had FPG/T2DM in the MetS group, compared to 13.8 % in the subgroup without MetS. FPG/T2D, as one of the components of MetS, was thus present in a total of 70.7 % of patients in the MetS group. When the cohorts with and without MetS were divided by sex, 80 % of men and 60.7 % of women with MetS had FPG/T2DM. In the group of patients without MetS, 14.3 % of men and 13.3 % of women had FPG/T2DM present as a component of MetS. PGT/T2DM, one of the risk criteria for MetS, occurred in 80 % of men and 60.7 % of women with MetS.

The mean PWVAo in the group of 49 patients with increased fasting plasma glucose or diabetes mellitus type 2 (FPG/T2DM) (10.1±1.7 m/s) was significantly higher than in the group of 67 patients without FPG/T2DM (9.4±1.8 m/s, p=0.025), with a different association according to sex of the patient. In the female subgroup with FPG/T2DM the value of PWVAo was higher (10.5±1.4) in comparison with the male subgroup (9.7±2.0 m/s, p=0.03).

The return time (RT) in the female subgroup with FPG/T2DM was shorter (100.4±14.6 m/s) compared to the male subgroup (11.0 ±17.3, p=0.045).

When adjusted to systolic blood pressure, PWVAo was greater in the subgroup of 35 patients (10.4±1.7 m/s) with more risk factors (combination of central obesity together with FPG/T2DM) than in the subgroup of 81 patients without this combination (9.3±1.8 m/s, p=0.003).

In a study of 63 middle-aged and older subjects with and without MetS and with prehypertension and/or pre-diabetes, MetS components and carotid artery stiffness were determined using ultrasound at the baseline, at 8 weeks, and following 24 weeks of lifestyle intervention. Subjects with MetS were statistically significantly heavier than subjects without MetS, their BMI and waist circumference was greater, and their blood pressure, FPG, TAG, and LDL-C levels were elevated compared to the subjects without MetS. Baseline carotid artery structures and function did not differ between the groups. The carotid artery distensibility tended to be lower in the MetS group than in the group without MetS, whereas their beta stiffness index was comparably similar (44). Carotid artery distensibility significantly increased in the MetS subgroup following the 24 weeks of lifestyle intervention, compared with baseline measurements; similarly, the beta stiffness index in the MetS subgroup significantly decreased. After lifestyle intervention, blood pressure, FPG, and waist circumference also decreased (44).

In another study, the coexistence of prehypertension and impaired fasting glucose in middle-aged Japanese men was shown to synergistically increase the brachial–ankle pulse wave velocity (45). Thus, it appears that the presence of MetS in addition to prehypertension and/or prediabetes exacerbates age-associated central artery stiffness, and several studies support this theory.

However, a study by F.M.A.C. Martens in 2008 revealed that, although the presence of MetS without T2DM was associated with marginally higher carotid artery stiffness, the presence of MetS with T2DM was associated with a marked increase in carotid artery stiffness in patients with manifestations of arterial disease (46).

In another study, Aizawa K et al (2008) showed that the presence of MetS did not synergistically increase the carotid artery stiffness in MetS subjects with prehypertension and/or prediabetes (47). Although the discrepancy between studies might be due to the differences in populations studied, these findings in part indicate that the contribution of T2DM to the development of hypertension from prehypertension may be of great importance in MetS (44).

The study by Aizawa et al (44), which showed a decrease not only in carotid artery stiffness but also in both blood pressure and fasting glucose levels following the 24-week intervention, would suggest the usefulness of lifestyle modification programs in prevention of type 2 DM and hypertension as well as the possibility of reducing CVD as a result of the decrease in central arterial stiffness (44, 47).

We can speculate that there are several possible mechanisms by which a lifestyle modification program could reduce central artery stiffness in MetS subjects (44, 47).

A Mediterranean-style diet (Esposito et al, 2004) has been shown to improve endothelial function (48). The study by Aizawa et al. (2009) showed that a reduction in inflammatory markers (hsCRP and IL-6) was associated with improved endothelial function, suggesting the anti-inflammatory effect of a Mediterranean-style diet (49). These mechanisms may in part explain the reduction in carotid artery stiffness observed in the study by Aizawa et al (44).

Improved endothelial function has also been observed following aerobic exercise training (50).

Donley et al (2014) compared the effects of aerobic exercise training on arterial stiffening mechanics in MetS subjects without overt CVD or T2DM. MetS and healthy control subjects underwent 8 weeks of exercise training or remained inactive. A statistically significant reduction in carotid–femoral pulse wave velocity (ct-PWV) was observed in MetS patients and control group subjects after exercise training (51).

MetS, a cluster of metabolic disorders often associated with visceral obesity, increases cardiovascular mortality and morbidity (5). Because decreased insulin sensitivity is linked to MetS, the decreased adiponectin levels may be related to its development (23, 3). Adipokine dysregulation and insulin resistance are two hallmark sequelae attributed to the current clinical definition of MetS that are also linked to atherosclerotic vascular disease (24, 52). Adipokine dysregulation is involved with decreased nitric oxide, vascular inflammation, and insulin resistance itself to promote atherosclerosis. Insulin resistance is linked to endothelial dysfunction by direct and indirect mechanisms that also promote vascular inflammation and atherosclerosis (24).

These mechanisms are discussed in atherosclerosis irrespective of MetS, and also in order to evaluate the possibility of synergism in MetS. High retinol-binding protein-4 (RBP-4) and low cholesterol efflux in MetS may provide evidence of possible synergism and elevated atherosclerotic risk (24, 53).

Changes in the plasma lipid spectrum are an important risk factor for the development of CVD (2). CVD represents a serious global health problem. Even if the atherogenesis is a multifactorial process, dyslipoproteinemia is one of the most important risk factors in the pathological process (26).

In our study of patients with and without MetS, we investigated serum concentrations of basic lipid parameters, namely TAG, T-Chol, LDL-C, HDL-C, and non-HDL.

There were statistically significant differences in HDL-C (1.2±0.3 vs 1.5±0.3, $p<0.001$), TAG (1.8±0.9 vs 1.1±0.4, $p<0.001$), and non-HDL (3.9±1.1 vs 3.5±0.8, $p=0.031$).There were no statistically significant differences between the investigated groups with and without MetS in terms of either T-chol (5.1±1.1 vs 5.0±0.9, p=n.s.) or LDL-C (3.4±1.0 vs 3.2±0.8, p=n.s).

There was no association in our study between HDL-C and TAG, as components of MetS, with PWVAo, which can be explained by the fact that the patients were treated with hypolipidemic therapy. Regardless of the values of SBPAo, RT, AIx-Brach, and AIx-Aortic, their association with the presence of MetS was not statistically significant. The influence of hypolipidemic therapy should therefore be kept in mind when evaluating the function of the arterial tree.

In the study by Lopes-Vicente (2017), it was found that the number of risk factors seems to increase the arterial stiffness. Contrary to our study, in addition to age and increased systolic blood pressure, alterations in the triglycerides worsened the stiffness of large vessels, which emphasizes the importance in addressing this risk factor in MetS patients (35). In multivariate analysis, the variables that remained as predictors of PWV were age, systolic blood pressure, and TAG. The increased number of risk factors was reflected in a progressive increase in PWV (35).

The liver is an organ that significantly interferes with the metabolism of lipids and lipoproteins. It is the site of synthesis of apolipoproteins, VLDL, and LDL as well as cholesterol and phospholipids. Chylomicrons and LDL remnants are catabolized in the liver. Changes in the plasma lipid spectrum are important risk factors for the development of cardiovascular diseases (54, 2).

The main carrier of cholesterol in circulation is LDL. The monitoring of non-HDL-C levels is recommended as a secondary therapeutic objective in subjects with elevated TAG (55). The noticeable informative value of non-HDL cholesterol is similar to the value of apoB/apoAI indices and cholesterol/HDL-C (56, 2).

TAGs are mainly derived from the liver, from where they are excreted as VLDL (2).

In people with increased caloric intake, reduced physical activity, or increased insulin resistance, an imbalance occurs in the hepatocytes between the oxidation of free fatty acids and their incorporation into TAG (2). The increased production of TAG is manifested both by their storage in hepatocytes, and by increased formation and secretion of very low-density lipoproteins (VLDL) into the circulation (57, 2).

The white adipose tissue stores energy in form of TAG during nutritional affluence, but as its storage capacity becomes saturated, the excessive fat is redirected to nonadipose tissues and alternative nonoxidative pathways promoting organ-specific production of toxic lipid metabolites (3).

Pathological accumulation of lipids in the liver causes lipotoxicity, which increases the oxidative stress in hepatocytes and damages them (2). These processes result in metabolic dysfunction that may lead to dyslipidemia, insulin resistance, and CVD, and may also cause a progression of liver damage to severe liver disease (58, 2).

MetS is an interrelated cluster of risk factors for CVD andT-2DM, such as hyperglycemia, raised blood pressure, elevated TAG levels, low HDL-C levels, and central obesity (59).

MetS and nonalcoholic fatty liver disease (NAFLD) are strongly connected "civilization disorders" with continuously increasing incidence worldwide. This clinical condition is closely associated with visceral obesity and other features of MetS, including dyslipidemia, insulin resistance, and increased CVD (59).

Dyslipoproteinemia and T2DM are two serious independent risk factors for atherosclerosis, the current effect of which exponentially increases the risk of cardiovascular events and death (60). It is therefore logical that the diagnosis and treatment of dyslipoproteinemia is one of the basic procedures in the prevention of diabetic macroangiopathy, which increases cardiovascular mortality three-fold in subjects with T2DM (60).

The determination of cardiovascular risk has become the cornerstone of prevention of cardiovascular diseases. Although we know that atherosclerosis is a multifactorial process, the lipoprotein metabolism abnormalities are key factors in its development and represent approximately 50 % of the risk factors applicable to cardiovascular diseases. In addition to examinations of individual lipid parameters, which are used as "atherogenetic indicators", several lipoprotein indices are calculated on the basis of the values of individual lipid indicators (2).

MetS increases cardiovascular risk through the presence of a prothrombotic state which originates in the endothelial lesion and changes in the coagulation cascade. Some hemostatic factors may be considered as markers of inflammation and endothelial dysfunction at the same time (61). The endothelial lesions and changes in levels of procoagulation factors may lead to a prothrombotic state and higher susceptibility of thrombus creation in arterial as well as venous circulation (62). For the assessment of endothelial lesions caused by atherosclerosis, the intima–media thickness of carotid arteries is measured, while the atherosclerotic plates are confirmed using ultrasonography.

The change in stiffness has two aspects; both of these are morphological changes in the vascular wall (an increase in collagen content of the *interstitium*, and hypertrophy and remodeling of smooth-muscular cells in the vascular wall), which contribute to an increase in the stiffness of the arteries. There is also a reduction in the elasticity of arteries and narrowing of their inner diameter, which increases the resistance of peripheral arterial circulation. The hypertrophy of smooth muscle cells also increases the response to vasoconstriction (33, 62, 61).

The results of the study by Lopez-Vicente et al (2017) indicate that the severity of arterial stiffness depends on the number of risk factors (35). Alterations in SBP and TAG in the clustering may lead to a greater impairment in the stiffness of large vessels, which emphasizes the relevance of early treatment of these risk factors for MetS. This may contribute to the development of effective therapies for the treatment of MetS minimizes the damage to vascular function, and, consequently reduces the cardiovascular risk (35).

The findings of Donley et al (2014) suggest that some of the pathophysiological changes associated with MetS can be improved with aerobic exercise training, thereby lowering the cardiovascular risk (51). The present study indicates that aerobic exercise training is an effective approach to reduce the arterial stiffening and improve CVD risk profiles in individuals with MetS (without T2DM and overt CVD). The question as to whether long-term aerobic exercise training maintains the beneficial effects on arterial stiffness in MetS patients and delays the transition to T2DM requires to be further studied (51).

The results of the study by Aizawa et al. (2009) showed a reduction in carotid artery stiffness in MetS subjects following 24 weeks of SNAC (staged nutrition and activity counseling) intervention, and that the reduction was accompanied by improvements in some MetS components (waist circumference, BP, and fasting glucose). These results suggest favorable effects of lifestyle modification strategy in subjects with MetS on both central arterial stiffness as well as on the components of MetS (44).

Limitations

This study was a retrospective analysis of well-controlled treated hypertensive patients, who achieved target blood pressure values. Antihypertensive therapy was not strictly uniform; in the main it was based on ACE inhibitors or angiotensin II receptor blockers in combination with amlodipine and, as needed, a low dose of thiazide diuretic (primarily indapamide) was added. A small proportion of patients were also treated with beta-adrenergic blocking drugs. The hypolipidemic therapy was nonuniform and consisted mostly of statins and fibrates.

On the other hand, the aim of this work was to evaluate the effect of components of metabolic syndrome on aortic stiffness, rather than the effect of different drugs on this parameter.

We therefore consider the conditions of this study acceptable for the evaluation of results obtained from clinical practice, because it was not an experimental study but a view from the aspect of real clinical life.

Conclusion

The aim of this work was to study the association of PWVAo and MetS and its components in treated patients with well-controlled arterial hypertension. The arterial stiffness and PWVAo were associated with age and sex, as well as with the MetS components (BMI, FPG/T2DM). The data obtained in this study suggest a greater association of PWVAo values with MetS components in women than in men and indicate that arterial stiffness is greater where FPG/T2DM, BMI, and arterial hypertension are simultaneously present. The influence of hypolipidemic therapy should be borne in mind when evaluating the arterial tree function. An early and proactive diagnosis of MetS and its severity will allow medication and lifestyle optimization in order to prevent the occurrence of organ complications and improve health-related quality of life.

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