SIGNIFICANCE OF ARTERIAL STIFFNESS AND RELATIONSHIP WITH OTHER NONINVASIVE METHODS FOR THE ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH METABOLIC SYNDROME

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SIGNIFICANCE OF ARTERIAL STIFFNESS AND RELATIONSHIP WITH OTHER NONINVASIVE METHODS FOR THE ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH METABOLIC SYNDROME (Abstract): Measurement of arterial stiffness is an accurate method of assessment of endothelial dysfunction, together with other noninvasive methods, in the diagnosis of atherosclerotic burden in patients with MetS. Material and methods: The study included 63 patients: MetS group (18 men, 20 women, mean age 58.86±8.86 years) and the control group (14 men, 11 women, mean age 59.68±10.0 years). They underwent the following examinations: assessment of arterial stiffness - pulse wave velocity (PWVao), augmentation index of brachial artery (Aixbr) and aorta (Aixo), central systolic blood pressure (SBPao); carotid ultrasound for detection of plaques and measurement of intima-media thickness (IMT); echocardiography - left ventricular hypertrophy (LVH); ankle-brachial index (ABI); biochemical parameters: C-reactive protein (CRP), fibrinogen (Fb), cholesterol (Col), HDLcol, LDLcol and triglycerides. Results: MetS patients had higher PWVao (10.06±2.12 m/s vs 8.29±1.33 m/s, p=0.0001) and SBPao (135.06±19.80 mmHg vs. 121.76±18.62 mmHg, p=0.009). Carotid IMT was higher in MetS group (0.92±0.11 vs. 0.83±0.10 mm, p=0.003). Almost all MetS patients were hypertensive (94.7% vs. 52%, p=0.01); LVH was present in 57.9% of MetS patients and 20% of the controls (p=0.05). The MetS group presented higher Col (208.76±38.41 vs. 176.20±30.08 mg/dl, p=0.0003) and CRP levels (0.87±0.852 mg/dl vs. 0.476±0.392 mg/dl, p=0.01). Conclusions: In MetS patients the most reliable marker of arterial stiffness was PWVao, followed by SBPao. Higher values of carotid IMT are also parameters of high atherosclerotic risk. CRP and Col can be considered biomarkers of high risk in MetS. Keywords: METABOLIC SYNDROME, ARTERIAL STIFFNESS, SUBCLINICAL ATHEROSCLEROSIS.

Metabolic syndrome (MetS) consists in a constellation of cardiovascular risk factors with a direct impact on the initiation and progression of atherosclerotic cardiovascular disease. Several large studies showed that subjects with MetS are prone to adverse cardiovascular events. Such a patient is vulnerable, prone to acute coro-
nary syndrome, sudden death, or stroke, due to vulnerable atherosclerotic plaque (prone to disruption or thrombosis), vulnerable blood (prone to thrombosis) or vulnerable myocardium (prone to arrhythmia) (1, 2, 3).

The present cardiovascular risk charts, as Framingham in the U.S.A. or SCORE in Europe, can identify subjects at very high risk or low risk of cardiovascular events in the next ten years (4, 5). Yet, there are a large number of subjects with an intermediate risk score, often underestimated by the risk charts. In this group of individuals, noninvasive detection of asymptomatic atherosclerosis is indicated, before the occurrence of major adverse events (6, 7). The investigations suggest that carotid ultrasound (CU), ankle-brachial index (ABI), cardiac CT for calcium scoring, or magnetic resonance imaging is useful in detecting subclinical atherosclerosis. While ABI, intima-media thickness (IMT) and carotid plaque ultrasound assessment are widely used, the other two are less available. The measurement of arterial stiffness provides additional useful information in the evaluation of atherosclerotic risk together with the above mentioned noninvasive methods (8).

The aims of the study are: - assessment of arterial stiffness in patients with MetS by measuring aortic pulse wave velocity (PWV) as the gold standard for assessing arterial stiffness; - importance of arterial stiffness analysis as a parameter of cardiovascular risk in MetS; - significance of other noninvasive methods for the detection of subclinical atherosclerosis and some biochemical markers in MetS.

MATERIAL AND METHODS
The study included 38 patients with MetS (18 men, 20 women), group S, and 25 control patients (14 men, 11 women) – group C. Patients in group S met the MetS criteria according to ATP III: fasting glucose ≥ 110 mg/dl or known type 2 diabetes mellitus (type 2 DM); waist circumference (WC) ≥ 102 cm in men and ≥ 88 cm in women; serum triglycerides ≥ 150 mg/dl; HDL < 40 mg/dl in men and < 50 mg/dl in women; arterial pressure ≥ 130/85 mmHg or treatment for arterial hypertension (AHT). Patients were included in group C when at least three MetS criteria were not present.

The exclusion criteria were: secondary AHT, significant chronic renal disease, major cardiovascular complications (myocardial infarction, stroke, heart failure, cardiac or peripheral revascularization).

The following investigations were made: medical history and clinical examination; electrocardiography; ABI. Echocardiography studied markers of left ventricular hypertrophy (LVH), systolic and diastolic function, aortic and valvular atherosclerosis. CU measured IMT of the distal common carotid artery and bifurcation and revealed atherosclerotic plaques. The echographic examinations were performed with an Esaote MyLab50. The biochemical tests included determinations of fasting blood glucose, cholesterol (Col), HDL cholesterol, triglycerides (TG), calculation of LDL cholesterol with the formula Col – HDL – TG/5, C reactive protein (CRP), fibrinogen (Fb), plasma urea and creatinine, hepatic enzymes - alaninaminotransferase (ALAT), aspartataminotransferase (ASAT).

Arterial stiffness was assessed by a TensioMedArteriograph TL2. The following parameters were measured: brachial augmentation index (AIXbr), aortic augmentation index (AIXaao), aortic pulse wave velocity (PWVao), central pulse pres-
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Statistical analysis was performed in SPSS 11.0 software. The mean values, frequencies, standard deviations were calculated. "t" Student test was used to assess the significance of difference between two mean values; chi square test was used to analyze the difference between two frequencies.

RESULTS
Mean age of group S was 58.86 ± 8.86 years, and of group C 59.68 ± 10.0 years, age-matched controls.

Anthropometric data. In all group S patients WC was above the maximum admitted values, with a mean of 109.05 ± 9.53 cm in men and 110.10 ± 15.48 cm in women. In group C, mean WC was significantly lower (p=0.006). In group C most subjects were normal weight (36%) or overweight (32%), whereas in group S most were overweight (28.95%) or obese (68.42%) (tab. I).

TABLE I
General and anthropometric data in the two study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group S</th>
<th>Group C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>58.86 ± 8.86</td>
<td>59.68 ± 10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender (nr, %)</td>
<td>18 (47.4%)</td>
<td>14 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>90.89 ± 17.03</td>
<td>73.76 ± 20.51</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (W/H²)</td>
<td>33.36 ± 6.61</td>
<td>26.36 ± 6.33</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference in men (cm)</td>
<td>109.05 ± 9.53</td>
<td>92 ± 18.88</td>
<td>0.006</td>
</tr>
<tr>
<td>Waist circumference in women (cm)</td>
<td>110.10 ± 15.48</td>
<td>94.54 ± 10.15</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Analysis of arterial stiffness parameters showed that PWVao was 10.06 m/s in group S, and significantly lower (p=0.0001), 8.29 m/s, in group C. According to the reference values, in 64% of the controls it was optimal, in the remaining 36% being normal or elevated. In group S, in 50% it was normal, in 34.2% elevated and in 13.1% pathologic, above 12 m/s (with a maximum of 17.1 m/s) (fig. 1).

![Bar graph showing the prevalence of PWVao (m/s) according to value categories](image)

**Fig. 1.** The prevalence of PWVao according to value categories
SBPao in group S was 135.06 mmHg, higher than in group C (121.76 mmHg, p=0.009). There were no significant differences in AIXbr and AIXao between the two groups (tab. II).

**Carotid intima-media thickness (IMT)** in group S was 0.92 ± 0.11 mm, significantly higher than in the C group (0.83 ± 0.10 mm, p=0.003) (tab. II). **Carotid plaques** were present in both groups, more frequent in group S (86.8%) compared with C group (72%), but without statistical significance.

Mean values of **ABI** were not significantly different, but the analysis showed that in group S 9 patients (23.68%) had values outside the normal range (0.9 – 1.3) compared with only two subjects in group C (8%) (tab. II).

**AHT** was present in almost all group S (94.7%) and less in group C patients (52%, p=0.01). LVH was defined in the presence of a left ventricular mass index (LVMI) above 122 g/m² in women and 149 g/m² in men. LVH was found in 57.9% of the patients with MetS versus 20% in the controls (p=0.05) (fig. 2).

Echocardiography revealed **aortic atherosclerotic alterations** in almost all patients with MetS (97.4%), and in most controls (80%). Diastolic dysfunction, assessed by E/A ratio < 0.9, was present in 68.4% group S and 52% group C patients (fig. 2).

**Type 2 DM**, another component of MetS, was found in 42% of group S patients. No subject in group C had type 2 DM.

Analysis of **serum lipids** showed the following. In group S, 63% presented Col levels above 190 mg/dl, compared with 32% in group C, with mean values higher in group S. HDL was slightly higher in group S. Triglycerides were also higher in group S but without statistical significance (tab. II).

The studied **inflammation markers** were C reactive protein (CRP) and serum fibrinogen (Fb). CRP levels higher than 1 mg/l were found in 44% in group S and in only 16% in group C; no differences in Fb levels were found between the two groups (tab. II). When comparing the hepatic enzymes levels, higher ALAT values were found in group S, with ASAT values were similar in the two groups (tab. II).
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group S</th>
<th>Group C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWVao (m/s)</td>
<td>10.06 ± 2.12</td>
<td>8.29 ± 1.33</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBPao (mmHg)</td>
<td>135.06 ± 19.80</td>
<td>121.76 ± 18.62</td>
<td>0.009</td>
</tr>
<tr>
<td>AIXbr (%)</td>
<td>10.99 ± 24.28</td>
<td>10.54 ± 37.44</td>
<td>NS</td>
</tr>
<tr>
<td>AIXao (%)</td>
<td>42.03 ± 12.76</td>
<td>42.92 ± 18.96</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>0.92 ± 0.11</td>
<td>0.83 ± 0.10</td>
<td>0.0063</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>208.76 ± 38.41</td>
<td>176.20 ± 30.08</td>
<td>0.0003</td>
</tr>
<tr>
<td>HDL col (mg/dl)</td>
<td>54.56 ± 13.52</td>
<td>50.08 ± 7.98</td>
<td>NS</td>
</tr>
<tr>
<td>LDL col (mg/dl)</td>
<td>114.08 ± 34.03</td>
<td>103.08 ± 27.88</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>199.16 ± 100.01</td>
<td>115.96 ± 40.42</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>0.87 ± 0.85</td>
<td>0.47 ± 0.59</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>367.78 ± 85.71</td>
<td>336.08 ± 46.94</td>
<td>NS</td>
</tr>
<tr>
<td>ABI</td>
<td>1.11 ± 0.18</td>
<td>1.08 ± 0.11</td>
<td>NS</td>
</tr>
<tr>
<td>ALAT (UI)</td>
<td>39.41 ± 19.36</td>
<td>28.44 ± 9.89</td>
<td>0.004</td>
</tr>
<tr>
<td>ASAT (UI)</td>
<td>29.14 ± 19.81</td>
<td>25.72 ± 12.34</td>
<td>NS</td>
</tr>
</tbody>
</table>

DISCUSSION

The analysis of the clinical and biochemical features related to the criteria used to define MetS showed, as expected, higher WC and BMI in the MetS group. WC is a better predictor of cardiometabolic risk than BMI. Type 2 DM was present in about half of MetS group and this could be explained by insulin resistance. The risk of developing DM is three times higher in MetS compared to general population. AHT was present in almost all MetS patients and it doubled the cardiovascular risk (9).

The assessment of asymptomatic atherosclerosis by the noninvasive methods described in the study showed some peculiarities. LVH is more frequent in MetS and is an independent cardiovascular risk factor (10). IMT is another marker of atherosclerosis, together with carotid plaques, and their presence has to be interpreted as atherosclerotic disease, even if asymptomatic and adequate measures must be taken (11).

Mean serum cholesterol is higher in MetS patients and increases cardiometabolic risk. In this study there were not significant differences in HDL and TG between the two groups; this can be partially explained by the relative small groups, but also by the fact that most patients were under hypolipemiant treatment. The finding of higher CRP levels is in agreement with other studies that showed a correlation between the inflammation markers and MetS (12).

Focusing on the results of arterial stiffness in MetS patients, it could be asserted that PWVao is the parameter that correlates best with the presence of MetS, followed by SBPao. The differences between groups could be explained in part by the higher prevalence of AHT in the MetS group. Arterial stiffness is known to be a marker of early endothelial dysfunction, which is influenced by several factors, not only by elevated arterial pressure levels (13). AIXbr and AIXao are mentioned in studies as indicators of arterial stiffness and cardi-
vascular risk; in the present study they did not prove to have diagnostic significance.

CONCLUSIONS
Increased arterial stiffness is an early finding in patients with MetS compared with controls. The most reliable parameter is PWVbao, followed by SBPao; AIXbr and AIXao have a less predictive value.

Other markers of early atherosclerosis in MetS are carotid IMT and LVH. Of the biochemical investigations, CRP and cholesterol have better predictive value while LDL and TG have less predictive value.

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REFERENCES