AJH 2007; 20:784–791

Metabolic

Markers of Inflammation and Fibrosis Are Related to Cardiovascular Damage in Hypertensive Patients with Metabolic Syndrome

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Background: Previous studies have shown that metabolic syndrome (MS) is associated with an increased susceptibility to develop cardiovascular damage (CD). Experimental evidence indicates that inflammation and fibrosis could play a critical role in the development of CD in hypertension. This issue has not been clarified yet in patients with MS. The aim of our study was to investigate the relationship between markers of inflammation and fibrosis with CD in hypertensive patients with and without MS.

Methods: One hundred twenty-eight essential hypertensive patients were included in the study: 51 with MS and 77 without MS. Clinical, biochemical parameters, 24-h urinary albumin excretion rate (UAER), levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and procollagen type 1 carboxy-terminal propeptide (PICP) were measured. All patients underwent an echocardiographic examination with transmitral Doppler and tissue Doppler imaging (TDI).

Results: Left ventricular mass indexed by height$^{2.7}$ (LVM/h$^{2.7}$) ($P < .001$), early diastolic peak flow velocity/early myocardial diastolic velocity ratio (E/Em ratio), a TDI index of diastolic function ($P < .001$), and 24-h UAER ($P < .05$) were significantly higher in the group with MS, whereas peak myocardial systolic velocity (Sm), a TDI index of systolic function ($P < .001$), was lower. Serum levels of CRP ($P < .001$), TNF-α ($P < .05$), TGF-β ($P < .01$), and PICP ($P < .001$) were significantly increased in MS. These markers were significantly related to higher LVMI$^{2.7}$, higher E/Em ratio, and increased 24-h UAER and a lower Sm in the whole population, with a further significant enhancement in MS.

Conclusions: Cardiovascular damage is more frequent in hypertensives with MS than in hypertensives without MS, and this is significantly related to the increased levels of inflammation and fibrosis found in hypertensives with MS. Am J Hypertens 2007;20:784–791

Key Words: Inflammation, essential hypertension, metabolic syndrome, cardiovascular damage.

The metabolic syndrome (MS) is a cluster of cardiovascular risk factors that exposes to an increased cardiovascular risk.[1,2] In this regard, the increased occurrence of cardiovascular damage (CD), such as left-ventricular hypertrophy (LVH) and microalbuminuria, which are viewed as markers of preclinical cardiovascular disease and are more common in hypertensives with MS,[3–5] could represent an important link between MS and cardiovascular morbidity and mortality. The mechanisms underlying the development of CD in hypertensives with MS are still unknown.

Experimental evidence indicates that inflammation and fibrosis could play a critical role in the development of CD in hypertension. An increase in reactive oxygen species (ROS) production is implicated in the development of endothelial dysfunction and LVH.[6,7] Several cytokines, such as tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β), cause cardiomyocyte hypertro-

Received November 5, 2006. First decision December 13, 2006. Accepted January 30, 2007.

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This work was supported by a grant from the Italian Ministry of Health (IRCCS) to M.V.; grants from MURST 2005 to M.V. and MURST 2004 to S.R.

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0895-7061/07/$32.00
doi:10.1016/j.amjhyper.2007.01.023

phy in vitro,[8,9] and they are both elevated in pressure overload states leading to the development of cardiac fibrosis and diastolic dysfunction in vivo.[10,11] Furthermore, the blockade of nuclear factor-κB (NF-κB) reduces myocardial hypertrophy in response to chronic infusion of angiotensin II.[12]

The relationship between inflammation and CD has not been well characterized in a clinical setting, particularly in MS.

The aim of our study was to characterize the influence of MS on left-ventricular mass (LVM), systolic and diastolic function, and 24-h urinary albumin excretion rate (UAER), as markers of CD, in hypertensives without known cardiovascular disease, and to explore the role of inflammation and fibrosis on the development of preclinical organ damage in hypertensives with and without MS.

Methods

Selection of Patients

Consecutive hypertensive patients were recruited at the Outpatient Clinic of the Department of Cardiology of the Sant'Andrea Hospital, Rome.

Patients were required: (1) to be of the same race/ethnicity; (2) to have a recent diagnosis of grades 1–2 hypertension (clinical systolic blood pressure [BP] 140 to 179 mm Hg or clinical diastolic BP 90 to 109 mm Hg) confirmed at our clinic; (3) absence of secondary hypertension, left-ventricular (LV) systolic dysfunction (ejection fraction [EF] <55%), heart failure, previous myocardial infarction, history of coronary artery disease, clinical or instrumental evidence of myocardial ischemia, mild valvular disease, arrhythmias, left or right bundle block, renal insufficiency (serum creatinine >1.4 mg/dL in men, >1.2 mg/dL in women), diabetes mellitus (fasting glucose [FG] >126 mg/dL or current antidiabetic treatment), previous stroke; (4) no pharmacologic treatment with antihypertensive drugs, statins, or fibrates for at least 3 months before the study and during the study; and (5) absence of any acute or chronic inflammatory disease (ie, fever and acute infections within the previous 3 months; no history of autoimmune disease, connective tissue disease, chronic lung and liver disease, nephropathies, cancer, arthritis, psoriasis, or surgery in the previous year) based on history, clinical examination, and biochemistry parameters.

These criteria supplied a population of 128 white patients. Presence of MS was diagnosed according to the Adult Treatment Panel III (ATP III) report[13] as two or more of the following criteria in addition to high BP levels: (1) waist circumference (WC) >102 cm in men and > 88 cm in women; (2) triglyceride (TG) level ≥150 mg/dL; (3) HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women; and (4) FG ≥110 mg/dL.

They underwent: (1) medical history and physical examination; (2) repeated BP measurements; (3) biochemical and hormonal assays; (4) urine collection to estimate the 24-h UAER; and (5) echocardiographic examinations by transmitral Doppler and tissue Doppler imaging (TDI).

A control group of 27 age-matched healthy normotensive individuals, not presenting MS and free of acute or chronic inflammatory diseases, was used for assessment of the normal range levels of markers of inflammation and fibrosis.

All subjects provided an informed written consent and the study protocol was approved by the local ethical committee.

Blood Pressure Measurements

Blood pressure was measured by a physician using a mercury sphygmomanometer with patients in the sitting position. Three measurements were taken at 2-min intervals, and the average was used to define clinical systolic and diastolic BP.

Echocardiography

The echocardiographic and Doppler investigations were performed with a phased array sector scan (Acuson Sequoia, Mountain View, CA) using a multifrequence probe and an S-VHS tape recorder. End-diastolic and end-systolic left-ventricular internal diameters (LVIDd, LVIDs), end-diastolic interventricular septum thickness (IST), and end-diastolic posterior wall thickness (PWT) were measured according to the guidelines of the American Society of Echocardiography.[14] The LVM was calculated by using Penn convention (Devereux and Reichek's modified formula[15]) and normalized by body surface area (LVM/BSA) and by height$^{2.7}$ (LVMI$^{2.7}$).[16] The LVH was defined for values of LVMI$^{2.7}$ >51 g in men and >47 g in women. The relative wall thickening (RWT) was calculated as (2 × PWT) / LVIDd. Stroke volume was estimated using Teicholz and colleagues' correction of the cube formula[17] and used to calculate cardiac output and peripheral resistance. Left-ventricular filling was assessed by recording mitral flow by standard pulsed Doppler technique, and the following parameters were considered: early diastolic peak flow velocity (E), late diastolic flow velocity (A), and the ratio of early to late peak (E/A ratio).

Myocardial velocities were recorded using a standard pulse-wave Doppler technique as previously described.[18] The TDI was performed from the apical four-chamber view, with the sample volume placed along the myocardial lateral wall and along the left side of the interventricular septum, 1 cm above the mitral annulus. Early (peak myocardial systolic velocity [Sm], early myocardial diastolic velocity [Em], early septal myocardial diastolic velocity [E′]) and late (late myocardial

Table 1. Clinical and biochemical characteristics of the hypertensive and normotensive subjects

	Control group (n = 27)	Hypertensive group (n = 128)	P
Sex (female:male)	9:18	46:82	NS
Age (y)	54.72 ± 1.74	55.38 ± 0.95	NS
Height (cm)	169.65 ± 1.68	170.62 ± 1.12	NS
Body mass index (kg/m^2)	23.78 ± 0.80	28.31 ± 0.41	<.0001
Current smokers (%)	20 (5)	20 (26)	NS
Duration of hypertension (y)	–	3.19 ± 1.77	–
Waist circumference (cm)	84.79 ± 1.25	102.23 ± 1.15	<.0001
Systolic blood pressure (mm Hg)	120.55 ± 1.13	148.93 ± 1.55	<.0001
Diastolic blood pressure (mm Hg)	76.98 ± 0.91	94.50 ± 1.08	<.0001
Fasting glucose (mg/dL)	85.54 ± 1.06	98.24 ± 1.48	<.001
Triglycerides (mg/dL)	86.92 ± 3.09	144.72 ± 9.48	<.001
HDL cholesterol (mg/dL)	63.08 ± 1.38	52.73 ± 1.38	<.01
Total cholesterol (mg/dL)	168.41 ± 4.69	211.10 ± 4.22	<.0001
LDL cholesterol (mg/dL)	126.11 ± 4.50	131.62 ± 3.67	NS

NS = not significant.

diastolic velocity [Am], late septal myocardial diastolic velocity [A′]) diastolic velocities were measured. The early diastolic peak flow velocity (E)/Em ratio and the E/E′ ratio were considered as parameters of diastolic function.

Biochemical Assays

Total cholesterol (TC), TG, and FG were determined by enzymatic colorimetric method. Serum HDL was measured by enzymatic colorimetric method after precipitation with polyethyleneglycol. LDL was calculated by Friedewald formula. Twenty-four-hour UAER was determined by an RIA kit (Sclavo SPA, Siena, Italy).

Levels of TGF-β were measured by an ELISA kit (R&D Systems, Minneapolis, MN). Levels of TNF-α were measured by an ELISA kit (high-sensitive TNF-α; R&D Systems). Levels of procollagen type 1 carboxy-terminal propeptide (PICP) were measured by an ELISA kit (Takara, Shiga, Japan).

Serum high-sensitivity C-reactive protein (CRP) was measured by a latex-enhanced immunonephelometric assay (N High Sensitivity CRP Assay; Dade Behring, Marburg, Germany).

Statistical Analysis

Statistical analysis was performed using SPSS system (version 12.0; SPSS Inc., Chicago, IL). Values are expressed as mean ± SEM. Intergroup means were compared using Student's t-test for independent samples and one-way ANOVA followed by Bonferroni post hoc test when more than two groups were compared.

Categorical variables are expressed as percentages, and they were compared using the χ^2 test.

The correlation between variables was tested by linear correlation and multiple linear regression analysis. Variables with skewed distribution were logarithmically transformed before statistical analysis. A P value $< .05$ was considered to declare significance.

Results

Characteristics of the Study Sample

Main anthropometric, clinical, and biochemical characteristics of the entire hypertensive population and of the control group are reported in Table 1.

According to the ATP III criteria for diagnosis of MS,[13] hypertensives were divided into two groups: 51 with MS and 77 without MS.

Main anthropometric, clinical, biochemical, and echocardiographic parameters of the two groups are reported in Tables 2 and 3.

The two groups differed for all parameters that characterize the MS, whereas BP levels were comparable. Furthermore, there were no differences among patients with and without MS in the number of never-treated or previously treated subjects, as well as in the known duration of previous antihypertensive treatment (Table 4).

Relation of Metabolic Syndrome to Cardiovascular Damage

As shown in Table 3, LVM/BSA, LVMI$^{2.7}$, IST, PWT, and LVIDd were significantly higher in the MS group. Furthermore, when LVM was analyzed as a categorical variable, the prevalence of LVH considered as LVMI$^{2.7}$ was significantly higher in MS (46% v 21% in patients without MS; $P < .01$).

All parameters of diastolic function obtained by TDI were significantly different between the two groups. In fact, Em and E′ were lower, whereas E/Em and E/E′ ratios were higher in the group with MS. The Sm was also significantly lower in the MS group. The two groups did not differ significantly for E/A ratio, although it tended to be lower in MS.

Table 2. Clinical and biochemical characteristics of the hypertensive patients with and 24-h UAER = 24-h urinary albumin excretion rate

	Metabolic syndrome (n = 51)	No metabolic syndrome (n = 77)	P
Sex (female:male)	16:35	34:43	NS
Age (y)	53.92 ± 1.37	55.88 ± 1.29	NS
Height (cm)	173.43 ± 1.28	169.41 ± 1.21	<.05
Body mass index (kg/m^2)	30.93 ± 0.60	27.16 ± 0.40	<.0001
Current smokers (%)	22 (11)	19 (15)	NS
Duration of hypertension (y)	3.32 ± 2.33	3.01 ± 1.44	NS
Waist circumference (cm)	111.38 ± 1.65	96.18 ± 1.12	<.0001
Systolic blood pressure (mm Hg)	151.15 ± 2.43	147.92 ± 2.11	NS
Diastolic blood pressure (mm Hg)	96.28 ± 1.51	93.85 ± 1.07	NS
Fasting glucose (mg/dL)	105.29 ± 2.81	93.14 ± 1.20	<.0001
Triglycerides (mg/dL)	208.3 ± 14.09	104.1 ± 5.60	<.0001
HDL cholesterol (mg/dL)	47.17 ± 1.62	59.58 ± 1.85	<.0001
Total cholesterol (mg/dL)	228.48 ± 5.69	202.92 ± 4.15	<.001
LDL cholesterol (mg/dL)	137.17 ± 5.50	128.73 ± 3.41	NS
24-h UAER (mg)	31.21 ± 9.68	18.17 ± 4.07	<.05

Abbreviation as in Table 1.

As shown in Table 2, 24-h UAER was significantly higher in the MS group, and the prevalence of microalbuminuria, using a cutoff of 30 mg/day, was significantly higher in MS than in patients without MS (35% *v* 6%; $P <$ .0001).

When multiple linear regression analysis was performed, adjusting for age, sex, and MS components (systolic and diastolic BP, FG, TG, HDL, WC), the MS itself was significantly associated with LVMI$^{2.7}$ (β = 0.31; $P <$ .05) but not with 24-h UAER. Moreover, the presence of MS was significantly related to Em (β = −0.43; $P <$ .01), E/Em ratio (β = 0.46; $P <$ .01), and Sm (β = −0.36; $P <$ .01), independently from age, sex, MS components, and LVMI$^{2.7}$.

Relation of C-Reactive Protein, Tumor Necrosis Factor-α, Transforming Growth Factor-β, and Procollagen Type 1 Carboxy-Terminal Propeptide to Metabolic Syndrome and Cardiovascular Damage

The CRP, TNF-α, TGF-β, and PICP levels were significantly higher in hypertensives compared with the normotensive control group. Among hypertensives, levels of these markers were higher in the group with MS (Fig. 1).

To investigate the relation of these markers to CD, a multiple linear regression analysis was performed in the

Table 3. Echocardiographic parameters in patients with and without MS

	Metabolic syndrome (n = 51)	No metabolic syndrome (n = 77)	P
Ejection fraction (%)	63.96 ± 0.80	64.59 ± 0.57	NS
LVM/BSA (g/m^2)	123.54 ± 3.02	105.31 ± 3.41	<.0001
LVM/h$^{2.7}$ (g/m$^{2.7}$)	50.2 ± 1.61	42.4 ± 1.44	<.001
Relative wall thickening	0.39 ± 0.006	0.38 ± 0.006	NS
Interventricular septum thickness (mm)	10.75 ± 0.18	10.09 ± 0.19	<.05
Posterior wall thickness (mm)	10.58 ± 0.18	9.55 ± 0.13	<.0001
LVIDd (mm)	53.06 ± 0.79	50.97 ± 0.54	<.05
E/A ratio	0.96 ± 0.04	1.02 ± 0.05	NS
Em (m/sec)	0.13 ± 0.004	0.15 ± 0.005	<.01
Am (m/sec)	0.14 ± 0.004	0.14 ± 0.004	NS
E/Em ratio	6.01 ± 0.27	4.80 ± 0.19	<.001
E′ (m/sec)	0.11 ± 0.004	0.13 ± 0.004	<.001
E/E′ ratio	6.87 ± 0.34	5.17 ± 0.26	<.001
Sm (m/sec)	0.12 ± 0.003	0.14 ± 0.004	<.01

Am = late myocardial diastolic velocity; E′ = early septal myocardial diastolic velocity; E/A ratio = early diastolic peak flow velocity/late diastolic peak flow velocity ratio; E/E′ ratio = early diastolic peak flow velocity/early septal myocardial diastolic velocity ratio; E/Em ratio = early diastolic peak flow velocity/early myocardial diastolic velocity ratio; Em = early myocardial diastolic velocity; LVIDd = end-diastolic left-ventricular internal diameter; LVM/BSA = left-ventricular mass indexed by body surface area; LVM/h$^{2.7}$ = left-ventricular mass indexed by height$^{2.7}$; Sm = peak myocardial systolic velocity; other abbreviation as in Table 1.

Table 4. Percentages of never-treated and previously treated subjects

	Metabolic syndrome (n = 51)	No metabolic syndrome (n = 77)	P
Never-treated (%)	35.2	49.3	NS
Duration of previous antihypertensive treatment (months)	21 ± 2.21	19 ± 2.01	NS
RAAS inhibitors in monotherapy (%)	27.2	25.6	NS
RAAS inhibitors combined to other antihypertensive drugs (%)	48.4	46.1	NS
Statins (%)	11.7	2.5	NS

RAAS = renin-angiotensin-aldosterone system; other abbreviation as in Table 1.

overall population (Tables 5 and 6). Serum levels of CRP, TNF-α, TGF-β, and PICP were significantly associated with higher LVM, independently from age, sex, and MS components, and they were significantly related to an impairment of systolic and diastolic function, adjusting also for LVMI$^{2.7}$. Furthermore, CRP, TNF-α, and PICP were directly and significantly related to 24-h UAER, independently from age, sex, and MS components.

When the relationship between these markers and CD was evaluated separately in the two groups by multiple linear regression analysis, adjusting for the same variables as previously, it was significantly stronger in the MS group, particularly with regard to LVM (Table 7). Furthermore, after adjusting for previous antihypertensive therapy and different classes of drugs, we found that these factors were not related to CD or to its relationship with inflammation.

Discussion

Our study confirms that MS is characterized by an increased development of preclinical CD. In fact, hyperten-

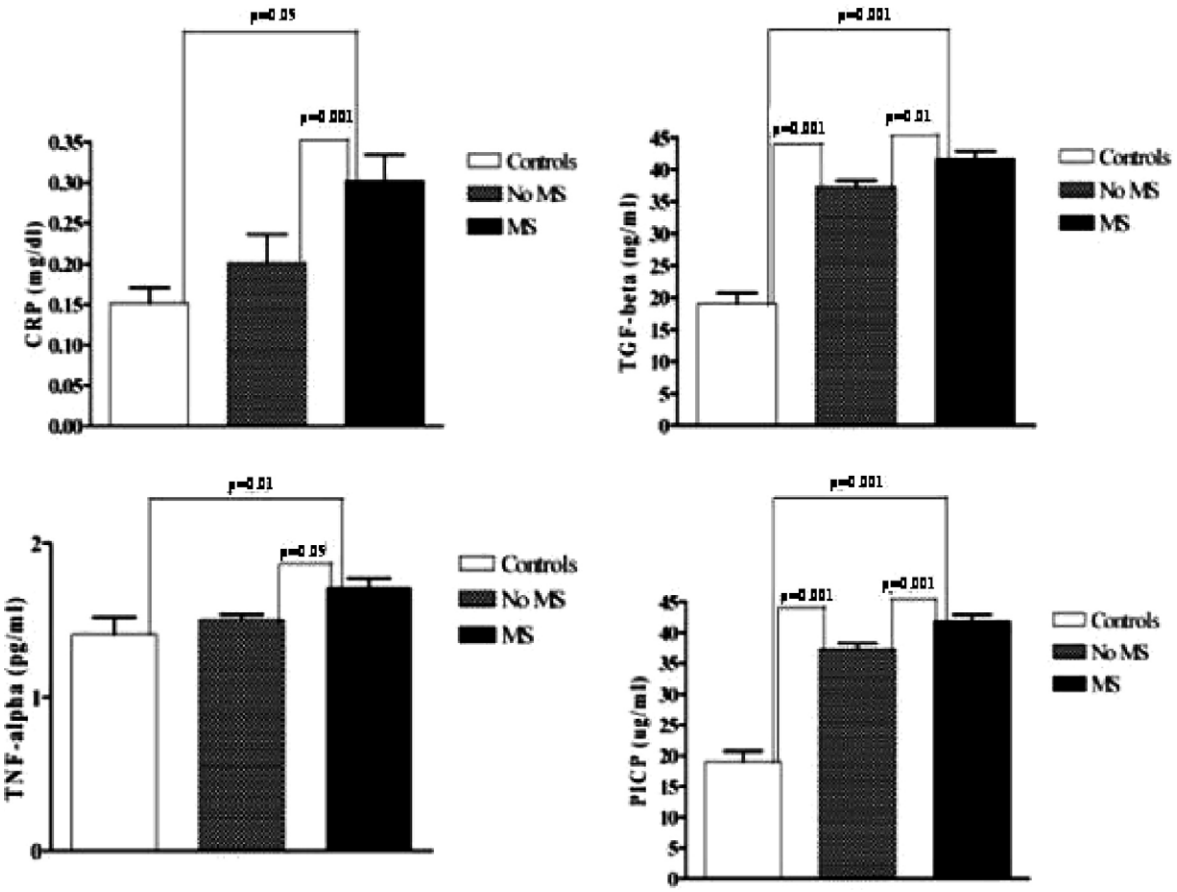

FIG. 1 Inflammation and fibrosis marker levels in normotensives and hypertensives with and without metabolic syndrome (MS) (one-way ANOVA). P value of one-way ANOVA was <.01 for tumor necrosis factor-α (TNF-α), and <.0001 for C-reactive protein (CRP), transforming growth factor-β (TGF-β), and procollagen type 1 carboxy-terminal propeptide (PICP).

Table 5. Multiple linear regression analysis to assess the relationship between inflammatory and fibrosis markers with LVM

	LVM/BSA (g/m^2)		LVM/$h^{2.7}$ ($g/m^{2.7}$)		IST (mm)		PWT (mm)	
	Beta	***P***	**Beta**	***P***	**Beta**	***P***	**Beta**	***P***
Log(hs-CRP) (mg/dL)	0.37	<.001	0.29	<.01	0.34	<.01	0.36	<.01
Log(TNF-α) (pg/mL)	0.35	<.001	0.33	<.01	0.32	<.01	0.47	<.001
TGF-β (ng/mL)	0.29	<.01	0.33	<.001	0.42	<.001	0.40	<.001
PICP (μg/mL)	0.25	<.01	0.26	<.05	0.37	<.001	0.26	<.05

hs-CRP = high-sensitive C-reactive protein; IST = interventricular septum thickness; LVM/BSA = left-ventricular mass indexed by body surface area; PICP = procollagen type 1 carboxy-terminal propeptide; PWT = posterior wall thickness; TGF-β = transforming growth factor-β; TNF-α = tumor necrosis factor-α; other abbreviations as in Tables 1 and 3.

The other variables in the model are: age, sex, systolic and diastolic BP, waist circumference, triglycerides, fasting glucose, HDL, and presence of metabolic syndrome.

sives with MS had increased LVM and 24-h UAER. Moreover, we demonstrated that the presence of MS not only alters left-ventricular geometry, but it also leads to an impairment of left-ventricular diastolic and systolic functions. In fact, although the EF and E/A ratio did not differ among hypertensives with and without MS, the E/Em ratio was significantly higher, whereas Em and Sm were significantly lower in MS, as well as previously demonstrated in patients with type 1 diabetes,[19] thus documenting an initial impairment of both systolic and diastolic performances. The latter were accurately evaluated by TDI echocardiography, which, as previously demonstrated, is more sensitive for the detection of left-ventricular systolic and diastolic dysfunctions than conventional echocardiography.[20]

Of note, the MS itself was directly related to all parameters of cardiac damage (LVMI$^{2.7}$, Em, E/Em ratio, and Sm) independently from age, sex, and from the known factors that characterize the syndrome. We failed to find a direct association of MS with 24-h UAER, and this was probably due to the small sample size.

The main finding of our study was the evidence of a possible link between inflammation and fibrosis with the increased development of preclinical CD in hypertensives with MS. In fact patients with MS had increased levels of CRP, TNF-α, and TGF-β, markers of inflammation, and of PICP, a marker of fibrosis, as compared with patients without MS. Interestingly, all these markers were significantly related to increased LVM and 24-h UAER and to impaired diastolic and systolic functions in the overall population, independently from the known MS parameters and from the MS itself. Remarkably, these correlations were enhanced in patients with MS and they were unrelated to either previous antihypertensive therapy or different classes of drugs.

Previous experimental evidence has suggested a role for inflammation in the development of CD in hypertension. Hypertension exerts a number of proinflammatory effects, through the increased expression of several mediators such as cytokines, ROS, acute phase proteins, and leukocyte adhesion molecules (intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and monocyte chemoattractant protein-1 (MCP-1)).[21,22] An increased vessel wall stretch[23] and elevated levels of angiotensin II have been shown to activate the NADPH oxidase and the NF-κB, to increase adhesion molecule expression by endothelial cells, and to upregulate endothelial cell secretion of proinflammatory cytokines.[24,25] These effects can enhance monocyte adhesion to the endothelium, their transmigration into the vessel wall and

Table 6. Multiple linear regression analysis to correlate inflammatory and fibrosis markers with systolic/diastolic function and microalbuminuria

	Em† (m/sec)		E/Em ratio†		Log(Sm)† (m/sec)		Log(24-h UAER)* (mg)	
	Beta	***P***	**Beta**	***P***	**Beta**	***P***	**Beta**	***P***
Log (hs-CRP) (mg/dL)	−0.14	NS	0.24	<.05	−0.15	NS	0.32	<.01
Log (TNF-α) (pg/mL)	−0.29	<.05	0.36	<.001	−0.001	NS	0.20	<.05
TGF-β (ng/mL)	−0.03	NS	0.28	<.05	−0.21	<.05	0.07	NS
PICP (μg/mL)	−0.15	NS	0.24	<.05	−0.25	<.05	0.26	<.05

Abbreviations as in Tables 1 and 3.

* Adjusted for age, sex, systolic and diastolic BP, waist circumference, triglycerides, fasting glucose, HDL and presence of metabolic syndrome; † Adjusted for age, sex, systolic and diastolic BP, waist circumference, triglycerides, fasting glucose, HDL, left-ventricular mass indexed by height$^{2.7}$, and presence of metabolic syndrome.

Table 7. Multiple linear regression analysis to correlate inflammatory and fibrosis markers with LVM/$h^{2.7}$ and 24-h UAER

	LVM/$h^{2.7}$ (g/$m^{2.7}$)				Log(24-h UAER) (mg)			
	No metabolic syndrome		Metabolic syndrome		No metabolic syndrome		Metabolic syndrome	
	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*
Log (hs-CRP) (mg/dL)	0.11	NS	0.31	<.05	0.21	NS	0.31	<.05
Log (TNF-α) (pg/mL)	0.05	NS	0.37	<.05	0.18	NS	0.21	NS
TGF-β (ng/mL)	0.17	NS	0.51	<.0001	−0.06	NS	0.20	NS
PICP (μg/mL)	0.28	<.05	0.37	<.05	0.14	NS	0.40	<.05

Abbreviations as in Tables 1 and 3.

The model was adjusted for age, sex, systolic and diastolic BP, waist circumference, triglycerides, fasting glucose, and HDL.

into the tissue interstitium, and the development of endothelium dysfunction and tissue inflammation.[25] It has been shown that hypertension favors inflammation in cardiovascular tissues, with an increased amount of ROS, cytokines, and other mediators that lead to alterations of organ structure and function.[26,27]

Reactive oxygen species are involved in the development of left ventricular hypertrophy,[7] and their reduction by antioxidant agents leads to regression of such alterations.[27]

On the other hand, TNF-α induces cardiac myocyte hypertrophy, probably through the PI3-kinase-Akt/PKB pathway,[8–28] whereas TGF-β_1 induces cardiac hypertrophic responses through protein kinase C (PKC)-dependent activating transcription factor-2 (ATF 2) activation.[9] Both mediators stimulate the synthesis of matrix molecules, block matrix degradation, and lead to fibrosis.[11,29] Furthermore, the blockade of NF-κB reduces myocardial hypertrophy in response to chronic infusion of angiotensin II,[14] and the blockade of MCP-1 in pressure overload rats leads to the regression of diastolic dysfunction caused by TGF-β-induced fibrosis. Transforming growth factor-β and PICP were shown to be related to both cardiac and renal damage in human hypertension.[30] However, the role of inflammation into the development of CD, and particularly cardiac damage, in human hypertension has not been clearly assessed.

We found that circulating markers of inflammation and fibrosis were significantly elevated in patients with MS and they were both related to increased LVM, increased 24-h UAER, and to impaired systolic and diastolic performances, independently from the known MS parameters and from the MS itself. Remarkably, these relationships were significantly stronger in patients with MS. In this regard, an increased degree of CD, an increased level of markers of inflammation, or an increased level of markers of fibrosis has been previously shown in hypertensives with MS in separate studies.[3–5,31] On the other hand, it has been also demonstrated in human experimental studies that fibrosis is associated with CD in hypertensives and that its regression is related to an improvement of left-ventricular function.[32] Our data are consistent with and actually implement these findings by providing the first evidence of a concomitant increase of inflammatory and fibrosis markers in hypertensive patients with MS. Moreover, we could demonstrate a clear significant relationship between an increased CD and both indices of inflammation and fibrosis in patients with MS. Of note, our study was conducted on the basis of the most achievable restrictive inclusion criteria. It excluded all patients with other recognizable clinical causes of inflammation and fibrosis. Thus, our current findings may support the hypothesis that an increased process of inflammation and fibrosis may, at least in part, mediate the higher occurrence of CD in MS, along with other factors such as dyslipidemia, insulin resistance, impaired FG, and hemoglobin A_{1c}, which are associated with diastolic dysfunction, as previously reported.[19]

In summary, the present study confirmed that MS associates with an increased development of CD in essential hypertension, and it provided the first evidence that an increased degree of cardiovascular disease and a concomitant increased degree of tissue inflammation and fibrosis are significantly related in hypertensive patients with MS.

Although the relevance of our findings is limited by the size of our study sample, the results regarding the relationship between inflammation and CD support previous experimental evidence in hypertension. Our results, especially if confirmed in larger populations, may help to identify one of the possible mechanisms directly linking MS with CD. They may also have significant implications for management of hypertensives with MS by indicating the need of a more aggressive treatment of hypertension in high-risk patients, starting at the prehypertensive state, as already reported.[33]

Acknowledgments

We thank Dr. Elisa Cristadoro for her collaboration.

References

1. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C, for the American Heart Association; National Heart, Lung, and Blood Institute: Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109:433–438.

2. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24: 683–689.
3. Cuspidi C, Meani S, Fusi V, Severgnini B, Valerio C, Catini E, Leonetti G, Magrini F, Zanchetti A: Metabolic syndrome and target organ damage in untreated essential hypertensives. J Hypertens 2004;22:1991–1998.
4. Leoncini G, Ratto E, Viazzi F, Vaccaro V, Parodi D, Parodi A, Falqui V, Tomolillo C, Deferrari G, Pontremoli R: Metabolic syndrome is associated with early signs of organ damage in nondiabetic, hypertensive patients. J Intern Med 2005;257:454–460.
5. Schillaci G, Pirro M, Pucci G, Mannarino MR, Gemelli F, Siepi D, Vaudo G, Mannarino E: Different impact of the metabolic syndrome on left ventricular structure and function in hypertensive men and women. Hypertension 2006;47:881–886.
6. Bauersachs J, Bouloumie A, Fraccarollo D, Hu K, Busse R, Ertl G: Endothelial dysfunction in chronic myocardial infarction despite increased vascular endothelial nitric oxide synthase and soluble guanylate cyclase expression: role of enhanced vascular superoxide production. Circulation 1999;100:292–298.
7. Nakagami H, Takemoto M, Liao JK: NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. J Mol Cell Cardiol 2003;35:851–859.
8. Yokoyama, T, Nakano M, Bednarczyk, JL, McIntyre BW, Entman M, Mann DL: Tumor necrosis factor-alpha provokes a hypertrophic growth response in adult cardiac myocytes. Circulation 1997;95: 1247–1252.
9. Lim JY, Prk SJ, Hwang HY, Park EJ, Nam JH, Kim J, Park SI: TGF-beta1 induces cardiac hypertrophic responses via PKC-dependent ATF-2 activation. J Mol Cell Cardiol 2005;39:627–636.
10. Kapadia SR, Yakoob K, Nader S, Thomas JD, Mann DL, Griffin BP: Elevated circulating levels of serum tumor necrosis factor-alpha in patients with hemodynamically significant pressure and volume overload. J Am Coll Cardiol 2000;36:208–212.
11. Kuwahara F, Kai H, Tokuda K, Takeya M, Takeshita A, Egashira K, Imaizumi T: Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? Hypertension 2004;43:739–745.
12. Kawano S, Kubota T, Monden Y, Kawamura N, Tsutsui H, Takeshita A, Sunagawa K: Blockade of NF-kappaB ameliorates myocardial hypertrophy in response to chronic infusion of angiotensin II. Cardiovasc Res 2005;67:689–698.
13. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final report. Circulation 2002;106: 3143–3421.
14. Quinones MA, Douglas PS, Foster E, Gorcsan J 3rd, Lewis JF, Pearlman AS, Rychik J, Salcedo EE, Seward JB, Stevenson JG, Thys DM, Weitz HH, Zoghbi WA, Creager MA, Winters WL Jr, Elnicki M, Hirshfeld JW Jr, Lorell BH, Rodgers GP, Tracy CM, Weitz HH, for the American Society of Echocardiography; Society of Cardiovascular Anesthesiologists; Society of Pediatric Echocardiography: ACC/AHA clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine Task Force on clinical competence. J Am Soc Echocardiogr 2003;16:379–402.
15. Devereux RB, Reichek N: Echocardiographic determination of left ventricular mass in man. Circulation 1977;55:613–618.
16. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH: Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992;20:1251–1260.
17. Teicholz LE, Kreulen T, Herman MV, Gorlin R: Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976;37:7.
18. Ho CY, Solomon SD: A clinician's guide to tissue Doppler imaging. Circulation 2006;113:e396–e398.
19. Shishehbor MH, Hoogwerf BJ, Schoenhagen P, Marso SP, Sun JP, Li J, Klein AL, Thomas JD, Garcia MJ: Relation of haemoglobin A1c to left ventricular relaxation in patients with type 1 diabetes mellitus and without overt heart disease. Am J Cardiol 2003;91: 1514–1517.
20. Yu CM, Wang Q, Lau CP, Tse HF, Leung SK, Lee KL, Tsang V, Ayers G: Reversible impairment of left and right ventricular systolic and diastolic function during short-lasting atrial fibrillation in patients with an implantable atrial defibrillator: a tissue Doppler imaging study. Pacing Clin Electrophysiol 2001;24:979–988.
21. Redón J, Oliva MR, Tormos C, Giner V, Chaves J, Iradi A, Sáez GT: Antioxidant activities and oxidative stress byproducts in human hypertension. Hypertension 2003;41:1096–1101.
22. Hilgers KF, Hartner A, Porst M, Mai M, Wittmann M, Hugo C: Monocyte chemoattractant protein-1 and macrophage infiltration in hypertensive kidney injury. Kidney Int 2000;58:2408–2419.
23. Wang DL, Wung BS, Shyy YJ, Lin CF, Chao YJ, Usami S, Chien S: Mechanical strain induces monocyte chemotactic protein-1 gene expression in endothelial cells: effects of mechanical strain on monocyte adhesion to endothelial cells. Circ Res 1995;77: 294–302.
24. Schieffer B, Luchtefeld M, Braun S, Hilfiker A, Hilfiker-Kleiner D, Drexler H: Role of NAD(P)H oxidase in angiotensin II-induced JAK/STAT signaling and cytokine induction. Circ Res 2000;87: 1195–1201.
25. Hernandez-Presa M, Bustos C, Ortego M, Tunon J, Renedo G, Ruiz-Ortega M, Egido J: Angiotensin-converting enzyme inhibition prevents arterial nuclear factor-kappa B activation, monocyte chemoattractant protein-1 expression, and macrophage infiltration in a rabbit model of early accelerated atherosclerosis. Circulation 1997; 95:1532–1541.
26. Tanito M, Nakamura H, Kwon YW, Teratani A, Masutani H, Shioji K, Kishimoto C, Ohira A, Horie R, Yodoi J: Enhanced oxidative stress and impaired thioredoxin expression in spontaneously hypertensive rats. Antioxid Redox Signal 2004;6:89–97.
27. Sun L, Gao YH, Tian DK, Zheng JP, Zhu CY, Ke Y, Bian K: Inflammation of different tissues in spontaneously hypertensive rats. Sheng Li Xue Bao 2006;58:318–323.
28. Hiraoka E, Kawashima S, Takahashi T, Rikitake Y, Kitamura T, Ogawa W, Yokoyama M: TNF-alpha induces protein synthesis through PI3-kinase-Akt/PKB pathway in cardiac myocytes. Am J Physiol Heart Circ Physiol 2001;280:H1861–H1868.
29. Li YY, Feng YQ, Kadokami T, McTiernan CF, Draviam R, Watkins SC, Feldman AM: Myocardial extracellular matrix remodeling in transgenic mice overexpressing tumor necrosis factor alpha can be modulated by anti-tumor necrosis factor alpha therapy. Proc Natl Acad Sci USA 2000;97:12746–12751.
30. Laviades C, Varo N, Diez J: Transforming growth factor β in hypertensives with cardiorenal damage. Hypertension 2000;36:517–522.
31. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH: The metabolic syndrome and insulin resistance: relationship to haemostatic and inflammatory markers in older nondiabetic men. Atherosclerosis 2005;181:101–108.
32. Diez J, Querejeta R, Lopez B, Gonzalez A, Larman M, Martinez Ubago JL: Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002;105:2512–2517.
33. Sipahi I, Tuzcu EM, Schoenhagen P, Wolski KE, Nicholls SJ, Balog C, Crowe TD, Nissen SE: Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. J Am Coll Cardiol 2006;48:833–838.