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Metabolic syndrome and multiple organ damage in essential hypertension

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Abstract

Aim. We investigated the prevalence of the metabolic syndrome (MS) in hypertensive patients categorized according to the number of markers of organ damage (OD) in order to assess the value of a systematic search for cardiac and extra-cardiac OD in the MS setting. *Methods*. A total of 3119 untreated and treated essential hypertensives included in the Evaluation of Target Organ Damage in Hypertension (ETODH), an observational registry of hypertension-related OD, were considered for this analysis. All patients underwent extensive investigation for left ventricular hypertrophy (LVH) or LV concentric remodeling (cardiac OD), carotid plaques and/or intima-media thickening (vascular OD) and microalbuminuria (MA) and/or increased serum creatinine (renal OD). Subjects were classified as: positive for none (group 0), one (group I), two (group II) or three markers (group III) of OD. *Results.* MS prevalence rates progressively rose across the groups stratified according to the OD score, reaching a 2.3-fold increase in group III compared with their MS counterparts in group 0. The distribution of subjects with and without the MS across the groups was 15% vs 29% (group 0), 32% vs 38% (group I), 39% vs 26% (group II) and 14% vs 7% (group III), respectively. Thus, subjects having two or three markers of OD were 53% among those with MS and 33% ($p < 0.01$) among those without it. *Conclusion.* Our findings indicate a strong association between the MS and OD by showing that a clustering of two or three markers of OD is the prevalent cardiovascular phenotype in MS hypertensives referred to a specialist center and call for a systematic evaluation of cardiac and extracardiac OD in this setting.

Key Words: *Hypertension, metabolic syndrome, multiple organ damage*

Introduction

Subclinical organ damage (OD) is currently regarded as an intermediate stage in the continuum of vascular disease and as a strong determinant of total cardiovascular (CV) risk in both normotensive and hypertensive individuals (1). A growing body of evidence underlines the relevance of OD as a determinant of CV morbidity and mortality. Quantitative markers of OD [i.e. increased left ventricular mass (LVM), carotid intima-media thickening and urinary albumin excretion] have been shown to be associated with an increased incidence of CV events (2–5). Because of the role of high blood pressure (BP) *per se* or associated with other risk factors in determining subtle structural and functional alterations in target organs, signs of organ involvement should be carefully sought in the initial evaluation of each patient in order to quantify total CV risk (6–8).

Numerous studies have shown that cardiac, vascular and renal damage are more pronounced in hypertensives with the MS compared with their counterparts without MS, indicating that this condition may amplify hypertension-related pre-clinical abnormalities (9–11). This synergistic effect has

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been shown to promote early OD in young hypertensives and enhance age-associated CV alterations in the elderly (12).

Despite a large body of evidence about the association between MS and OD, systematic data on the prevalence of this phenotype in hypertensive patients with different degrees of OD (i.e. single vs multiple OD) are rather scanty.

In the present cross-sectional study including 3119 untreated and treated essential hypertensive patients, we sought to investigate the clinical relevance of the association of MS with multiple OD to provide a wider evidence on the value of a systematic search for cardiac and extracardiac OD in this phenotype.

Methods

The Evaluation of Target Organ Damage in Hypertension (ETODH) study is our observational registry of hypertension-related OD and concomitant CV risk factors in subjects with uncomplicated essential hypertension aimed at estimating total CV risk in patients referred or self-referred to our outpatient clinic according to the International (6,7) and European hypertension guidelines (1,8). High BP was defined as a systolic BP (SBP) $\geqslant$140 mmHg and/or diastolic BP (DBP) $\geqslant$90 mmHg in untreated subjects. Treated hypertensive subjects were included regardless of BP values. Main exclusion criteria included a history of congestive heart failure, atrial fibrillation, previous stroke, significant cardiac valve disease, previous myocardial infarction or coronary by-pass, secondary causes of hypertension and neoplastic disease. After an informed consent had been obtained during the initial visit, all patients were subjected to the following procedures within a 1–4-week interval: medical history and physical examination, clinic BP measurement, blood and urine sampling, standard 12-lead electrocardiogram, 24-h urine collection for microalbuminuria (MA), non-mydriatic retinography, cardiac, renal and carotid ultrasonography. In all subjects, laboratory tests for secondary hypertension were performed when considered appropriate on clinical grounds.

The study protocol was approved by the ethics committee of one of the institutions involved. For the present analysis, patients were categorized according to the number of markers of OD: patients positive for none (group 0), one (group I), two (group II) or three markers (group III) of OD with or without the metabolic syndrome (MS+, MS−).

BP measurement

Clinic BP was measured during two different visits in the outpatient clinic using a mercury sphygmomanometer and taking the first and fifth phases of Koroktoff sounds to identify SBP and DBP, respectively. Measurements were performed after the subjects had comfortably rested for 5 min in the sitting position. Three measurements were taken at 1-min intervals and the average was used to define clinic SBP and DBP.

Echocardiography

Technical details have been reported previously (12,13). In brief, M-mode, two-dimensional and Doppler echocardiographic examinations were performed with commercially available instruments. LVM was estimated from end-diastolic left ventricular internal diameter (LVIDd), interventricular septum and posterior wall thickness (PWT) according to the Devereux's formula (14) and normalized to height$^{2.7}$ to obtain LVM index (I). Relative wall thickness (RWT) was calculated as $(2 \times \text{PWT})/\text{LVIDd}$. Patterns of left ventricular geometry were defined according to Ganau et al. (15) as follows: LV concentric remodeling, when normal LVMI was combined with RWT$\geqslant$0.45; eccentric LVH, when increased LVMI was associated with RWT$<$0.45; and concentric LVH, when LVH occurred with RWT$\geqslant$0.45. LV filling was assessed by mitral flow with standard pulsed Doppler technique. The following parameters were considered: early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and their ratio (E/A).

Carotid ultrasonography

Technical details have been previously reported (12). In brief, images of the extra-cranial carotid artery walls (common, bifurcation and internal carotid arteries) were obtained in several projections by high-resolution, linear array 7.5–10.0-MHz probes. Plaques were sought in the near and far walls of the entire extra-cranial tree based on the presence of focal wall thickenings. Intima-media thickness (IMT) was measured in the posterior wall of both common carotid arteries at 5, 10, 15, 20 and 25 mm caudally to bifurcation (16). To obtain the mean value of common carotid IMT, all five measurements were averaged. Carotid RWT was calculated as $(2 \times \text{IMT}/\text{Dd})$ where Dd is the value of the common carotid internal diameter.

Microalbuminuria

The concentration of albumin in a 24-h urine sample was measured using a commercially available radioimmunoassay kit (Sclavo SPA, Cinisello Balsamo, Italy). The detection limit of the method was 0.5 mg/l. In order to limit false-positive tests, all patients included in the study were advised to avoid heavy physical exercise during the 24-h urine collection period; a urinalysis was performed in order to exclude concomitant urinary tract infections.

Definition of OD

OD was defined by increased serum creatinine ($\geqslant$1.3 mg/dl in men and $\geqslant$1.2 mg/dl in women) (1,8), presence of MA (urinary albumin excretion: 20–300 mg/24-h) or proteinuria ($>$300 mg/24h) (*renal OD*) (7), ultrasonographic evidence of LVH or LV concentric remodeling (*cardiac OD*), presence of at least one carotid atherosclerotic plaque or diffuse IM thickening (*vascular OD*). In particular, LVH was defined as a LVMI equal to or higher than 51 g/m$^{2.7}$ in men and 47 g/m$^{2.7}$ in women (17). A plaque was defined as a focal thickening greater than 1.3 mm in any segment of carotid arteries (18). Diffuse intima-media thickening was diagnosed when the average common carotid wall thickness exceeded 0.9 mm (1,8).

Definition of the MS

MS was diagnosed when three or more of the following criteria were present: abdominal obesity (waist circumference $>$102 cm in men and $>$88 cm in women), hypertriglyceridemia ($>$150 mg/dl or 1.69 mmol/l) or on drug treatment for elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol ($<$40 mg/dl or 1.04 mmol/l in men and $<$50 mg/dl or 1.29 mmol/l in women) or on drug treatment for reduced HDL cholesterol, high BP (SBP$\geqslant$130 mmHg or DBP$\geqslant$85 mmHg or on antihypertensive medication) and high fasting blood glucose ($\geqslant$100 mg/dl or $\geqslant$5.6 mmol/l) or on drug treatment for elevated glucose (19). Waist circumference was measured to the nearest of 0.5 cm at the midpoint between the bottom of the rib cage and the top of the iliac crest in patients at maximal expiration.

Statistical analysis

Statistical analysis was performed by the SAS system (version 6.12; SAS Institute Inc., Cary, North Carolina, USA). Values were expressed as means $\pm$ SD or as percentages. Means were compared by the Student's *t*-test for independent samples. Analysis of categorical data was carried out with the χ^2 test or Fischer's exact test when appropriate. Differences within groups were tested using analysis of variance (ANOVA). Pearson correlations were calculated to examine univariate relations between BP values and OD parameters. To investigate the association between OD and demographic/clinical variables, multiple logistic regression analyses were performed by calculating odd ratios (OR) and their 95% confidence limits (CI). For all analyses a $p<0.05$ was considered statistically significant.

Results

The ETODH registry started in January 1999 and by the end of June 2006 had consecutively enrolled 3266 Caucasian subjects with untreated or treated essential hypertension; the 3119 subjects (53% males) having complete clinical, laboratory and ultrasonographic records were included in the present analysis. Mean age was 53.1 $\pm$ 12.4 (range 18–90) years. Mean SBP and DBP values were 147.1 $\pm$ 16.0 and 92.7 $\pm$ 9.3 mmHg, respectively; 71.0% of patients were on antihypertensive treatment (29.8% on monotherapy, 23.9% on two drugs, 17.2% on three or more drugs). With regards to other risk factors, smokers were 21.9%, type 2 diabetes mellitus was present in 5.2% and MS in 38.9% of the study sample. The most common component of the MS (other than high BP) was low HDL cholesterol (39.6%) followed by high fasting glucose (35.5%), abdominal obesity (30.8%) and hypertriglyceridemia (26.5%).

In the whole population, the most common phenotype of OD was carotid atherosclerosis (i.e. carotid plaque and/or carotid thickening: 54.5%) followed by alterations in LV structure and geometry (i.e. LVH or LV concentric remodeling: 50.1%), MA (20.0%) and increased serum creatinine (2.9%).

Overall, prevalence rates of patients categorized according to the absence (group 0) or presence of one (group I), two (group II) or three (group III) markers of OD were: 23.6%, 35.6%, 30.8% and 9.8%, respectively. Prevalence of the MS phenotype progressively rose across the groups (0=25%, I=34%, II=49%, III=58%) with a 2.3-fold increase of the syndrome in patients with multiple OD compared with their MS counterparts without signs of OD. The distribution of subjects with and without

the MS in the various groups was substantially different (Figure 1); in particular, the patients positive for two or three markers of OD were 53% among MS+ and 33% among MS− ($p<0.01$).

Clinical and demographic characteristics of the patients categorized according to the number of OD and presence or absence of the MS are reported in Table I. Age, body mass index (BMI), clinic SBP, duration of hypertension, fasting blood glucose, total cholesterol, triglycerides, serum creatinine, prevalence of MS, type 2 diabetes, smoking and antihypertensive association therapy all showed a progressive increase from group 0 to group III; HDL cholesterol, in contrast, showed the opposite trend. MS was less prevalent in group 0 and I (24.9% and 34.5%) than in groups II and III (48.9% and 57.3%, $p<0.01$). A significant difference in plasma glucose, HDL cholesterol, triglycerides, uric acid levels, BMI, prevalence of diabetes but not in SBP/DBP values was observed in patients with and without the MS**.** The mean age of subjects with MS was slightly but significantly lower in groups II and III. The frequency of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, beta-blockers, calcium-antagonists, diuretics use did not substantially differ between patients with and without MS in group 0 and I, whereas the frequency of diuretics and beta-blockers use was higher in patients with MS than in their counterparts in groups II and III (data not shown).

Echocardiographic, carotid artery and MA values are shown in Table II. As expected, echocardiographic values such as LV absolute wall thickness, RWT, left atrium diameter, absolute LV mass and LVMI showed a progressive increase across the groups, whereas the E/A value showed the opposite trend. Carotid artery diameter, IMT and RWT were also characterized by a progressive increase from group 0 to group III. In all groups, a number of cardiac parameters (i.e. wall thickness, LVMI, RWT, LA diameter) were markedly altered in patients with MS compared with those without it, the difference being in most instances statistically significant. The prevalence of concentric LVH showed a stepwise increase from group I to group III and was higher in all MS groups than in their counterparts (Figure 2). This was also the case for MA, but not for carotid atherosclerosis.

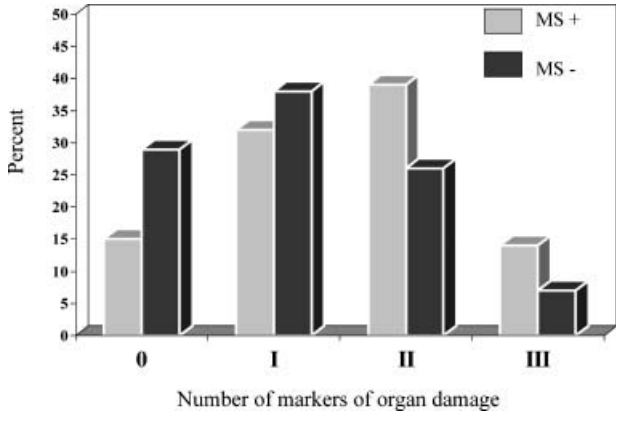

Figure 1. Prevalence rates of patients with and without the metabolic syndrome (MS) according to the number of markers of organ damage (OD): patients positive for none (group 0), one (group I), two (group II) or three markers (group III) of OD.

Univariate analyses

In the overall population, all markers of OD defined by continuous variables (LVMI, IMT and UAE) showed significant and positive correlations with clinic SBP (LVMI: $r=0.30$, $p<0.0001$; IMT: $r=0.22$, $p<0.0001$; UAE: $r=0.14$, $p<0.001$) and DBP (LVMI: $r=0.18$, $p<0.0001$; IMT: $r=0.10$, $p<0.0001$; UAE: $r=0.08$, $p=0.0002$). Significant correlations were found between OD variables and age, BMI, cholesterol, triglycerides, fasting blood glucose and serum creatinine. Significant associations were also observed between LVMI and common carotid IMT ($r=0.24$, $p<0.001$) or UAE ($r=0.12$, $p=0.001$), IMT and UAE ($r=0.03$, $p=0.001$).

Multivariate analyses

The relation of variables such as age (<55 vs ⩾ 55 years), gender, BMI (<25 vs ⩾25 kg/m^2), SBP (<150 vs ⩾150 mmHg), plasma glucose (<100 vs ⩾100 mg/dl), total cholesterol (<200 vs ⩾200 mg/dl), triglycerides (<170 vs ⩾170 mg/dl), HDL cholesterol (<40 vs ⩾40 mg/dl in men, <50 vs ⩾ 50 mg/dl in women), current smoking (no–yes), duration of hypertension (<10 vs ⩾10 years) with multiple TOD (three markers) was analyzed by a logistic regression model with stepwise selection. In this model, age (OR=1.98, 95% CI 1.61–2.49), male gender (OR=1.67, 95% CI 1.34–1.97), SBP (OR=1.89, 95% CI 1.48–2.32), MS (OR=2.52, 95% CI 2.08–3.15), duration of hypertension (OR=1.59, 95% CI 1.20–1.89) and current smoking (OR=1.41, 95% CI 1.17–1.71) were all significant ($p<0.01$) variables in the analysis.

Discussion

We have recently reported that the finding of damage in one or two organs is rather frequent in

Table I. Clinical characteristics of the study population according to the number of markers of organ damage (OD): patients positive for none (group 0), one (group I), two (group II) or three markers (group III) of OD with or without the metabolic syndrome (MS+, MS−).

	Group 0		Group I		Group II		Group III	
Variable	MS−, n=554	MS+, n=184	MS−, n=728	MS+, n=385	MS−, n=491	MS+, n=470	MS−, n=131	MS+, n=176
Age (years)	44.3±10.7	44.8±10.7	52.9±12.1	52.2±10.6	59.0±11.3	57.4±10.7**	60.6±11.4	58.8±10.9**
Male gender (%)	48.7	61.9**	47.5	54**	52.7	53.8	67.1	67.6
BMI (kg/m^2)	24.4±3.1	28.3±4.0*	24.5±3.4	28.9±4.4*	25.1±3.2	29.1±4.2*	25.3±3.3	29.3±4.3*
Clinic SBP (mmHg)	140±14	141±14	144±15	143±16	151±19	150±19	157±23	156±22
Clinic DBP (mmHg)	93±8	94±8	92±9	93±9	92±10	93±11	94±13	94±12
Clinic HR (beats/min)	74±12	75±12	72±11	73+12	71+12	71±11	71±12	72±13
Duration of HTN >10 years (%)	8.1	12.5	17.2	23.7**	23.7	32.6**	31.7	40.9**
Fasting glucose (mg/dl)	89±9	102±16.2	92±13	106±21	94±12	110±29	104±25	125±44
Total cholesterol (mg/dl)	207±38	218±40	216±38	222±41	219±36	232±40	224±44	228±49
HDL cholesterol (mg/dl)	54.8±15.3	40.7±12.1	56±16	41±11	55±15	41±12	51±15	39±11
LDL cholesterol (mg/dl)	133.2±35	142.6±35	141.2±36	146.2±39	143.2±35	156.3±71	150.5±41	149.5±45
Triglycerides (mg/dl)	98.6±48.1	172.7±87.9	99±45	174±101	103±45	175±109	112±54	198±131
Uric acid (mg/dl)	4.8±1.4	5.5±3.1*	4.9±1.3	5.6±1.4**	5.1±2.2	5.7±1.5**	5.9±3	6.3±1.7**
Creatinine (mg/dl)	0.8±0.2	0.9±0.2**	0.9±0.2	0.9±0.2	0.9±0.2	0.9±0.2	1.1±0.5	1.1±0.4
Diabetes (%)	0	2.1	1.2	4.9	2.2	12.9	8.4	24.4
Smoking (%)	17.5	18	19.8	21.2	23.8	25.6	29	31.2
Association therapy	21.6	27.7	39.9	47.2**	43.3	58*	52.6	63**
Untreated (%)	49	45.1	29.2	24.4	26	17.4**	14.5	8.5

*$p<0.01$ MS− vs MS+, **$p<0.05$ MS− vs MS+. Statistical differences between variables/components of the MS are not reported. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HTN, hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table II. Cardiovascular ultrasonographic parameters and 24-h urinary albumin excretion of the study population according to the number of markers of organ damage (OD): patients positive for none (group 0), one (group I), two (group II) or three markers (group III) of OD with or without the metabolic syndrome (MS+, MS−).

	Group 0		Group I		Group II		Group III	
Variable	MS−, n=554	MS+, n=184	MS−, n=728	MS+, n=385	MS−, n=491	MS+, n=470	MS−, n=185	MS+, n=176
LVIDd (mm)	46.8±3.7	47.9±3.1*	47.1±4.1	48.3±4.1*	47.9±4.6	48.8±4.6*	49.0±4.8	49.0±5.3
LVIDs (mm)	27.9±3.8	28.9±3.8*	27.9±3.9	28.7±4.3*	28.3±4.6	29.2±4.6	28.1±4.7	29.8±5.3*
IVSTd (mm)	9.2±1.0	9.8±1.0*	9.9±1.1	10.3±1.1	10.8±1.2	11.1±1.3	11.4±1.5	11.8±1.4*
PWTd (mm)	8.5±0.8	9.7±1.0*	9.1±0.9	9.4±1.0	9.7±1.0	10.0±1.0	10.3±1.2	10.5±1.0
LV RWT	0.38±0.03	0.39±0.03**	0.40±0.05	0.41±0.05**	0.43±0.05	0.44±0.06**	0.45±0.06	0.46±0.06**
LVM (g)	162±37	181±39**	181±44	200±51**	208±51	224±54**	236±60	244±61
LVMI (g/m$^{2.7}$)	39±6.1	42±6.6	44±9.4	49±10.7**	52±10.8	56±11.5	58±13.3	60±13.9
LA (mm)	34.3±4.5	37.1±4.8*	35.4±4.3	37.6±4.2*	36.8±4.9	38.7±4.6*	37.2±4.8	39.5±4.8*
E velocity (cm/s)	72.5±15.3	71.7±14.7	68.8±15.6	68.9±15.7	65.4±16.0	66.3±16.6	63.1±16.8	66.0±17.4
A velocity (cm/s)	60.3±14.3	62.5±14.7	67.3±16.1	67.2±16.2	71.1±17.4	73.5±17.3	73.4±17.7	75.5±18.8
E/A ratio	1.27±0.40	1.21±0.39	1.07±0.33	1.08+0.33	0.98±0.35	1.00±0.58	0.90±0.32	0.93±0.37
CCA IMT (mm)	0.59±0.09	0.62±0.09**	0.68±0.13	0.70±0.19**	0.76±0.15	0.76±0.15	0.81±0.14	0.81±0.15
CCA diameter (mm)	5.64±0.60	5.74±0.52*	5.83±0.64	6.04±0.65**	6.23±1.1	6.23±0.74	6.55+0.74	6.61±0.90
CCA RWT	0.22±0.06	0.22±0.04	0.24±0.05	0.24±0.07	0.25±0.06	0.25±0.05	0.25+0.05	0.25±0.05
UAE (mg/24 h)	5.2±4.2	5.5±4.4	11.7±33.4	15.6±35.1	19.5±74.9	32.7±81.1**	127.1±106.1	139.1±101.3**

*$p<0.01$ MS− vs MS+,**$p<0.05$ MS− vs MS+. LVIDd, left ventricular internal diameter diastole; LVIDs, left ventricular internal diameter systole; IVSTd, interventricular septum thickness diastole; PWTd, posterior wall thickness diastole; LV, left ventricular; RWT, relative wall thickness; LVM, left ventricular mass; LVMI, left ventricular mass index; LA, left atrium; E, early diastolic mitral flow; A, late diastolic mitral flow; CCA, common carotid artery; IMT, intima-media thickness; UAE, urinary albumin excretion.

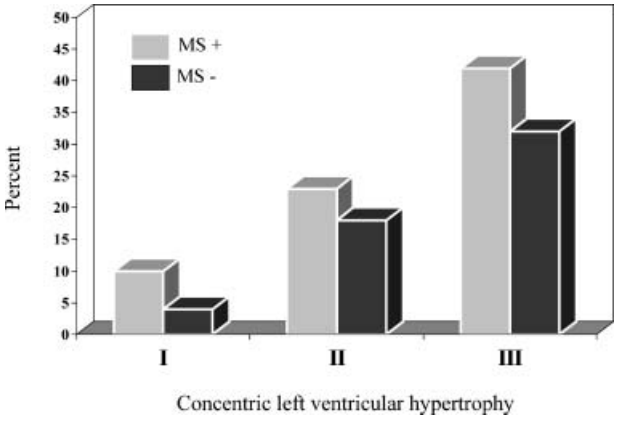

Figure 2. Prevalence rates of concentric left ventricular hypertrophy in patients with and without the metabolic syndrome (MS) according to the number of markers of organ damage (OD): one (group I), two (group II) or three markers (group III) of OD.

the initial phases of essential hypertension, whereas the parallel involvement of three organs (i.e. heart, carotid artery and kidney) is quite rare at this stage (20). The present study based on a larger and more representative sample of hypertensive patients attending a specialist center, provides new and wider evidence on this topic, by showing that: (i) a stepwise increase in MS prevalence occurred from the group without OD, to the groups with one, two and three markers of damage, (ii) an association of two or three markers of OD is prevalent over a single organ involvement in patients with the MS; up to 53% of MS patients, indeed, exhibited two or more ODs compared with 15% and 32% without or with one marker of damage, respectively. Several aspects of our study deserve some discussion.

First, in order to provide clinically oriented information, the current study analyzed the prevalence of single and multiple OD by using widely accepted categorical variables instead of continuous ones. Carotid atherosclerosis and MA were defined according to the criteria recommended by the 2007 ESH/ESC (1) and WHO/ISH (7) guidelines, respectively. For LV involvement, sex-specific thresholds indexed to body height$^{2.7}$ were chosen instead of partition values indexed to body surface area, as suggested by the 2007 ESH/ESC guidelines (125 g/m^2 in men and 110 g/m^2 in women), in order to avoid a substantial underestimation of obesity-related LVH (17). Moreover, LV concentric remodeling was included as additional marker of cardiac damage because even this subtle change in LV morphology has been shown to confer a greater risk of CV events (21).

A novel finding of our study is that the prevalence of MS phenotype progressively rose across the groups stratified according to their OD score, with a 2.3-fold increase of the syndrome in patients with multiple OD compared with their MS counterparts without any sign of OD. The distribution of subjects with and without the MS in the various groups showed that more than half (53%) of the MS patients had a simultaneous involvement of two (39%) or three (14%) organs compared with approximately one-third of patients without the syndrome; this finding was unrelated to several confounding factors including age and BP. As expected, the association between the MS and increasing OD was characterized by a parallel increase in age confirming previous evidence of a close relationship between the MS and advancing age. Data from the Third National Health and Nutrition Examination Survey (NANHES) on 8814 subjects have shown that MS prevalence was clearly age related, increasing from 6.7% among participants aged 20–29 years to 42% for participants aged 70 years or above (22). In a northern Italian population aged 25–74 years the prevalence of the syndrome progressively increased with age, with an approximately five times difference between the youngest (from 25 to 34 years) and oldest decade (from 65 to 74 years) (5% vs 27%) (23).

A further interesting aspect of our study is that, in spite of the fact that we compared subjects with and without MS according to the same OD score, in all groups cardiac parameters (i.e. LV wall thickness, RWT, LVMI, left atrial diameter) were markedly altered in patients with MS compared with those without it, the difference being in most instances statistically significant. This was also the case for MA, but not for carotid atherosclerosis, probably related the slight but clinically relevant higher age of subjects without the syndrome in groups II and III. Notably, when cardiac OD was analyzed in a categorical way, according to the patterns of LV geometry, prevalence rates of concentric LVH, the most dangerous adaptive pattern, were higher across all MS groups than in their counterparts. Our present evidence that MS is associated with a concentric LV geometry is in accordance with recent data indicating that the predominant form of LVH in obesity is concentric LVH (24). Of note, the relation between MS and concentric LVH in the present study was independent of gender, age and clinic BP.

Carotid atherosclerosis as well as abnormalities in LV structure and geometry as assessed by ultrasonography were identified in approximately one half of the population study, whereas only one-fifth of the patients exhibited sub-clinical renal involvement. This finding, in accordance to previous

reports, suggests that: (i) alterations in large arteries may proceed simultaneously with cardiac damage as consequence of a interaction between the heart and the elastic properties of the arterial wall, (ii) MA is a less sensitive marker of OD than subclinical ultrasonographic CV alterations with proven prognostic significance (25).

Finally, the multivariate model of our study adds a further piece of evidence on the clinical profile of hypertensive subjects with multiple OD, by showing and independent association between the MS and this phenotype at very high CV risk.

Limitations

Our data pertain to a selected hypertensive population referred to a specialist center; therefore, the present results may not apply to the general population. In particular, the prevalence rates of a single or multiple OD may be substantially lower in patients referring to the general practitioners' care, who represent the majority of the hypertensive population. Other limitations of our study include the assessment of OD as a dichotomous rather than continuous trait, the cross-sectional nature of our study design and the fact that the study was performed in a single racial sample. Finally, controversy exists on whether MS is a specific entity or a cluster of atherogenic factors. Furthermore, it should be remarked that some studies have shown that individual components of the MS predicted CV risk by a similar extent to that of the syndrome *per se*.

Conclusion

In conclusion, the present study conducted in a large cohort of untreated and treated selected essential hypertensives suggests that ATP III defined MS may substantially enhance the risk of multiple OD and concentric LVH, independently of BP and age. This finding calls for a systematic search for cardiac and extracardiac OD in all hypertensives with the MS referred to a specialist center.

Acknowledgment

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