Influence of metabolic syndrome on hypertension-related target organ damage

G. MULÈ, E. NARDI, S. COTTONE, P. CUSIMANO, V. VOLPE, G. PIAZZA, R. MONGIOVI, G. MEZZATESTA, G. ANDRONICO & G. CERASOLA
From the Dipartimento di Medicina Interna, Malattie Cardiovascolari e Nefrourologiche, Cattedra di Medicina Interna e Centro Ipertensione, Università di Palermo, Palermo, Italy


Objectives. The aim of our study was to analyse, in a wide group of essential hypertensive patients without diabetes mellitus, the influence of metabolic syndrome (MS) (defined according to the criteria laid down in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) on markers of preclinical cardiac, renal and retinal damage.

Design. Cross-sectional study.

Setting. Outpatient hypertension clinic.

Subjects and methods. A total of 353 young and middle-aged hypertensives, free from cardiovascular and renal diseases (and 37% of whom had MS), underwent echocardiographic examination, microalbuminuria determination and non-mydriatic retinography.

Results. When compared with subjects without MS, hypertensive patients with MS exhibited more elevated left ventricular (LV) mass (either normalized by body surface area or by height elevated by a power of 2.7), higher myocardial relative wall thickness, albumin excretion rate (AER) and a greater prevalence of LV hypertrophy (57.7% vs. 25.1%; \( P < 0.00001 \)), of microalbuminuria (36.2% vs. 19.3%; \( P = 0.002 \)) and of hypertensive retinopathy (87.7% vs. 48.4%; \( P < 0.00001 \)). These results held even after correction for age, 24-h blood pressures, duration of hypertension, previous antihypertensive therapy, and gender distribution. The independent relationships between LV mass and MS, and between AER and MS, were confirmed in multivariate regression models including MS together with its individual components.

Conclusions. MS may amplify hypertension-related cardiac and renal changes, over and above the potential contribution of each single component of this syndrome. As these markers of target organ damage are well-known predictors of cardiovascular events, our results may partly explain the enhanced cardiovascular risk associated with MS.

Keywords: essential hypertension, left ventricular hypertrophy, metabolic syndrome, microalbuminuria, target organ damage.

Introduction

Arterial hypertension is often associated with various metabolic abnormalities including abdominal obesity, dyslipidaemia, elevated plasma glucose and insulin resistance, which are the main features of the metabolic syndrome (MS), previously known as either the insulin resistance syndrome, or X syndrome or deadly quartet [1], or dysmetabolic syndrome [2]. Recently, the World Health Organization (WHO) [1], the American Association of Clinical Endocrinologists [1] and the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) [3] proposed working definitions for this syndrome.

© 2005 Blackwell Publishing Ltd
Amongst these definitions the one suggested by NCEP-ATPIII is the simplest and the most practical and according to which MS may be diagnosed when three or more abnormalities (impaired glucose metabolism, elevated blood pressure, hypertriglyceridaemia, low HDL cholesterol and central obesity) cluster in the same person [3]. The adverse prognostic impact of the MS, as defined by NCEP-ATPIII, has recently been documented in men [4] and in women [5] with no history of cardiovascular disease, in hypercholesterolaemic men [6] and in hypertensive patients [7]. It is conceivable that the increased cardiovascular risk conferred by MS in hypertensive subjects may in part be mediated through preclinical end-organ damage.

Our study was undertaken to evaluate the influence of MS, defined according to the NCEP-ATPIII criteria, on some cardiac, renal and retinal markers of target organ damage, in a large group of non-diabetic young and middle-aged essential hypertensives without clinical or laboratory evidence of cardiovascular and renal diseases.

Methods

The study population was selected from 478 hypertensive patients consecutively attending our hypertension centre. Most of them had been referred to our institution by their general practitioners for specialist advice. Eighty subjects were not enrolled because of secondary or malignant hypertension, heart failure, positive history or clinical signs of ischaemic heart disease, cerebrovascular disease, renal insufficiency (serum creatinine >133 \(\mu\)mol L\(^{-1}\) (1.5 mg dL\(^{-1}\)) in men and >124 \(\mu\)mol L\(^{-1}\) (1.4 mg dL\(^{-1}\)) in women), overt proteinuria, major non-cardiovascular diseases, dyslipidaemia requiring pharmacological treatment, and known diabetics or fasting glycaemia \(\geq\)126 mg dL\(^{-1}\).

Of the remaining hypertensive individuals 45 were also excluded, because of suboptimal echocardiographic tracings (39 subjects) or unreliable urine collections (six patients). Hence, the final statistical analysis involved 353 patients. Before entering the study, 230 hypertensives had been pharmacologically treated. These patients were studied for at least 2 weeks, after the discontinuation of all antihypertensive drugs. Written informed consent was obtained from each patient and the study was approved by the local ethics committee.

Study design

In all subjects careful clinical history and physical examination were performed. After the period of pharmacological washout, body weight, height, and waist circumference were measured by a nurse and clinical blood pressure was recorded by a doctor. The latter was considered as the average of three consecutive measurements obtained by a mercury sphygmonanometer, after the subject had been supine for 5 min.

Additionally, urine analysis was performed and a 24-h urine sample was collected to evaluate the levels of albumin excretion rate (AER) and creatinine clearance. The following morning, after an overnight fast of at least 10 h, blood samples were drawn to perform routine blood chemistry. The 24-h urine collection was repeated within 1 week to assay AER again. Both urine collections were carried out on two non-working days, during which the patients were advised to avoid excessive physical effort. Furthermore, 24-h ambulatory blood pressure monitoring (ABPM), echocardiographic study and fundal examinations were carried out.

Measurements

Determination of routine biochemical parameters was performed with standard techniques by using an autoanalyser (Boehringer Mannheim for Hitachi system 911, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL) was calculated by the Friedewald formula. Microalbuminuria was analysed by radioimmunological assay (Techno Genetics RIA Kit, Techno Genetics, Milan, Italy). The sensitivity of this method is 0.5 \(\mu\)g mL\(^{-1}\), the transferrine cross-reactivity is \(<\)0.01% and the intra-assay and inter-assay coefficient of variation were \(\leq\)5.1% and \(\leq\)7.2% respectively.

The average of two AER determinations was considered as the level of albuminuria in each subject. The currently considered threshold for the definition of microalbuminuria was used to separate microalbuminuric (AER \(\geq\)20 \(\mu\)g min\(^{-1}\)) from normoalbuminuric subjects (AER \(<\)20 \(\mu\)g min\(^{-1}\)).

As detailed in the NCEP-ATPIII report [3], the MS was defined by the presence, in addition to hypertension, of two or more of the following criteria: high-density lipoprotein (HDL) \(<\)1.04 mmol L\(^{-1}\) (40 mg dL\(^{-1}\)) in men or \(<\)1.29 mmol L\(^{-1}\)
(50 mg dL\(^{-1}\)) in women; fasting glucose between 6.1 and 6.94 mmol L\(^{-1}\) (110–125 mg dL\(^{-1}\)); triglycerides >1.69 mmol L\(^{-1}\) (150 mg dL\(^{-1}\)); and waist circumference >102 cm in men or >88 cm in women [2].

A portable, non-invasive SpaceLabs 90207 recorder (Redmond, WA, USA) was used to perform the 24-h ABPM. M-mode echocardiography, guided by a two-dimensional echocardiography, was performed with the patient maintained in a partial left decubitus position, using an Acuson Sequoia 512 (Siemens, Mountain View, CA, USA).

M-mode measurements were taken at end diastole and end systole in line with the American Society of Echocardiography (ASE) recommendations [8]. Only those frames with optimal visualization of interfaces and showing simultaneous visualization of septum, left ventricular (LV) internal diameter and posterior wall were used for readings. Myocardial relative wall thickness was calculated as twice posterior wall in diastole divided by internal diameter, and was used as an estimate of LV geometry.

Left ventricular mass was determined using the ASE-corrected cube formula [9]: 0.80 × \{1.04 \times ([septal thickness + LV internal diameter + posterior wall thickness])\} \ + \ 0.6 \ g. It was indexed by both body surface area (LVMI) and by height elevated by a power of 2.7, as suggested by de Simone et al. [10], in order to provide a more stringent allowance for obesity (LVMH\(^{2.7}\)).

Left ventricular hypertrophy was defined as LVMI \(\geq 125\) g m\(^{-2}\) for men and \(\geq 110\) g m\(^{-2}\) for women, as suggested by the 2003 guidelines of the European Society of Hypertension [11] and as LVMH\(^{2.7}\) \(\geq 49.2\) g m\(^{-2.7}\) for men and \(\geq 46.7\) g m\(^{-2.7}\) for women, which represent the upper limits of normal sex-specific 95% confidence intervals (95% CIs) in reference populations [12].

Left ventricular shortening at the endocardium and mid-wall were used as estimates of LV chamber and myocardial systolic function. Fractional shortening at the endocardium was calculated as the difference between the end-diastolic and end-systolic internal diameter divided by the end-diastolic diameter and then multiplied by 100. Myocardial function was assessed as mid-wall circumferential shortening and calculated using a two-shell cylindrical model, as previously described [13].

The pulsed-Doppler examination of transmitral blood flow was performed from the apical four-chamber view by using a 2.5-MHz transducer, with the sample at the level of the tip of mitral valve leaflets. The parameters measured from the Doppler waveform were: the early filling peak velocity (E wave), the late filling peak velocity (A wave) and their ratio (E/A ratio). Moreover, the time of E velocity deceleration was measured as the interval between the peak E velocity and the point at which the descending segment of the E-wave, or its asymptote, crosses the zero-velocity line.

Echocardiographic data is expressed as the average of five consecutive cardiac cycles. Images were read blindly by a single cardiologist, unaware of the patient’s clinical characteristics. In our laboratory, the mean intra-observer variability was 8.6% for LV mass and 7.8% and 8.9%, respectively, for peak velocities in early and late filling. The ocular fundus examination was carried out by means of a bilateral non-mydriatic retinography (Canon CR4–45 NM, Tokio, Japan). A single examiner, unaware of the patient’s clinical data, assessed the presence and the grading of hypertensive retinopathy, using this simplified Keith, Wagener and Barker classification [14]: grade I was taken as an arteriolar diameter \(\leq 50\%\) of the venous diameter; grade II as arteriovenous crossing changes (nicking) situated at more than one papillary diameter from the papilla; grade III as the presence of retinal haemorrhages or exudates; grade IV as the presence of papillary oedema and retinal haemorrhages and/or exudates.

**Statistics**

Continuous variables were given as mean ± SD, except for AER, which, because of its skewed distribution, was expressed as the median and interquartile range. It was subsequently log-transformed before starting the statistical tests. Differences between groups with and without MS were evaluated using the independent-sample Student’s t-test for continuous variables and the chi-square test, with Yates’ correction, for the categorical variables. Adjustment for age, gender and other potential confounders was carried out, where appropriate, by analysis of covariance and multiple logistic regression analysis.

Stepwise multiple linear regression analyses were used to test independent correlates of LV mass and AER. Initially, age, gender, duration of hyperten-
sion, 24-h blood pressures, previous antihypertensive therapy and each individual component of MS (the latter either as continuous or as dichotomous variables) were considered in order to build the multiple regression models. Subsequently we ran the models again, after adding MS as a dummy variable.

Because of the high degree of collinearity between MS and its individual components, ordinary least-squares multiple regression analysis may lead to inaccurate estimates of the regression coefficients [15]. For this reason we also use an additional method of multiple regression, the ridge regression, which is one of the techniques proposed to overcome the problem of multicollinearity. A ridge estimator of regression coefficients is obtained by modifying the method of least squares (this is made by introducing a constant ‘lambda’ in the normal equations) to allow shrunken and biased estimators of regression coefficients [15]. All tests were considered to be significant at the level of $2p \leq 0.05$. The statistical analyses were performed using the systat data software package, version 11 (Systat, Richmond, CA, USA).

Results

Table 1 gives clinical and demographic characteristics of all the subjects included in the study and of the subgroups into which the study population was divided in line with the NCEP-ATPIII definition of MS.

The prevalence of MS in our hypertensive population was $37\%$ (130/353). As expected the values of all anthropometric and metabolic parameters used for the definition of MS were significantly higher, and HDL cholesterol level was lower in hypertensive subjects with MS, when compared with those without it. Furthermore, patients with MS were older, had a longer duration of hypertension and showed higher clinical and 24-h systolic blood pressures (BP). In the group with MS it was observed that there was a higher percentage of patients previously treated pharmacologically for hypertension and a greater proportion of women. The over-representation of females in the MS group was chiefly explained by a greater prevalence of visceral obesity ($59\%$ vs. $27\%; P < 0.0001$) and of lower HDL values ($62\%$ vs. $28\%; P < 0.0001$) in females than in males. The two groups did not differ in terms of smoking habits, total and LDL cholesterol levels.

Echocardiographic parameters of the study population are reported in Table 2. Participants with MS exhibited significantly higher LV chamber diameter, posterior wall and interventricular septum thicknesses, relative wall thickness, left atrial size, LV mass, either normalized for body surface area (BSA) or for height$^{2.7}$, even after controlling for age, gender, 24-h blood pressures and duration of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical data of the overall study population and of the two subgroups with and without metabolic syndrome (MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study population ($n = 353$)</td>
<td>Patients with MS ($n = 130$)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$45.9 \pm 10.1$</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>202 (57)/151 (43)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>97 (27)</td>
</tr>
<tr>
<td>Body mass index (kg m$^{-2}$)</td>
<td>$27.9 \pm 4$</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>$95.2 \pm 10.9$</td>
</tr>
<tr>
<td>Glycaemia (mmol L$^{-1}$)</td>
<td>$5.17 \pm 0.64$</td>
</tr>
<tr>
<td>Total cholesterol (mmol L$^{-1}$)</td>
<td>$5.39 \pm 1.02$</td>
</tr>
<tr>
<td>Triglycerides (mmol L$^{-1}$)</td>
<td>$1.15 \pm 0.76$</td>
</tr>
<tr>
<td>HDL cholesterol (mmol L$^{-1}$)</td>
<td>$1.18 \pm 0.26$</td>
</tr>
<tr>
<td>LDL cholesterol (mmol L$^{-1}$)</td>
<td>$3.54 \pm 0.99$</td>
</tr>
<tr>
<td>Known hypertension duration (months)</td>
<td>$57.1 \pm 65.4$</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>230 (65)</td>
</tr>
<tr>
<td>Clinical systolic blood pressure (mmHg)</td>
<td>$156.9 \pm 18.5$</td>
</tr>
<tr>
<td>Clinical diastolic blood pressure (mmHg)</td>
<td>$95.2 \pm 10.8$</td>
</tr>
<tr>
<td>24-h systolic blood pressure (mmHg)</td>
<td>$134.3 \pm 12.1$</td>
</tr>
<tr>
<td>24-h diastolic blood pressure (mmHg)</td>
<td>$85.2 \pm 9$</td>
</tr>
<tr>
<td>24-h heart rate (b min$^{-1}$)</td>
<td>$75 \pm 8.6$</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or $n$ (%).
Prevalence of LV hypertrophy was greater in MS group, either using LVMI (31.5% vs. 13.5%; \( P = 0.0008 \)) or LVMH \( 2.7 \). The increased risk of having LV hypertrophy, in subjects with MS, remained significant, also taking into account age, gender, 24-h systolic and diastolic BP, duration of hypertension, previous antihypertensive therapy and AER by multiple logistic regression analyses (odds ratio, OR \( = 2.20 \), 95% CI: 1.20–4.05; \( P = 0.01 \), when LV mass was indexed for BSA and OR \( = 2.89 \), 95% CI: 1.68–4.98; \( P = 0.0001 \), when LV mass was indexed for height\( ^{2.7} \)). Moreover, analysis of covariance documented that LV mass, regardless of the method of indexation, was higher in subjects with MS, also after adjustment for age, sex, duration of hypertension, previous antihypertensive therapy, 24-h systolic and diastolic blood pressures and each individual component of MS (glycaemia, HDL, triglycerides and waist circumference) (\( P = 0.009 \) for LVMI and \( P = 0.004 \) for LVMH\( ^{2.7} \)).

Similar results were obtained in the subset (n = 123) of hypertensive subjects never pharmacologically treated for hypertension, amongst whom those

### Table 2: Cardiac parameters of the overall study population and of the two subgroups with and without metabolic syndrome (MS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall study population (n = 353)</th>
<th>Patients with MS (n = 130)</th>
<th>Patients without MS (n = 223)</th>
<th>P</th>
<th>P adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic left ventricular internal dimension (mm)</td>
<td>49.3 ± 5</td>
<td>50 ± 5</td>
<td>48.9 ± 4.9</td>
<td>0.035</td>
<td>0.008</td>
</tr>
<tr>
<td>End-diastolic interventricular septum thickness (mm)</td>
<td>10.4 ± 1.7</td>
<td>10.9 ± 1.7</td>
<td>10 ± 1.6</td>
<td>&lt;0.00001</td>
<td>0.00005</td>
</tr>
<tr>
<td>End-diastolic posterior wall thickness (mm)</td>
<td>9.8 ± 1.6</td>
<td>10.4 ± 1.7</td>
<td>9.4 ± 1.4</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Myocardial relative wall thickness (ratio)</td>
<td>0.41 ± 0.08</td>
<td>0.43 ± 0.08</td>
<td>0.39 ± 0.07</td>
<td>0.0002</td>
<td>0.01</td>
</tr>
<tr>
<td>Left ventricular mass indexed for BSA (g m(^{-2}))</td>
<td>98.3 ± 24.6</td>
<td>106.9 ± 27</td>
<td>93.4 ± 21.5</td>
<td>&lt;0.00001</td>
<td>0.0007</td>
</tr>
<tr>
<td>Left ventricular mass indexed for height(^{2.7}) (g m(^{-2.7}))</td>
<td>46.3 ± 13</td>
<td>53.1 ± 14.4</td>
<td>42.3 ± 10.3</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Left atrial dimension (mm)</td>
<td>34.7 ± 4.6</td>
<td>36.4 ± 4.6</td>
<td>33.9 ± 4.4</td>
<td>&lt;0.00001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Endocardial fractional shortening (%)</td>
<td>37.9 ± 5.8</td>
<td>37.5 ± 7</td>
<td>38.5 ± 5</td>
<td>0.12</td>
<td>0.59</td>
</tr>
<tr>
<td>Mid-wall fractional shortening (%)</td>
<td>17.2 ± 1.6</td>
<td>16.8 ± 1.7</td>
<td>17.5 ± 1.6</td>
<td>0.0002</td>
<td>0.01</td>
</tr>
<tr>
<td>Mitral E-wave/A-wave ratio</td>
<td>1.3 ± 0.41</td>
<td>1.14 ± 0.39</td>
<td>1.35 ± 0.4</td>
<td>&lt;0.00001</td>
<td>0.08</td>
</tr>
<tr>
<td>E-wave deceleration time (ms)</td>
<td>208.5 ± 41.2</td>
<td>226.8 ± 50.1</td>
<td>201.8 ± 30.8</td>
<td>&lt;0.00001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. BSA, body surface area.

*Adjustment was made for age, gender, 24-h systolic and diastolic BP and duration of hypertension.
with MS (n = 37), when compared with patients without MS (n = 86), tended to be older (43 ± 9.1 vs. 40.1 ± 9.8; P = 0.13), and showed higher 24-h systolic BP (135.9 ± 11.5 vs. 130 ± 9.4; P = 0.003) and more elevated values of LVMII (100.5 ± 17.6 g m⁻² vs. 86 ± 14.3 g m⁻²; P < 0.0001, which becomes P = 0.002 after adjustment for age and 24-h systolic BP) and of LVMH².⁷ (47.3 ± 7.8 g m⁻².⁷ vs. 38.6 ± 6.7 g m⁻².⁷; P < 0.0001, which becomes P = 0.0001 after adjustment for age and 24-h systolic BP).

To confirm that the differences in LV mass were not explained by visceral obesity alone we compared LVMII and LVMH².⁷ in two subgroups of the study population, including obese subjects (waist circumference >102 cm in men and >88 cm in women) without MS (n = 93) and obese individuals without MS (n = 43). Waist circumference and BMI did not differ in the two groups. Still, we found higher values of LVMII (106.9 ± 28.6 g m⁻² vs. 92.1 ± 22.4 g m⁻²; P = 0.001) and of LVMH².⁷ (54.5 ± 15.5 g m⁻².⁷ vs. 45 ± 11.3 g m⁻².⁷; P = 0.0001) in obese hypertensives with MS. These differences were significant also after adjustment for age, sex, 24-h blood pressures and duration of hypertension (P = 0.02 and 0.007 respectively).

As shown in Table 2, mid-wall fractional shortening and the mitral E-wave/A-wave ratio were lower and E-wave deceleration time was longer in hypertensive patients with MS when compared with those without it. These results, with the exception of the E-wave/A-wave ratio, held also after adjustment for age, gender, 24-h systolic and diastolic BP, and duration of hypertension.

When we looked at renal and retinal indices of hypertensive target organ damage (presented in Table 3), we found that the AER and prevalence of microalbuminuria (Fig. 1b) were significantly higher in hypertensive subjects with MS, even after adjusting for age, gender, 24-h systolic and diastolic BP, and duration of hypertension. The chance of having microalbuminuria remained greater in the group of patients with MS also taking into account age, gender, 24-h systolic and diastolic BP, duration of hypertension, and previous antihypertensive therapy (OR = 2.45, 95% CI: 1.44–4.18; P = 0.0001). The difference regarding AER as a continuous variable, was also confirmed in the subgroup of untreated patients with MS (n = 37) when compared with those without MS (n = 86) (P = 0.0001), even after correction for age and 24-h systolic BP (P = 0.006).

Similar conclusions were also reached when comparing obese subjects with MS (n = 93) to those without MS (n = 43), AER being higher in the former than in the latter [13.9 (6–26.5) vs. 9.9 (6–18) µg min⁻¹; P = 0.04, after correction for age, sex, duration of hypertension and levels of BP]. The groups with and without MS did not differ regarding serum creatinine and creatinine clearance indexed for BSA, although, after controlling for age and other confounding variables the latter parameter became significantly higher in hypertensive patients with MS. The prevalence of hypertensive retinopathy was greater in subjects with MS, even after adjustment for age, gender, 24-h blood pressures, duration of hypertension, and previous antihypertensive therapy (OR = 1.99, 95% CI: 1.13–3.52; P = 0.01).

Linear multiple regression analysis, aiming to explore the independent determinants of LV mass, revealed that in a model (R² = 0.33) including age,
sex, duration of hypertension, previous antihypertensive therapy, AER, glycaemia, HDL, triglycerides, waist circumference, and 24-h systolic and diastolic blood pressures, the following parameters remained significant predictors of LVMH^{2.7}: age (β = 0.19; \(P = 0.0001\)), male gender (β = 0.15; \(P = 0.002\)), duration of hypertension (β = 0.10; \(P = 0.04\)), AER (log-transformed) (β = 0.12; \(P = 0.01\)), waist circumference (β = 0.34; \(P < 0.00001\)), 24-h systolic BP (β = 0.20; \(P = 0.00009\)). When we added MS to this model as a dummy variable (0 = no; 1 = yes), MS continued to be associated with LVMH^{2.7} (β = 0.20; \(P = 0.00009\)), independently of its individual components and other covariates. A similar association between MS and LV mass (β = 0.21; \(P = 0.0003\)) was obtained when the single components of MS, with the exception of blood pressures, were introduced into this multivariate model as dichotomous rather than continuous variables.

Analogous conclusions were also reached when ridge multiple regression analysis was used to overcome the problem of multicollinearity. In particular, for a lambda of 0.09, the ridge standardized coefficient of regression relating MS to LVMH^{2.7} was 0.19 (\(P = 0.0001\)). The inclusion in the multivariate model of clinic systolic and diastolic BP values, instead of the corresponding 24-h ambulatory BP, did not significantly modify the results. The same was true when waist circumference was replaced by the body mass index. Similar findings were also obtained when adopting LVM as dependent variable, instead of LVMH^{2.7}.

When a multiple regression model was built to assess the independent correlates of AER, glycaemia (β = 0.14; \(P = 0.007\)) and 24-h systolic BP (β = 0.16; \(P = 0.002\)) emerged as the main predictors of AER. When this model was run again after adding MS, along with its individual components and other potential confounders, MS continued to be related to the AER (β = 0.12; \(P = 0.03\)), even when we calculated the standardized ridge coefficient of regression (β = 0.11; \(P = 0.03\), for a lambda of 0.46) to avoid the problems of multicollinearity.

**Discussion**

The main finding of the present study was the identification of a close association between MS, defined in accordance with NCEP-ATPIII criteria, and some indices of preclinical cardiac, renal and retinal damage. With regard to echocardiographic parameters, hypertensive patients with MS exhibited higher LV mass (either normalized by BSA or by height elevated by a power of 2.7), relative wall thickness, left atrial size, and greater prevalence of LV hypertrophy, lower mid-wall fractional shortening and a longer E-wave deceleration time than subjects without MS. These results were maintained even after correction for several confounding variables, such as age, gender distribution, severity and duration of hypertension and previous antihypertensive therapy. In particular, after adjustment for these covariates, the likelihood of LV hypertrophy was 2.89-fold (95% CI: 1.68–4.98) higher in subjects with MS than in those without it, when LV mass was indexed by height^{2.7}.

Moreover, it is noteworthy that the relationship between MS and LV mass was confirmed in multivariate regression models including MS together with its individual components, as independent variables; this suggests that MS may have a deleterious effect on cardiac structure over and above the potential contribution of each single component of this syndrome, and that the confluence of abnormalities that comprise MS may have a synergistic negative impact on LV mass. The data in the present study, obtained from a wide sample of White hypertensive patients, concurs with the results of two previous investigations conducted on the general population [16] and hypertensive subjects [17].

In the Strong Heart Study, a longitudinal investigation conducted in American Indian communities, a subset of the study population, including 1 436 non-diabetic participants without prevalent cardiovascular disease (61.2% of which had high BP), was examined to analyse the impact of the MS on cardiac structure and function. Subjects with MS showed greater LV dimension, mass and relative wall thickness, and left atrial diameter, and a higher prevalence of LV hypertrophy, with lower mid-wall shortening than those who did not have MS [16]. Cuspidi et al. [17], in 447 untreated middle-aged hypertensives, found that patients with MS had a more pronounced cardiac and extra-cardiac involvement than those without it.

Our paper, being a clinical study with a cross-sectional design, only permits us to make hypotheses...
about the association of MS with cardiac hypertrophy. For example, the latter might be explained by insulin resistance and the accompanying compensatory hyperinsulinaemia, which are regarded as the patho-physiological key features underlying the MS [1]. Trophic effects of insulin on myocardial tissue have been demonstrated in cell cultures and animal models [18, 19] and could be mediated, at least in part, by the insulin-like growth factor-1 receptors [20, 21]. However, the in vivo studies that have sought an association between insulin and LV mass have yielded conflicting results [21–27].

Moreover, insulin may affect LV mass indirectly by increasing sodium retention [28, 29] or endothelin-1 levels [30, 31] or by inducing sympathetic activation [32–34]. Other potential biological mediators of LV hypertrophy in subjects with MS may be certain peptide hormones, secreted from white adipose tissue, such as angiotensin II, a potent growth factor in myocardial tissue [35], and leptin, whose mitogenic effect in cardiomyocytes has been recently evaluated with discrepant conclusions [27, 36–38].

There are other important findings from our study that deserve a special mention: the greater level of AER and the consequent higher prevalence of microalbuminuria, and the more elevated age-adjusted creatinine clearance values, observed in hypertensive subjects with MS in comparison with those without it. These results are in keeping with a recent cross-sectional evaluation of the Third National Health and Nutrition Examination Survey data in 5360 US civilian non-institutionalized subjects, in which a close association was found between microalbuminuria and MS (defined according to NCEP-ATPIII criteria) [39]. In the same study, as well as in ours, the main predictors of microalbuminuria were blood pressure and glucose levels [39].

The relationship between AER and MS is so close that WHO recommendations include microalbuminuria amongst the criteria for diagnosing MS [1]. Indeed, the inclusion of microalbuminuria as part of the MS has been controversial because its association with insulin resistance has been described in several [40–42], but not all, reports [43, 44]. Glomerular hyperfiltration, expressed by an increased creatinine clearance rate, is a functional renal change that precedes glomerulosclerosis [45–47]; it is associated with obesity [48] and with insulin resistance [49].

Several studies showed that the MS confers an increased risk of cardiovascular morbidity and mortality [4–6, 50]. Recently it has been demonstrated that the adverse prognostic impact of MS may also be extended to hypertensive patients [7]. Indeed, in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale study, a prospective observational investigation of Italian adult subjects with essential hypertension, those patients with this syndrome (34% of the whole population), defined in accordance with NCEP-ATPIII criteria, ran an increased risk of developing cardiac and cerebrovascular events. The risk was attenuated but still significant amongst participants without diabetes mellitus [7].

It is likely that the enhanced cardiovascular risk associated with MS may be partly mediated through an increased prevalence of preclinical cardiovascular and renal changes in patients with essential hypertension and MS. Indeed, preclinical cardiac and renal abnormalities, such as LV hypertrophy and microalbuminuria, are recognized as significant independent predictors of adverse cardiovascular outcomes [11, 50–53].

Another finding from our study merits a comment, this being the increased prevalence of grade I and grade II hypertensive retinopathy observed in subjects with MS when compared with persons without MS. This result is consistent with a recent cross-sectional investigation involving 11 265 participants in the Atherosclerosis Risk in Communities Study, in which associations were noted between MS and arterio-venous nicking, focal arteriolar narrowing and generalized arteriolar narrowing, even in people without diabetes or hypertension [54]. However the prognostic significance of this finding is unclear, because the studies exploring the association between the first two degrees of hypertensive retinopathy and cardiovascular outcomes have shown inconsistent results [55]. Some other aspects of our paper need to be discussed.

First, the greater proportion of women observed in the group with MS. It was explained by a greater prevalence of visceral obesity and of low HDL values in females than in males. The over-representation of women in the MS group may appear surprising in the light of the higher percentage of males reported in MS in previous papers, such as in the Botnia study.
in which the WHO criteria [1] were used to diagnose MS. These criteria require very different limits and modalities to define obesity and low HDL values, from those proposed by the NCEP-ATPIII definition of MS. Indeed, when the latter definition was used it was frequently observed that there was no gender difference [7, 17] or there was a greater proportion of women in the MS group [16, 39, 56, 57], as was the case in our study.

Secondly, previous antihypertensive treatment that had been stopped may have affected the results because of the persisting influence on target organ damage, even though patients’ blood pressure may have returned to control values. However, in the subset of hypertensive patients who had never pharmacologically treated we found results similar to those obtained in the whole population, with regard to LV mass and the AER. Moreover, the greater extent of preclinical cardiac, renal and retinal damage in patients with MS was confirmed, also taking into account previous treatment in multivariate analyses.

Thirdly, patients with MS were older and showed more elevated systolic BP and a longer duration of hypertension, than those without MS. These factors may partially explain the greater extent of end-organ damage found in subjects with MS. However, the differences regarding LVM, prevalence of LV hypertrophy, AER and prevalence of microalbuminuria remained significant after adjustment for these covariates, even in the subgroups of untreated patients.

In conclusion, MS seems to amplify hypertension-related cardiac and renal changes, over and above the potential contribution of each single component of this syndrome. As these markers of target organ damage are well-known predictors of cardiovascular events, our results may partly explain the enhanced cardiovascular risk associated with MS.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

This work was supported in part by a grant from the Italian Ministry for University and Scientific Research (MURST). We express our gratitude to Mrs Concetta Truscillo and Mr Nicola Cirano for their nursing assistance.

References


51 Vakili BA, Okin PM, and Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J 2001; 141: 314–41.


Correspondence: Giuseppe Mulè MD, Via Monte San Calogero, 29, 90146 Palermo, Italy.
(fax: 91 6554331; e-mail: giusemme@email.it).