Metabolic Syndrome Affects Cardiovascular Risk Profile and Response to Treatment in Hypertensive Postmenopausal Women

Rosario Rossi, Annachiara Nuzzo, Giorgia Origliani, Maria Grazia Modena

Abstract—Metabolic syndrome is increasingly recognized as an important cardiovascular risk factor in hypertension, but its influence on the cardiovascular risk profile in hypertensive postmenopausal women has not been studied. The aim of the present study was to investigate the impact of metabolic syndrome on the cardiovascular risk profile and the response to treatment. We enrolled 350 hypertensive postmenopausal women, 55±6 years of age (range 47 to 60 years of age). Patients were divided into 2 groups according to the presence of metabolic syndrome. Compared with those without, women with metabolic syndrome had higher waist circumference, body mass index, and levels of glucose, triglycerides, and HDL cholesterol, as would be expected, based on definition. In addition, patients with metabolic syndrome had a cardiovascular risk profile less favorable, characterized by a significantly higher highly sensitive C-reactive protein (2.2±0.6 versus 1.7±0.7 ng/mL; P<0.01), a more compromised endothelial function (flow-mediated vasodilation 2.4±2.2 versus 4.4±2.5%; P=0.01), and a significantly higher left ventricular mass (44±15 versus 41±16 g/m²). Also, antihypertensive treatment induced a more modest improvement of both endothelial dysfunction and subclinical inflammation in women with metabolic syndrome. The results of our study show that in postmenopausal women, there are 2 different forms of hypertension: that which is isolated, and that which is associated with metabolic syndrome. This last form is related to a more severe risk profile, and response to therapy is less favorable. (Hypertension. 2008;52:865-872.)

Key Words: women ■ metabolic syndrome ■ hypertension ■ cardiovascular diseases ■ drugs ■ risk factors

Hypertension is highly prevalent in postmenopausal women, and the postmenopausal period is a well-established risk factor for cardiovascular disease in women.1 As one example of this phenomenon, the prevalence of hypertension is higher in males 30 to 45 years of age than in females of similar age, whereas the prevalence of hypertension in females after this age increases to levels similar to2 or exceeding that3 in males. Hypertension can be considered an isolated disease or part of the metabolic syndrome (MS). MS, a clustering of lipid and nonlipid cardiovascular risk factors, is estimated to affect ≈20% to 30% of the middle-aged population,4 and the prevalence of the disorder appears to be increasing in the US population.5 Postmenopausal status is associated with a 60% increased risk of MS, even after adjusting for confounding variables.6

MS is increasingly recognized as an independent predictor of cardiovascular disease in hypertension.7 Moreover, in those studies in which the prognostic impact of MS has been examined separately in men and women, the coronary or cardiovascular morbidity/mortality hazard ratios associated with MS were almost invariably found to be higher in the female sex.8–10 Therefore, the risk of cardiovascular disease attributed to MS appears to be especially high in women, and it is estimated that half of all cardiovascular events in women are related to MS.11 However, we have no evidence that MS directly influences the cardiovascular risk profile or resistance to treatment. To the best of our knowledge, this issue has never been studied in a specific population of postmenopausal women.

Therefore, the aim of the present study was to investigate the impact of MS on the cardiovascular risk profile and the response to treatment. This question was addressed in a sample of white postmenopausal women with essential hypertension, free from diabetes and cardiovascular disease, who had never received antihypertensive drug treatment.

Methods

Study Sample

The study sample consisted of consecutive postmenopausal women with never-treated essential hypertension who were self-referred to the “Bene Essere Donna” center, an institution dedicated to the study, prevention, and treatment of menopause-related disorders. This service, located in a third-level university hospital, is open to all
women provided they are in their postmenopausal period (postmeno-
pausal status was defined as the absence of menstruation for ≥6
months or by a follicle-stimulating hormone blood level >40 IU/L
and 17 β-estradiol levels <120 pmol/L) and are ≥60 years of age.
These women were initially drawn to the center through local media
advertising, have free access, and can make queries or obtain advice
about particular symptoms they are having by making appointments
beforehand. All participants gave their written informed consent to
participate in this study, which had been approved by the science
and ethics committee of our institution.

Evaluation of the Cardiovascular Risk Profile

Physical examination variables measured at baseline included body
weight, height, waist circumference, and systolic and diastolic blood
pressure (BP). BP was measured by a physician with a mercury
sphygmomanometer and cuff adapted to arm circumference, with
the subject sitting for ≥10 minutes. The appearance of Korotkoff
sounds was taken to be the systolic and their point of disappearance (phase
5) the diastolic BP. The average of 5 measurements was considered
for the analysis.

Participants provided questionnaire data concerning lifestyle po-
tential risk factors for cardiovascular disease (cigarette smoking,
hypercholesterolemia, diabetes, and hypertension).

We collected, in all patients, a venous blood sample to determine
the concentrations of fasting glucose, a complete lipid profile, and
fasting insulin. A homeostasis model assessment of insulin resistance
index was performed to assess insulin resistance. It was calculated as follows:
(fasting insulin(μU/mL)×fasting glucose (mmol/L))/22.5.

Total cholesterol, high-density lipoprotein cholesterol, and triglycerides
were determined by enzymatic colorimetric method. Serum HDL
cholesterol was measured by enzymatic colorimetric method after
precipitation with polyethilenglycole. LDL cholesterol was calcu-
lated by means of the Friedewald formula.

MS was defined, according to the Third Report of the National
Cholesterol Education Program Expert Panel on Detection, Evalua-
tion, and Treatment of High Blood Cholesterol in Adults,12 by the
presence, in addition to hypertension, of ≥2 of the following criteria:
(1) serum triglyceride levels >150 mg/dL; (2) serum HDL cholest-
erol <50 mg/dL; (3) fasting plasma glucose ≥110 mg/dL; and (4)
waist circumference ≥88 cm.

In addition to the classic risk factors, we included in the
definition of the cardiovascular risk profile the study of endothe-
lial function and the determination of C-reactive protein, an acute
phase reactant, which was the most sensitive marker of subclinical
inflammation.

Diagnosis of Hypertension and Treatment Protocol

Postmenopausal patients with newly diagnosed hypertension were eligi-
ble for the study. The cases of hypertension were identified in
the following ways: (1) self-report of physician diagnosis; (2)
comparison of systolic BP values ≥140 mm Hg or diastolic BP
values ≥90 mm Hg during the visit. If this latter condition was
encountered, we took steps to check the BP, before diagnosing
hypertension, on 2 further occasions: the first after 1 week and the
second after 1 month from the initial anomalous measurement. Only
in cases in which these values remained persistently high
(≥140 mm Hg for systolic BP or ≥90 mm Hg for diastolic BP) was
hypertension diagnosed.

Once the diagnosis of hypertension was made, patients were to
receive optimal antihypertensive treatment according to the recom-
mendations of the Seventh Joint National Committee on Prevention,
Detection, Evaluation, and Treatment of High Blood Pressure.13 All
women were advised to modify their lifestyle habits according to the
recommendations of the Seventh Joint National Committee on
Prevention, Detection, Evaluation, and Treatment of High Blood
Pressure.13 If these measures were unable to reduce BP, pharma-
cotherapy was initiated. Therapies were assigned to maintain
systolic BP <140 mm Hg and diastolic BP <90 mm Hg. Patients
were visited every 4 weeks. The choice of the antihypertensive drug
was at the discretion of the study investigators and was made on
the basis of a “step-by-step approach” when the BP values were
unsatisfactory (>140/>90 mm Hg). When BP values were <140/
90 mm Hg for 3 consecutive measurements (ie, ≥3 months of
controlled BP), the number and the class of the drugs taken from
the patient were recorded.

Exclusion Criteria of the Study

Patients with a past medical history of chest pain, diagnostic
coronary angiography, coronary revascularization, myocardial in-
farction, stroke, or transient ischemic attack were excluded from
the study. Women were also excluded for the following reasons: (1) past,
present, or suspected neoplastic, degenerative, or inflammatory
pathology; (2) past or present use of any estrogen or progestin-
containing compounds or other hormonal agents such as tibolone or
selective estrogen receptor modulators such as tamoxifen or ralox-
ifene; (3) cardiomyopathies; (4) alcoholism or other drug abuse; (5) a
failure to achieve a BP <140/<90 mm Hg after 6 months of
treatment; or (6) a current participation in other ongoing clinical
trials.

Echocardiographic Examination

Echocardiographic examination information can be found in an
online supplement available at http://hyper.ahajournals.org.

Evaluation of Endothelial Function

Endothelial function was evaluated through the measure of the
flow-mediated (endothelium-dependent) vasodilation performed on
the brachial artery. The study of the endothelial function was
completed by the dosage of the plasma levels of endothelin-1 and
von Willebrand factor. The study of endothelial function was
performed at baseline and after 1 year of follow-up.

Flow-mediated dilation (endothelium-dependent) of the brach-
ial artery was measured unaware of the other data. The technique
for assessing flow-mediated dilation has been described in detail
previously.14,15

In our laboratory, the methodology had an interobserver variabil-
ity in diameter measurements of 0.45±0.25%, yielding a coefficient
of variation of 1.34% and a coefficient of repeatability of 0.8%.
Levels of endothelin-1 and von Willebrand factor were measured on
plasma samples using commercially available kits. Endothelin-1 was
dosed using an enzyme immunoassay kit (TiterZyme enzyme
immunoassay; Assay Designs Inc). Von Willebrand factor antigen
levels were measured quantitatively using an immunoturbidimetric
method (Dade Behring von Willebrand factor Ag*).

Study of Subclinical Inflammation

To measure C-reactive protein level, we used a highly sensitive
immunoturbidimetric assay and an automated clinical chemistry
analyser (C-reactive protein [Latex] US Modular P method, Roche
Hitachi). This test is based on creation of an immunocomplex
between an anti–C-reactive protein monoclonal antibody and the
C-reactive protein–specific antigen. The intra-assay coefficient of
variation was <5%. To avoid elevation of C-reactive protein level
attributable to exogenous inflammatory stimuli, subjects with a
serum C-reactive protein level >3 SD above the mean were
excluded.

Two dosages of highly sensitive C-reactive protein were per-
formed: at baseline and after 12 months of follow-up.

Statistical Analysis

The continuous variables were expressed as mean±1 SD, and
the categorical variables were expressed as percentages. The 2
groups were compared by the Student t test for unpaired data and the χ²
test with the Yates correction for continuity, when appropriate.
Baseline values and those recorded after 12 months were compared by
repeated measures of variance. All P values are 2-tailed. P<0.05 was
taken as significant.
Results

We enrolled 350 hypertensive postmenopausal women, 55±6 years of age (range 47 to 60 years of age) and divided them into 2 groups according to the presence of MS. The baseline characteristics of our population are illustrated in Table 1. Compared with those without MS, women with MS had higher waist circumference, body mass index, and levels of glucose, triglycerides, and HDL cholesterol, as would be expected based on the definition of MS. Significant differences were not observed in baseline BP, renal function, total and LDL cholesterol plasma concentrations, left atrium and left ventricular dimensions, and left ventricular performance. However, patients with MS had a cardiovascular risk profile that was less favorable, characterized by a significantly higher highly sensitive C-reactive protein, a more compromised endothelial function, and a significantly higher left ventricular mass.

Table 1. Baseline Characteristics of the Study Patients Divided in 2 Groups According to the Presence of MS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MS</th>
<th>No MS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>180</td>
<td>170</td>
<td>NS</td>
</tr>
<tr>
<td>White, %</td>
<td>100 (n=180)</td>
<td>100 (n=170)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, years</td>
<td>54±8</td>
<td>53±10</td>
<td>NS</td>
</tr>
<tr>
<td>Time from menopause, months</td>
<td>37±14</td>
<td>38±12</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of hypertension, %</td>
<td>52.8 (n=95)</td>
<td>53.5 (n=91)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of diabetes, %</td>
<td>56.1 (n=101)</td>
<td>36.4 (n=62)</td>
<td>0.003</td>
</tr>
<tr>
<td>History of gestational diabetes, %</td>
<td>12.2 (n=22)</td>
<td>5 (n=6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Anthropometric parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30±3</td>
<td>25±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>91±14</td>
<td>80±15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Traditional cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>154±14</td>
<td>155±13</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>94±7</td>
<td>94±8</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking habits, %</td>
<td>35.5 (n=64)</td>
<td>30.5 (n=52)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212±24</td>
<td>198±27</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>137±16</td>
<td>125±17</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>37±13</td>
<td>51±15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>221±26</td>
<td>169±22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>105±12</td>
<td>95±14</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin-resistance indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma insulin, U/L</td>
<td>6.6±4.9</td>
<td>3.5±2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>7.9±4.9</td>
<td>3.5±3.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal function–related parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>38±14</td>
<td>36±13</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9±0.2</td>
<td>1.0±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Subclinical inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP, ng/L</td>
<td>2.2±0.6</td>
<td>1.7±0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Endothelial function–related parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMD, %</td>
<td>2.4±2.2</td>
<td>4.4±2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Endothelin-1, pg/mL</td>
<td>4.3±0.6</td>
<td>3.1±0.8</td>
<td>0.002</td>
</tr>
<tr>
<td>von Willebrand factor, mU/mL</td>
<td>173±16</td>
<td>149±17</td>
<td>0.02</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, mm</td>
<td>42±13</td>
<td>43±12</td>
<td>NS</td>
</tr>
<tr>
<td>EDLVD, mm</td>
<td>47±14</td>
<td>49±14</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular FS, %</td>
<td>29±7</td>
<td>31±8</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass, g/m²²</td>
<td>44±15</td>
<td>41±16</td>
<td>0.03</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
<td>30.5 (n=55)</td>
<td>24.1 (n=41)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are expressed as mean±1 SD or as a percentage.

BUN indicates blood urea nitrogen; EDLVD, end-diastolic left ventricular diameter; FMD, flow-mediated dilation; HOMA-IR, homeostasis model assessment–insulin resistance; hs-CRP, highly sensitive C-reactive protein; FS, fractional shortening; LAD, left atrium diameter.
The antihypertensive regimens and proportion of subjects who received a lifestyle modification only, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, β-blockers and thiazide diuretics, alone or combined, or other drugs, are shown in Table 2. The number of antihypertensive drugs used to maintain BP in the chosen normal range (<140/90 mm Hg) was on average higher in hypertensive patients with MS (4.5 ± 1) versus others (3.5 ± 1; P < 0.05). The mean reduction of SBP/DBP for every added antihypertensive drug was −5.2/−2.4 mm Hg in patients with MS versus others (−7.2/−2.9 mm Hg; P < 0.05 for DBP, P < 0.01 for SBP).

The proportion of patients taking statins was not statistically different in the 2 groups (52 of 180 [28.9%] in the MS group versus 39 of 170 [22.9%] in the other group; P = NS), whereas the proportion of patients with MS taking fibrates or omega-3 (65 of 180 [36.1%] in the MS group versus 12 of 170 [7.0%] in the other group; P < 0.0001) was significantly higher.

### Outcome

During the study period (1 year of follow-up), there was 1 death, from a neoplasm. No difference was found in the dropout rate: 3 patients in the MS group and 2 patients in the other group (P = NS) were lost from the follow-up.

The effects of treatment on our studied parameters are shown in Table 3. The most relevant differences between the 2 groups are summarized in Figure 1, which shows that, among all the parameters that have shown significant changes induced by 1 year of treatment, only the behavior of highly sensitive C-reactive protein and indices of endothelial dysfunction are statistically different in women with MS compared with others. In particular, in hypertensive patients with MS, antihypertensive treatment produced a more modest improvement of both endothelial dysfunction and subclinical inflammation.

### Effects of Obesity

To better study the influence of overweight and obesity on the response to treatment, we divided our patients with MS (n = 180) into 2 groups: normal weight (body mass index between 20 and 25 kg/m²; n = 54; 30% of the women with MS) and overweight/obese (body mass index > 25 kg/m²; n = 126; 70% of the women with MS), according to the definition of the World Health Organization. The baseline comparison between the 2 subgroups is shown in Table 4. All of the normal weight patients with hypertension and MS had a family history of type 2 diabetes or a history of gestational diabetes; no other parameters were significantly different between the 2 groups. Figure 2 takes into account the same relevant parameters shown in Figure 1. We found no significant differences in the improvement in the study parameters by body weight or obesity status.

### Discussion

The results of our study show that in postmenopausal women, there are 2 different forms of hypertension: the isolated form, and the one associated with MS. This last form is associated with a more severe cardiovascular risk profile, and the response to therapy is less favorable. In other words, the presence of MS seems to aggravate the severity of hypertension and reduce the capacity to respond to specific treatments. It is then reasonable to consider MS a potentially unfavorable prognostic factor in hypertensive postmenopausal women.

About one third of our postmenopausal patients who experienced both hypertension and MS (according to the criteria of Adult Treatment Panel III) were of normal weight. According to our results, these patients respond to treatment in a similar way to overweight/obese patients. We believe that
practitioners should pay particular attention to this population to accurately diagnose the presence of MS in these patients. Indeed, most physicians tend to consider the diagnosis of MS only in obese patients. In reality, MS can be found in lean but insulin-resistant postmenopausal women. According to the data from our study, these women generally have a normal weight, are hypertensive, have high triglycerides and low HDL, have a family history of diabetes, or have a history of gestational diabetes. It is well known that in a population with a family history of type II diabetes, individuals with MS have a higher mortality.16

A main finding of our study was the evidence of a possible link between inflammation and endothelial dysfunction in postmenopausal hypertensive women with MS. In our study, in fact, among patients with MS, there was a significant proportion of women with left ventricular hypertrophy, increased levels of highly sensitive C-reactive protein, and markers of endothelial dysfunction (flow-mediated dilation and levels of endothelin-1 and Von Willebrand factor) compared with patients without MS. Interestingly, all these markers were significantly related to the presence of MS and were unrelated to either antihypertensive therapy or different classes of used drugs. These data are also independent from the presence of overweight/obesity.

It is well known that MS is an aggravating factor in hypertensive patients. Many studies identify MS, especially in postmenopausal women, as an important risk factor for cardiovascular and cerebrovascular disease.9,17,18 Several studies have shown that insulin resistance/hyperinsulinemia, a hallmark of MS, is a predictor of ischemic heart disease in the population at large19,20–22 and in patients with type II diabetes.23

High BP is a major and independent cardiovascular risk factor. On the other hand, hypertension tends to cluster with other metabolic risk factors,24 and about half of patients with essential hypertension are insulin resistant.25 Individuals with MS tend to have systemic endothelial dysfunction26 and chronic subclinical inflammation,27 which are increasingly recognized as powerful risk factors.
for cardiac and cerebrovascular events.\textsuperscript{28,29} Previous experimental evidence did suggest a role for inflammation in the development of vascular damage in hypertension. Hypertension exerts a number of proinflammatory effects through the increased expression of several mediators.\textsuperscript{30,31} An increased vessel wall stretch has been shown to activate the reduced nicotinamide-adenine dinucleotide phosphate oxidase and the nuclear factor κB to increase adhesion molecule expression by endothelial cells and to upregulate endothelial cell secretion of proinflammatory cytokines.\textsuperscript{32} These effects can enhance monocyte adhesion to the endothelium, their transmigration into the vessel wall and into the tissue interstitium, and the development of endothelium dysfunction and inflammation.\textsuperscript{33} In this regard, an increased degree of left ventric-
This study explores the relationship among the presence or absence of MS, the cardiovascular risk profile, and the response to treatment in hypertensive postmenopausal women. This study is unique in that it addresses whether MS negatively influences both cardiovascular risk profile and resistance to treatment. Our data are in line with the innovative evidence that postmenopausal hypertensive women with MS are more compromised (in terms of end organ damage) and have a greater resistance to antihypertensive therapy compared with those without MS. The clinical implication of this fact is that a close follow-up and an aggressive management of hypertension are justified in these patients. Additional studies are needed to determine whether there are long-term differences in response to treatment in terms of hard outcome.

**Perspectives**

The broad implications of the present study are that MS should be considered a potentially negative prognostic factor in hypertensive postmenopausal women, able to adversely affect both the severity of hypertension (in the sense of more serious end organ damage, more impaired endothelial function, more frequent left ventricular hypertrophy, more severe subclinical inflammation) and the patient’s ability to respond to specific treatment. For these important implications, clinicians should give attention to accurately diagnosing MS in hypertensive postmenopausal women because this condition can occur not only in obese subjects but even in lean but insulin-resistant patients (approximately one third of our population), particularly in those with a family history of diabetes or history of gestational diabetes.

It is reasonable to assume that close follow-up and an aggressive pharmacological and nonpharmacological approach could improve outcomes for hypertensive postmenopausal women with MS. Further controlled studies would be needed to assess whether this approach can effectively reduce major cardiovascular events.

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### Disclosures

None.

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