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Metabolic Syndrome and Vascular Alterations in Normotensive Subjects at Risk of Diabetes Mellitus

Lorenzo Ghiadoni, Giuseppe Penno, Chiara Giannarelli, Yvonne Plantinga, Melania Bernardini, Laura Pucci, Roberto Miccoli, Stefano Taddei, Antonio Salvetti, Stefano Del Prato

Abstract—We evaluated the possible association between early vascular abnormalities and the metabolic syndrome (MS) in 77 normotensive subjects (mean age: 50 years) at risk of developing diabetes for family history of diabetes, obesity, or impaired fasting glucose. Fifty healthy subjects were recruited as controls. MS was defined according to the ATP III criteria. Brachial artery endothelium-dependent and -independent vasodilation were assessed as flow-mediated dilation (FMD) and response to glyceryl trinitrate (GTN, 25 µg sublingual), respectively, by automatic computerized edge detection system. Carotid-femoral pulse wave velocity (PWV) and radial augmentation index (AIx) were assessed by applanation tonometry. PWV was significantly (P<0.01) higher in subjects with MS (n=29, 9.0±1.9 m/s) as compared with those without MS (n=48, 7.7±1.2 m/s) and controls (7.2±1.5 m/s). FMD was significantly (P<0.05) reduced in both subjects with (5.8±2.7%) and without MS (6.1±3.7%) as compared with controls (6.9±2.5%). No significant differences were found for response to GTN and AIx. PWV and FMD were significantly (P<0.05) affected by increasing number of MS components. Among the components of the MS, only blood pressure significantly affected PWV, whereas blood pressure and fasting glucose influenced FMD. Logistic regression analysis showed that MS was associated with increased risk of altered PWV (odd ratio: 7.95, confidence limits: 1.06 to 69.11), whereas only blood pressure component was significantly related with increased risk of impaired FMD (odd ratio: 3.60, confidence limits: 1.01 to 12.78). In conclusion, in normotensive subjects at risk of developing diabetes mellitus, the presence of MS is associated with a selective alteration of central PWV. (Hypertension. 2008;51[part 2]:440-445.)

Key Words: arterial stiffness ■ pulse wave velocity ■ endothelium ■ metabolic syndrome ■ blood pressure

Metabolic syndrome (MS), a clustering of cardiovascular risk factors, such as central obesity, insulin resistance, dyslipidemia, and hypertension, is associated with an increased risk of developing cardiovascular disease and diabetes mellitus.1,2 Epidemiological studies suggest that MS per se might represent an independent predictor of cardiovascular morbidity and mortality.3–5 MS has also been associated to early vascular alterations, such as arterial stiffness and endothelial dysfunction.6–13 The association with these vascular alterations might account, at least in part, for the cardiovascular risk of patients with MS.14 Because both increased arterial stiffness15 and endothelial dysfunction16,17 have been demonstrated to be independent predictors of cardiovascular morbidity and mortality. Indeed, cross-sectional studies have shown an association between MS and increased arterial stiffness in unselected populations.8–10 However, some of these studies might be biased by the presence in the study populations, beside other factors encompassing the MS, of overt hypertension or diabetes, 2 major and well characterized determinants of increased arterial stiffness18–20 and endothelial dysfunction.16,21–23 Moreover, endothelial dysfunction in patients with MS has been documented with discrepant results.11–13,24

Thus, whether MS per se is associated with early vascular alterations, such as arterial stiffness and endothelial dysfunction, is still a major issue to investigate. Therefore, to gain further insight on the possible contribution of the MS to early vascular alterations, the present study was design to evaluate arterial stiffness and conduit artery endothelial function in a group of subjects at risk of developing diabetes mellitus, characterized by the absence of overt hypertension and diabetes mellitus. This selection criteria is justified by the fact that 40% to 50% of patients with MS did not show overt hypertension25 which, as well as diabetes, is per se associated with endothelial dysfunction and increased arterial stiffness,16,18–23 possibly masking the effect of MS.

Methods

Study Population

In this cross-sectional study, 77 subjects (age range: 20 to 70 years) were consecutively recruited for the study from those referring to the Department of Endocrinology and Metabolism for family history of diabetes mellitus. The study protocol was approved by the local ethics committee. All subjects gave written informed consent before study entry.

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diabetes, obesity, or elevated fasting glucose levels. They were enrolled if sitting clinic arterial blood pressure (after 10 minutes of rest) was consistently found to be lower than 140/90 mm Hg, confirmed in 2 separate occasions within 1 month according to European guidelines,20 and fasting plasma glucose levels were lower than 126 mg/dL. Subjects with medical history of cardiovascular events, cardiovascular diseases, or other diseases requiring medical treatment were excluded from the study. Subjects taking vitamins were also excluded. Fifty healthy volunteers were recruited from the hospital staff as controls according to the absence of familial history of hypertension and diabetes.

The local ethical committee approved the protocol, and all study participants gave written informed consent for the study.

Body weight, height, and waist circumference were measured in all subjects. Body mass index (BMI) was calculated as weight/height.2 Blood samples were collected after an overnight fast for measurement of lipid and glucose profile by standard techniques. Information on current smoking status (smoker/nonsmoker) was also collected. Smoking was defined as at least 1 cigarette per day.

The MS was diagnosed on the basis of the most recent revision of the National Cholesterol Education Program Adult Treatment panel III (ATP III).2 Subjects were considered to have the MS if they had at least 3 of the following 5 characteristics: (1) serum triglyceride levels $\geq$1.69 mmol/L (150 mg/dL); (2) serum HDL cholesterol $< 1.04$ mmol/L (40 mg/dL) in men and $< 1.30$ mmol/L (50 mg/dL) in women; (3) fasting plasma glucose $\geq 5.55$ mmol/L (100 mg/dL); (4) waist circumference $> 102$ cm in men and $> 88$ cm in women; (5) blood pressure (BP) $\geq 130/85$ mm Hg.

Vascular Function

All measurements were performed after an overnight fast, with subjects in supine position in a quiet air-conditioned room (22 to 24°C). Blood pressure (BP) was measured 3 times at 3-minute intervals by an automatic device (OMRON-950 CP) at the dominant arm and calculated as mean value of the last 2 measurements. Arterial tonometry was performed according to the international recommendations.15 A hand held probe was placed on the selected artery 10 to 15 subsequent images were recorded. Pulse wave analysis (PWA) (SphygmoCor, AtCor Medical) was used to transform radial pressure waveform into aortic pressure waveform by using a validated transfer function.27 Three successive measurements were recorded. Augmented pressure was calculated as the difference between the second systolic peak, and the first systolic peak and AIx was calculated as the ratio between augmented pressure and pulse pressure. Time to reflection and central BP were also obtained. Because AIx correlates with heart rate, values have been normalized at a heart rate of 75 bpm. Central pulse wave velocity (PWV) was assessed with the same device, recording waveforms at the femoral and carotid site, sequentially. Surface distance between the 2 recording sites and simultaneously recorded ECG were used to calculate wave transit time. Coefficient of variation for repeated measurement of AIx and PWV in our laboratory was 14% and 13%, respectively.28

Carotid and brachial scans were obtained by high-resolution B-mode ultrasound by a 7.5 to 12 MHz linear array transducer (MyLab25; ESAOTE). Left and right common carotids were examined in antero-lateral, postero-lateral, or medio-lateral directions. Longitudinal images of the distal common carotid, in which the interfaces were very clear, were obtained. Carotid intima-media-thickness (IMT) was measured in the far wall of the common carotid artery, 1 cm proximal to the carotid bulb in a region free of plaques, by a real-time computerized edge detection system.29 Coefficient of variation for repeated carotid IMT measurements was 2%. Endothelium-dependent response was assessed as dilation of the brachial artery to increased flow (flow mediated dilation, FMD) as previously described.23,30 Briefly, a B-mode scan of the right brachial artery was obtained in longitudinal section between 5 cm and 10 cm above the elbow, with the probe held by a stereotactic clamp to ensure a constant image. B-mode images were triggered to the ECG signal to obtain end-diastolic frames. A cuff was placed around the forearm just below the elbow, inflated for 5 minutes at 250 mm Hg, and then deflated to induce reactive hyperemia (RH). Endothelium-independent dilation was obtained by administration of a low dose (25 $\mu$g) of sublingual glyceryl trinitrate (GTN). Diameter measurements were performed by a real-time computerized edge detection system.20 FMD and response to GTN were calculated as maximal percent increase in diameter above baseline (mean value of measures obtained during 1 minute before cuff inflation). Coefficient of variation for FMD repeated measurements is 14%.29,31 Arterial flow velocity, obtained by pulsed Doppler signal at $70^\circ$ to the vessel with the range gate (1.5 mm) in the center of the artery, was measured at baseline and within 15 seconds after cuff release. Volume blood flow was calculated as product of Doppler flow velocity, heart rate, and vessel cross-sectional area ($\pi r^2$). RH was calculated as maximum percent increase in flow.

Statistical Analysis

Data are expressed as means $\pm$SD. Triglycerides are expressed as median and interquartile range, because of their skewed distribution, and were logarithmically transformed when appropriate. Characteristics of study groups are compared using Student t tests or nonparametric test, as appropriate. Differences in outcome parameters, according to the presence and absence of the MS, were tested with the analysis of covariance, adjusted for age and, for PWV, also for mean BP and heart rate. The effects of the increasing number of MS components (from 0 to more than 3) was analyzed by general linear model, whereas those of the single dichotomized MS components on the vascular parameters were tested by analysis of covariance. Simple regression analyses were performed to examine the correlations of the vascular parameters with the MS components. Logistic regression was performed to evaluate the predictive value of the effect of single dichotomized MS components or the MS as a whole on impaired FMD (considered as a PWV below the 95% lower confidence limit) and or increased PWV (considered as a FMD above the 95% upper confidence limit). This analysis was adjusted for age and, for PWV, also for mean BP and heart rate. Differences were considered statistically significant when probability value $< 0.05$. All statistical procedures were performed using the NCSS statistical package (NCSS).

Results

Clinical and anthropometric characteristics of the study population are shown in Table 1. Twenty-nine (38%) of the 77 subjects at risk of diabetes met the criteria of the MS. Subjects with MS showed higher values of BMI, waist circumference, systolic and diastolic BP, plasma glucose and triglycerides, as well as total cholesterol and LDL cholesterol levels as compared with both subjects without MS and controls. HDL levels were significantly lower in subjects with MS as compared with the other 2 groups. Subjects without MS had significantly higher plasma glucose levels than controls. Age, gender, and smoking habits were not significantly different among the 3 groups.

Carotid IMT was similar among subjects with or without MS and controls (Table 2).

AIx, central systolic BP, and pulse pressure were significantly ($P<0.01$) higher, and time to reflection lower ($P<0.05$), in both groups of subjects with and without the MS as compared with controls (Table 2). Central systolic BP and pulse pressure were significantly ($P<0.05$) higher in subjects with than those without the MS (Table 2). AIx and time to reflection were different, but not significantly, between subjects with and without the MS (Table 2).

Central PWV was significantly ($P=0.02$) higher in subjects with MS as compared with those without MS and controls (Figure 1). No significant difference in PWV was
Table 1. Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls</th>
<th>Subjects Without MS</th>
<th>Subjects With MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>50</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>Gender, males/females</td>
<td>26/24</td>
<td>26/22</td>
<td>17/12</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>43/7</td>
<td>38/10</td>
<td>23/6</td>
</tr>
<tr>
<td>Age, years</td>
<td>51.2±8.7</td>
<td>49.8±9.9</td>
<td>52.8±8.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1±3.9</td>
<td>27.4±5.4</td>
<td>29.1±4.1*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>93.1±7.9</td>
<td>95.8±10.5</td>
<td>103.2±8.7*</td>
</tr>
<tr>
<td>Clinic systolic BP, mm Hg</td>
<td>118.7±9.1</td>
<td>122.6±14.8</td>
<td>133.5±12.8*</td>
</tr>
<tr>
<td>Clinic diastolic BP, mm Hg</td>
<td>78.2±6.8</td>
<td>76.0±11.9</td>
<td>84.5±12.9*</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>5.0±0.5</td>
<td>5.3±0.6</td>
<td>5.8±0.5*</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.1±0.9</td>
<td>5.3±1.0</td>
<td>6.0±1.1*</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.5±0.3</td>
<td>1.6±0.3</td>
<td>1.3±0.3*</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.2±0.7</td>
<td>3.5±0.9</td>
<td>4.2±1.1*</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.9 (0.3)</td>
<td>1.0 (0.7)</td>
<td>2.2 (1.4)*</td>
</tr>
</tbody>
</table>

Data are expressed as means±SD. Triglycerides are expressed as median and interquartile range, because of their skewed distribution, and were logarithmically transformed when appropriate.

MS indicates metabolic syndrome; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *P<0.01; †P<0.02 vs controls; ‡P<0.01 vs controls.

FMD was significantly (P<0.01) lower in both groups of subjects at risk of diabetes as compared with controls, but no difference was observed between subjects with or without the MS (Figure 1).

RH and response to GTN, as well as brachial artery diameter, were similar in all groups (Table 2).

PWV was significantly (P<0.05) increased and FMD decreased in parallel with increasing number of the MS components (Figure 2).

PWV (r=0.33; P<0.0001) and FMD (r=−0.28; P=0.01) were related to age. PWV (r=0.44; P<0.0001), but not FMD (r=−0.18; P=0.13) was significantly related to LDL cholesterol.

Among all the components of the MS, PWV was significantly related only to systolic BP (r=0.28; P=0.02) and fasting plasma glucose (r=0.24; P=0.04). Similarly, FMD was related only to systolic BP (r=−0.35; P=0.002) and fasting plasma glucose (r=−0.34; P=0.003).

When the age-adjusted effect of dichotomized single MS factors is considered, only elevated BP levels were associated with a significant (P<0.01) increase in PWV, whereas both elevated BP (P<0.001) and fasting glucose levels (P<0.05) were significantly associated with a reduced FMD (Figure 3).

Increased PWV, considered as a value above the 95% upper confidence limit of 8.5 mm/s, was more frequent (χ²=10.52; P=0.001) in subjects with MS (60%) as compared with those without MS (22%). In the age-adjusted logistic regression analysis, which included MS and its single components as independent variables, none of the single components were associated with a significant increased risk of an altered PWV, whereas a significant increased risk was observed in the presence of MS (R²=0.21; P=0.01; odd ratio for MS presence: 9.81, confidence limits 1.18 to 81.56). When adjusted also for mean BP and heart rate, the risk an altered PWV was still associated with the presence of MS (7.95, confidence limits 1.06 to 69.10), whereas none of the single components was associated with a significant increased risk (R²=0.23; P=0.005).

Impaired FMD, identified by values below the 95% lower confidence limit of 5.5%, was more frequent, although not significantly (χ²=2.81; P=n.s.), in subjects with MS (43%) as compared with those without MS (25%). Age-adjusted logistic regression analysis showed that only the BP component was significantly related with an increased risk of impaired FMD (R²=0.21; P=0.01; odd ratio for BP >130/85 mm Hg: 3.60, confidence limits 1.01 to 12.78), whereas an increased, but not significant, risk was associated with presence of MS (odd ratio for MS presence: 3.69, confidence limits 0.51 to 26.85).

Table 2. Vascular Parameters in the Study Populations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls</th>
<th>Subjects Without MS</th>
<th>Subjects With MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid IMT, mm</td>
<td>0.69±0.19</td>
<td>0.70±0.25</td>
<td>0.71±0.21</td>
</tr>
<tr>
<td>Augmentation index, units</td>
<td>12.5±8.4</td>
<td>17.1±11.2*</td>
<td>21.8±11.8*</td>
</tr>
<tr>
<td>Time to reflection, ms</td>
<td>148±9</td>
<td>139±9</td>
<td>140±12*</td>
</tr>
<tr>
<td>Central systolic BP, mm Hg</td>
<td>109±8</td>
<td>120±13*</td>
<td>128±13*†</td>
</tr>
<tr>
<td>Central pulse pressure, mm Hg</td>
<td>41±9</td>
<td>49±14*</td>
<td>54±15*†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72±8</td>
<td>71±10</td>
<td>74±12</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>3.85±0.72</td>
<td>3.94±0.39</td>
<td>3.78±0.66</td>
</tr>
<tr>
<td>Reactive hyperemia, %</td>
<td>485±324</td>
<td>401±324</td>
<td>388±286</td>
</tr>
<tr>
<td>Response to GTN, %</td>
<td>8.2±3.3</td>
<td>8.6±3.8</td>
<td>9.0±3.0</td>
</tr>
</tbody>
</table>

Data are expressed as means±SD. MS indicates metabolic syndrome; BP, blood pressure; GTN, sublingual glyceryl trinitrate. *P<0.01, subjects with and without MS vs controls; †P<0.01, subjects with MS vs subjects without MS.

Discussion

The present study demonstrates that in subjects at risk of developing diabetes, without overt hypertension and diabetes mellitus, the presence of the MS selectively impairs central arterial stiffness, whereas it does not account for a further deterioration of endothelial function.

Subjects with MS showed higher values of carotid to femoral PWV as compared with those without MS and controls. PWV significantly increased with the number of MS components.
components. These results are in agreement with previous studies conducted in general populations.\textsuperscript{6–10} In most of these studies, however, the presence of overt hypertension or diabetes, or even of pharmacological treatment, was not an exclusion criterion.\textsuperscript{7–9} This could represent a potential bias in interpreting results, because it is well known that hypertension induces arterial stiffness and that, conversely, increased central arterial stiffness and peripheral wave reflection are potent mechanisms to further increase peripheral and central systolic BP and pulse pressure.\textsuperscript{18–20} Indeed, in these studies systolic BP resulted an independent predictor of increased systolic BP and pulse pressure.\textsuperscript{18–20} These results are in agreement with previous studies conducted in general populations.\textsuperscript{6–10} In most of these studies, however, the presence of overt hypertension or diabetes, or even of pharmacological treatment, was not an exclusion criterion.\textsuperscript{7–9} This could represent a potential bias in interpreting results, because it is well known that hypertension induces arterial stiffness and that, conversely, increased central arterial stiffness and peripheral wave reflection are potent mechanisms to further increase peripheral and central systolic BP and pulse pressure.\textsuperscript{18–20} Indeed, in these studies systolic BP resulted an independent predictor of increased arterial stiffness.\textsuperscript{6–10} Thus, to investigate whether MS per se would be associated with arterial stiffness, in the present study we enrolled subjects at risk of diabetes, because of family history of diabetes, elevated fasting plasma glucose, or obesity, with a wide range of BP values but within the limit to define hypertension (<140/90 mm Hg) according to current guidelines.\textsuperscript{26} Moreover, subjects with diabetes mellitus were also excluded. Interestingly, central PWV was significantly reduced in the group of subjects with MS, not only as compared with controls, but also in comparison to subjects at risk of diabetes without the MS. However, in the latter group PWV was not different as compared with controls. Among these subjects at risk of diabetes, AIx, an integrated index of arterial stiffness and peripheral wave reflection,\textsuperscript{19,20} was higher, but not significantly, in subject with MS than those without MS. Thus, it is conceivable that a selective alteration of central arterial stiffness might contribute to the higher central BP observed in subjects with the MS. However, as already commented, it is also possible that higher BP values, which characterized subjects with MS in our study population, would be responsible for increased arterial stiffness. Systolic BP was significantly related to central PWV, and among the dichotomized single MS factors only elevated BP levels were associated with increased PWV, in agreement with previous results.\textsuperscript{7,8} However, when the logistic regression analysis was performed to test the global effect of MS or the effect of its single components on PWV, only the presence of the MS was associated with a significant risk of increased central PWV. This finding suggest that in relatively low-risk subjects the clustering of risk factors encompassing the MS are required to alter central arterial stiffness.\textsuperscript{10} It is worth noting that MS has been demonstrated to further impair central arterial stiffness even in the presence of an established risk factor, such as essential hypertension,\textsuperscript{32} leading to target organ damage, namely left ventricular hypertrophy.\textsuperscript{5}

Taken together, these considerations support the hypothesis that arterial stiffness might represent an important alteration contributing to the increased cardiovascular risk associated with the MS.\textsuperscript{14,15} Possible mechanism explaining selective alteration on central aortic stiffness includes increased oxidative stress,\textsuperscript{28} sympathetic nervous system activation,\textsuperscript{33} and inflammation.\textsuperscript{34} However, it has to be pointed out that an important cardiovascular risk factor, LDL cholesterol, which was higher in our patients with MS, was significantly associated with central arterial stiffness.\textsuperscript{35}

Our results are not in agreement with a recent study performed, in whom increased arterial stiffness was present in young normotensive normoglycemic first degree relatives of diabetic patients in the conduit arteries independently from the presence of MS components.\textsuperscript{36} The possible explanation for this discrepancy could reside in the different selection criteria, because only a part of our study population (40%) had a positive family history for diabetes.

Concerning conduit artery endothelial function, FMD was significantly lower in subjects at risk of diabetes as compared with controls, but no difference was observed between subjects with or without MS. Because RH, the stimulus for endothelium-dependent vasodilation, and endothelium-independent response to GTN were similar in all groups, these results indicate the presence of endothelial dysfunction in the conduit artery of subjects at risk of developing diabetes.
without a further impairment by the presence of MS. These results are in agreement with the study performed in normotensive normoglycemic first degree relatives of diabetic patients, in whom endothelial dysfunction in the conduit arteries was present independently from the presence of MS components and in studies performed in elderly populations. On the other hand, the presence of endothelial dysfunction has also been associated with the presence of MS in the peripheral microcirculation. A likely explanation for this discrepancy is that the evaluation of endothelial function in the conduit arteries by FMD technique may discriminate only within subjects at low cardiovascular risk, as shown by a recent meta-analysis, performed in over 200 available studies. In this analysis the relationship between FMD and risk factors was more evident in patient with a moderate-high risk such relationship disappeared. This FMD and risk factors was more evident in patient with a moderate-high risk such relationship disappeared. This FMD and risk factors was more evident in patient with a moderate-high risk such relationship disappeared. This FMD and risk factors was more evident in patient with a moderate-high risk such relationship disappeared. This FMD and risk factors was more evident in patient with a moderate-high risk such relationship disappeared. This FMD and risk factors was more evident in patient with a moderate-high risk such relationship disappeared. This