

Prehypertension Is Associated With Insulin Resistance State and Not With an Initial Renal Function Impairment

A Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry Substudy

Alberto Cordero, Martin Laclaustra, Montserrat León, Alberto Grima, Jose A. Casasnovas, Emilio Luengo, Alfonso del Rio, Ignacio Ferreira, and Eduardo Alegria

Background: The aim of this study was to assess the prevalence of metabolic syndrome (MS) and other surrogate markers of insulin resistance, and whether these markers are better for defining the prehypertensive state than is renal dysfunction.

Methods: Data from 19,041 healthy active workers, mean age 42.2 (10.7) years, from three health insurance companies, were prospectively collected. Presence of MS, assessed according to the modified criteria of the National Cholesterol Education Program Third Adult Treatment Panel, and the ratio of triglycerides to high-density lipoprotein were considered as surrogate markers of insulin resistance. Renal function was assessed by the Modification of Diet in Renal Disease Study equation. Blood pressure was classified as normotension (NT), prehypertension (PHT), or hypertension (HT) according to the guidelines of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Results: The global presence of MS was 11.8%. The higher prevalence was found in subjects with hypertension (30%), followed by those with PHT (9.6%). The prevalence in normotensive subjects was very low (0.9%). The presence of MS and hypertension increased in parallel with age. Metabolic syndrome (odds ratio [OR] 4.3), obesity (OR 2.2), overweight (OR 1.7), impaired fasting glucose (OR 1.3), and elevated triglycerides to HDL ratio (OR 1.2), but no degree of renal dysfunction, were independent risk factors for the progression from NT to PHT.

Conclusions: Prehypertension is associated with markers of insulin resistance, assessed by the presence of MS and other surrogate markers, and not with an initial renal dysfunction. In this study, MS was found to be present in almost one third of hypertensive but asymptomatic and otherwise healthy workers. *Am J Hypertens* 2006;19:189–196 © 2006 American Journal of Hypertension, Ltd.

Key Words: Prehypertension, insulin resistance, renal dysfunction, metabolic syndrome.

Insulin resistance^{1,2} and renal dysfunction^{2–4} have been widely implied in the development of hypertension and cardiovascular events. Prehypertension (PHT) has been recently described as an independent category of blood pressure (BP).⁵ Although some reports show that PHT is associated with lower insulin sensitivity,⁶

its pathologic mechanisms are not well described. According to the recent results to the Third National Health and Nutrition Examination Survey, PHT is present in 31% of adults in the United States,⁷ and this condition is associated with an increased prevalence of both heart disease and risk for stroke.⁸

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From the Cardiology Department, Clinica Universitaria de Navarra, Pamplona, Spain (AC, EA); Cardiovascular Research Unit, Hospital Clínico Universitario, Zaragoza, Spain (ML, ML, JAC, EL, AD, IF); and Department of Preventive Cardiology, Asepeyo, Valencia, Spain (AG).

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The Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry investigators are listed in the Appendix.

Address correspondence and reprint requests to Dr. Alberto Cordero, Clinica Universitaria de Navarra, Cardiology, Pio XII, 36, 31008 Pamplona, Navarra, Spain; e-mail:acordero@unav.es

Insulin resistance can be measured directly (although this option is not routinely available). However, it can also be estimated by the so-called surrogate markers,⁹ and of these the triglycerides-to-high density lipoprotein (TG/HDL) ratio has been proposed as one of the most accurate. Metabolic syndrome (MS) is an association of cardiovascular risk factors that cluster in the same individual linked by insulin resistance.¹⁰ Results of large studies have elucidated that above-normal BP is the most prevalent of the five components of the MS,^{11–13} and this plays a key role in the clinical management of the patients with MS.¹⁴ More recently, MS has been identified as a strong independent predictor of cardiovascular events in hypertensive individuals, amplifying the cardiovascular risk associated with hypertension.¹⁵

Presence of MS increases the cardiovascular risk associated with high BP, amplifying not only the deleterious vascular effects of hypertension¹⁶ but also increasing the atherosclerotic burden.¹⁷ Although the criteria of the National Cholesterol Education Program Third Adult Treatment Panel (ATP III) have specified a low sensitivity but high specificity for the detection of insulin resistance,^{18,19} these factors are strong predictors for cardiovascular outcomes linked to atherosclerosis.¹² Presence of MS is a strong independent predictor of any degree of renal dysfunction.²⁰ Renal function seems to be a continuous risk factor, as even mild or moderate decreases in renal function are associated with an increased prevalence of cardiovascular risk factors and coronary events.^{3,4}

In the present subanalysis of the Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry study, we tested whether insulin resistance, renal dysfunction, or both are associated with higher risk for developing PHT.

Methods

Study Subjects

The MESYAS Study is a national registry that has recruited active workers in Spain and that aims to describe the prevalence of MS and its impact on cardiovascular diseases. The first objective is planned as an epidemiologic cross-sectional design, and some preliminary data are presented here. Data from the annual health examinations will be collected from different Spanish cohorts of active workers. At the time of this subanalysis, data from three different cohorts were available, from the following: a large department store (1,901 persons; 10%), a automobile factory (5,357; 28.1%), and a national work insurance company (11,783; 61.9%); thus a total of 19,041 active workers were included. The prevalence of cardiovascular risk factors in the second cohort has previously been published.²¹ The only exclusion criterion was the lack of any factor for the diagnosis of MS. The protocol was approved by an ethic committee of the Preventive Cardiology and Rehabilitation Section of the Spanish Society of Cardiology (Sección de Cardiología Preventiva y Rehabilitación, Sociedad Española de Cardiología).

Data Collection and Assessment of MS

We designed a database unifying data from the three cohorts. Anonymity was preserved by the assignation of a worker-number by the medical unit of each company without any possibility of externally relating this number to either demographic or clinical data. Informed consent was not obtained individually but only for each physician or medical department. However, the workers and syndicates are aware of and annually informed about the results and use of their data.

The assessment of the MS was based on the presence of three of its five components according to the modified guidelines of ATP III²²: body mass index (BMI) >28.8 kg/m²; triglycerides (TG) ≥ 150 mg/dL; HDL cholesterol <40 mg/dL (in men) or <50 mg/dL (in women); BP $\geq 130/85$ mm Hg; and fasting glucose ≥ 110 mg/dL or diabetes mellitus previously diagnosed. Abdominal obesity was evaluated based on a body mass index (BMI) ≥ 28.8 kg/m² instead of a certain waist circumference, a modification already used by some groups.^{12,13,18} When the MESYAS Registry was initiated, annual health examinations of the participating companies did not measure waist circumference routinely and therefore this parameter was not available. All analytic samples were obtained after an overnight fast of ≥ 12 h. The metabolic score was calculated as the number of components of the MS that clustered in the same subject. Non-HDL cholesterol was calculated as the difference of total cholesterol and HDL levels. When serum creatinine was available, glomerular filtration rate (GFR) was estimated by the abbreviated Modification of Diet in Renal Disease Study (MDRD)²³ equation.

Categories of BP

The BP value was registered as the average of two measurements obtained with mercury-column sphygmomanometer after 10 min of physical resting. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7),⁵ subjects were considered to be normotensive when BP (systolic and diastolic) was <120 and <80 mm Hg; as prehypertensive when systolic BP was 120 to 139 mm Hg or diastolic BP was 80 to 89 mm Hg; and as hypertension (HT) if systolic BP was ≥ 140 or diastolic BP was >90 mm Hg.

Statistical Analysis

The Access 2000 (Microsoft, Redmond, WA) and SPSS 11.0 (SPSS Inc., Chicago, IL) programs were used for data processing. Quantitative variables are presented as mean (\pm SD). All variables except triglyceridemia had normal distribution. One-way analysis of variance (ANOVA) and the χ^2 test were used to analyze the statistical differences among characteristics of participants, and one-way ANOVA was applied to compare the three categories of BP. Adjustment by age and other variables was made by multivariate linear regression, and adjusted odds ratios

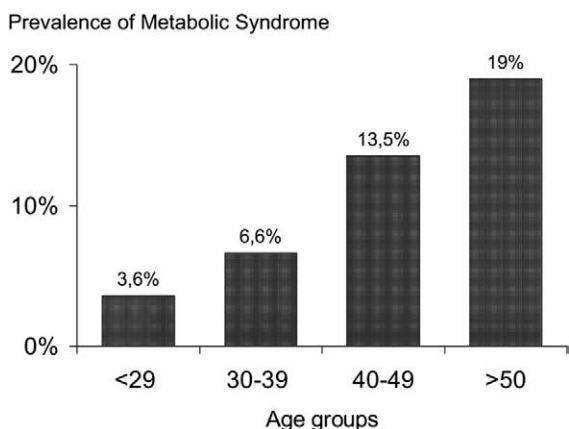


FIG. 1. Prevalence of metabolic syndrome according to groups of age. $P < .001$ between all age groups.

(OR) were assessed in normotensive subjects by logarithmic regression with the category prehypertension as dependent variable. Statistically significant difference were accepted at values of $P < .05$.

Results

Prevalence of MS

Men accounted for 80% of the sample; mean age was 42.2 (10.7) years, significantly higher in men than women (43.3 v 38.0). The global prevalence of the MS was 11.8% (2,239 of 19,041 subjects). The prevalence of each component was as follows: BP $>130/85$: 42.9%; BMI ≥ 28.8 kg/m²: 24.8%; hypertriglyceridemia: 20.4%; low HDL-cholesterol: 10.8%; and impaired fasting glucose: 7.8%. As presented in Figure 1, the prevalence of MS increased in parallel to age.

Subjects with MS were significantly older and had higher BMI, BP (systolic, diastolic, and mean), pulse pressure, total cholesterol, triglycerides, LDL cholesterol, and non-HDL cholesterol, and had lower HDL-cholesterol levels than did subjects without MS (Table 1). All differences remained significant after adjustments for age, BMI, and the presence of diabetes.

Categories of BP

The prevalence and characteristics of the three categories of BP are depicted in Table 2. Subjects with PHT represented the highest percentage of the sample. The prevalence of HT increased significantly in parallel to age, whereas PHT remained similar in all age groups (Fig. 2), and its prevalence was statistically significant only after dividing the overall group into subjects ≥ 40 years and <40 years of age. The prevalence of NT decreased significantly in the groups of 40 to 49 and >50 years of age. The highest prevalence of MS was found among HT subjects (30.2%), followed by PHT (9.6%). The metabolic score increased significantly in the three categories of BP, even adjustment for age and BMI. Subjects with PHT showed intermediate levels of pulse pressure, fasting glucose, total and LDL cholesterol, triglycerides, and non-HDL cholesterol. Differences in HDL cholesterol were slight and were observed only between subjects with NT and those without. Of note is that BMI was significantly lower in NT as compared with the other groups, as PHT and NT had very similar mean values. The presence of PHT, compared with NT, was associated with a fivefold risk for the presence of MS (OR 5.33, 95% CI 3.68 to 7.72) after gender, age, BMI, total cholesterol, and LDL adjustment.

Table 1. Characteristics of the population according to the presence or absence of metabolic syndrome

Characteristic	Total	No MS	MS	P value
Number of subjects	19,041	16,802	2,239	<.001
Age (year)	42.2 (10.7)	41.4 (10.6)	46.5 (9.7)	<.001
Male sex (%)	80%	77.7%	97.5%	<.001
BMI (kg/m ²)	27.5 (5.2)	26.2 (3.2)	34.5 (5.2)	<.001
Blood pressure (mm Hg)				
Systolic BP	124.0 (21.5)	121.4 (21.5)	137.5 (15.9)	<.001
Diastolic BP	77.0 (11.2)	75.4 (10.6)	86.0 (9.7)	<.001
Pulse pressure	46.9 (17.7)	46.1 (18.4)	51.5 (12.2)	<.001
Mean BP	92.7 (12.9)	90.7 (12.4)	103.2 (10.4)	<.001
Fasting glucose (mg/dL)	90.7 (20.3)	87.8 (14.7)	105.8 (24.1)	<.001
Plasma cholesterol (mg/dL)				
Total	206.4 (40.2)	203.3 (39.2)	222.5 (41.5)	<.001
HDL	51.0 (11.1)	52.3 (11.1)	44.5 (8.8)	<.001
LDL	132.4 (35.5)	131.0 (35.1)	140.3 (36.7)	<.001
Non-HDL cholesterol (mg/dL)	155.4 (39.5)	151.1 (38.0)	178.0 (40.0)	<.001
Triglycerides (mg/dL)	95.0 (67.0)	89.0 (54.0)	184.0 (9.6)	<.001
Ratio TC/HDL	4.2 (1.0)	4.0 (0.9)	5.1 (1.2)	<.001
Ratio TG/HDL	2.5 (2.3)	2.06 (1.5)	4.8 (3.6)	<.001

Data are presented as mean value (standard deviation) except for triglyceridemia, which is presented as median (interquartile range). BP = blood pressure; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MS = metabolic syndrome; TC = total cholesterol; TG = triglycerides.

Table 2. Characteristics of the three categories of subjects according to blood pressure categories

Characteristic	NT	PHT	HT	P value
Number of subjects	5,687	8,945	4,409	
% of Total	29.9%	47%	23.1%	<.001
Prevalence of MS (%)	0.9%	9.6%	30.2%	<.001
Metabolic score	0.32 (0.61)	1.1 (1.0)	2.1 (1.1)	<.001
Age (y)	38.4 (9.8)	41.9 (10.5)	47.7 (9.7)	<.001
BMI (kg/m ²)	24.9 (3.4)	28.3 (7.7)	29.1 (2.9)	<.001*
BP (mm Hg)				
Systolic BP	106.9 (7.4)	124.1 (6.7)	145.8 (31.3)	<.001
Diastolic BP	66.3 (6.6)	77.4 (6.2)	90.4 (8.9)	<.001
Pulse pressure	40.6 (7.3)	46.7 (8.4)	55.4 (31.8)	<.001
Mean BP	79.8 (6.0)	92.9 (18.6)	108.8 (12.4)	<.001
Fasting glucose (mg/dL)	85.6 (14.2)	90.6 (18.6)	97.5 (27.1)	<.001
IFG (%)	1.7%	4.4%	8.6%	<.001
Diabetes (%)	1.0%	2.8%	7.4%	<.001
Cholesterol (mg/dL)				
Total	197.6 (37.9)	206.3 (40.0)	218.1 (40.4)	<.001
HDL	52.4 (11.4)	50.6 (11.0)	50.2 (10.7)	<.001*
LDL	125.9 (33.8)	132.5 (35.6)	140.6 (35.7)	<.001
Triglycerides (mg/dL)	83.0 (49.0)	97.0 (67.0)	116.0 (83.0)	<.001
Non-HDL cholesterol	145.2 (37.1)	155.6 (39.2)	167.9 (39.4)	<.001
Ratio TC/HDL	3.9 (1.0)	4.2 (1.1)	4.5 (1.2)	<.001
Ratio TG/HDL	2.0 (1.6)	2.5 (2.2)	3.1 (2.8)	<.001

Data are presented as mean value (standard deviation) except for triglycerides, which are presented as median (interquartile range) or otherwise indicated. BP = blood pressure; BMI = body mass index; HDL = high-density lipoprotein; HT = hypertensive; IFG = Impaired fasting glucose (>100 mg/dL); LDL = low-density lipoprotein; MS = metabolic syndrome; NT = Normotensive; PHT = prehypertensive; TC = total cholesterol; TG = triglycerides.

* Difference between NT and the rest.

Data for GFR were available in 11,779 (61.9%) subjects. The characteristics of this subgroup did not differ from the total population (data not shown). Mean (\pm SD) creatinine was 0.94 (0.2) mg/dL and GFR was 90.2 (18.5).

The GFR significantly decreased as age increased (Fig. 2). As shown in Table 3, subjects with NT had slightly lower mean creatinine values, whereas GFR was equivalent in the BP categories of BP.

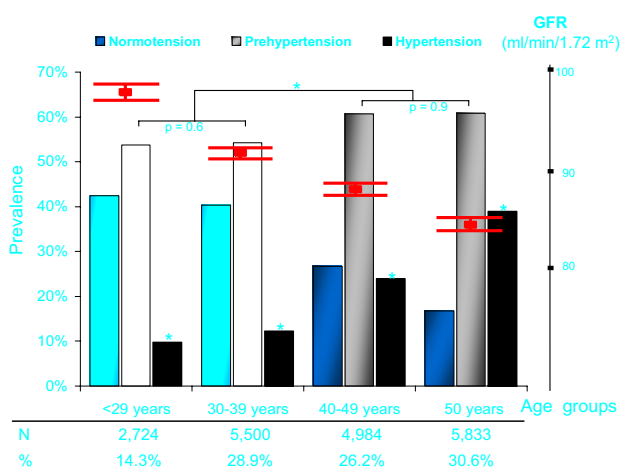


FIG. 2. Prevalence of the three categories of BP (bars) and glomerular filtration rate (boxes) expressed as mean and 95% confidence interval, according to groups of age. GFR = glomerular filtration rate. Mean GFR obtained $P < 0.001$ in the comparison between all groups of age. Differences in the prevalence of NT were statistically significantly in the comparison between subjects 40 to 49 years and the rest and, also, in the comparison between >50 years and the rest. Prehypertension obtained $P < .001$ in the comparison between groups of more and <40 years. The prevalence of hypertension obtained statistical significance in the comparison of any group of age. * $p < 0.001$.

Table 3. Glomerular filtration rate (mL/min/1.73 m²) in different clinical categories, assessed by the two different methods

Characteristic	Creatinine	MDRD
Total	0.94 (0.2)	90.2 (18.5)
Blood pressure category		
Normotension	0.91 (0.2)	90.6 (19.0)
Prehypertension	0.96 (0.2)	90.0 (17.8)
Hypertension	0.95 (0.3)	90.1 (17.8)
P value	<.001*	.4
Metabolic syndrome		
No metabolic syndrome	0.94 (0.2)	90.5 (18.4)
Metabolic syndrome	0.97 (0.3)	88.3 (18.6)
P value	<.001	<.001
Fasting glucose categories		
Normoglycemic	0.94 (0.2)	90.4 (18.4)
Impaired fasting glucose	0.95 (0.2)	87.4 (18.5)
Diabetes mellitus	0.94 (0.6)	89.7 (21.5)
P value	.5	<.001

MDRD: abbreviated Modification of Diet in Renal Disease Study Equation.

* Difference only significant between normotension and the rest.

Table 4. Crude odd ratios and corresponding 95% confidence intervals for the presence of prehypertension

Characteristic	Unadjusted OR (95% CI)
Overweight	1.52 (1.43–1.60)
Obesity	2.66 (2.30–3.1)
Diabetes mellitus	1.90 (1.30–2.80)
Impaired fasting glucose	3.15 (2.33–4.25)
Metabolic syndrome	9.51 (6.75–13.41)
Total cholesterol >200 mg/dL	1.20 (1.15–1.25)
Hypertriglyceridemia	0.89 (0.80–1.01)
TG/HDL >2.9	1.88 (1.71–2.11)
TC/HDL >4	1.36 (1.30–1.43)
GFR 60–90 mL/min/1.73 m ²	1.25 (1.15–1.37)
GFR <60 mL/min/1.73 m ²	1.06 (0.81–1.39)

CI = confidence interval; GFR = glomerular filtration rate; HDL = high density lipoproteins; OR = odds ratio; TG = triglycerides.

The prevalence of impaired fasting glucose and diabetes mellitus increased significantly in the three BP categories. The NT subjects showed prevalences of 4.4% and 2.8%, respectively, and the HT 8.6% and 7.4%, respectively. Subjects with impaired fasting glucose or diabetes had significantly lower GFR, but not lower creatinine, as compared with subjects without these conditions.

Presence of MS, overweight, impaired fasting glucose, and diabetes showed the highest crude OR for the progression from NT to PHT, as depicted in Table 4. After adjustments by age, gender, BMI, and BP, multivariate logarithmic regression showed that MS, impaired fasting glucose, obesity, and triglycerides:HDL ratio >2.9 were the only variables independently associated with the presence of PHT (Fig. 3). Overweight and mild renal dysfunction almost reached statistical significance. The OR for MS in subjects who did not have high BP or impaired fasting glucose was lower but still highly significant (OR

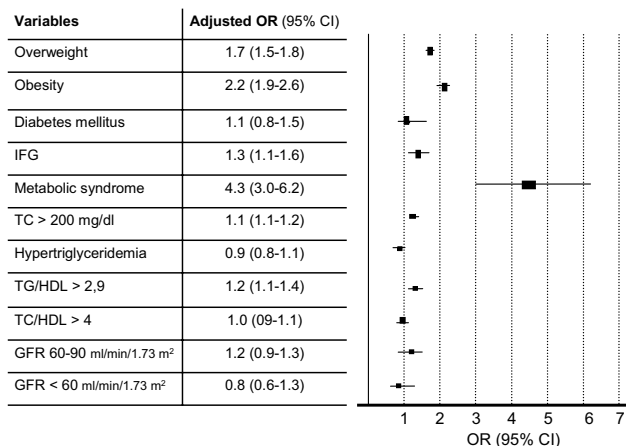


FIG. 3. Multivariate odd ratios, adjusted by age, gender and body mass index. CI = confidence interval; GFR = glomerular filtration rate; HDL = high density lipoprotein; IFG = impaired fasting glucose; OR = odds ratio; TC = total cholesterol; TG = triglycerides.

Table 5. Odd ratios and corresponding 95% confidence intervals for presenting prehypertension in the four possible triads of metabolic syndrome that do not include high blood pressure. Adjustment by age, gender and blood pressure

Characteristic	Adjusted OR (95% CI)
Obesity, hypertriglyceridemia, low HDL	3.2 (1.4–7.1)
Obesity, hypertriglyceridemia, IFG	1.6 (0.5–4.7)
Obesity, low HDL, IFG	2.1 (0.2–15.7)
Hypertriglyceridemia, low HDL, IFG	0.7 (0.6–4.2)

CI = confidence interval; IFG = impaired fasting glucose; HDL = high-density lipoproteins; OR = odds ratio.

2.9; 95% CI 1.9 to 4.6). Possible triads from the presence of MS without the component of BP were analyzed. As shown in Table 5, the only triad that conferred a significant risk for presenting PHT was the cluster of obesity, hypertriglyceridemia, and low HDL. Mild renal dysfunction, estimated by either equation, was associated with higher risk in the unadjusted model but was no longer significant after multivariate regression analysis.

Discussion Prevalence of PHT

The main finding of our study is that PHT can be considered a situation of insulin resistance, clinically assessed by the ATP definition of MS and other surrogate markers such as triglycerides-to-HDL ratio or impaired fasting glucose. As proposed by the JNC-7 report PHT is the most prevalent category of BP⁵ and is associated with a 10-fold increase in the prevalence of MS as compared with NT.

Almost one third of healthy and asymptomatic hypertensive subjects have MS. The global prevalence of MS in our population is lower than in other published cohorts.^{11–13,15} Nonetheless, the important finding is not the absolute value of prevalence but rather the differences in the prevalence and metabolic profiles among the three categories of BP. Our population is strictly constituted by active workers without overt daily-life-limiting diseases. The prevalence of classical cardiovascular risk factors is similar to that in other cohorts published^{2–4,7–9,11–13,15–20}, therefore we believe that our results are highly representative.

PHT, Renal Function, and MS

As expected, the prevalence of MS increased with age, whereas GFR showed a significant reduction with age; but the prevalence of PHT remained equivalent in the groups of age. Recent studies have reported a strong relationship between the MS and an impaired renal function²⁰ independently of blood pressure. Our results agree with these

findings in that subjects with MS, but not those with PHT, had lower GFR. Even more, the multivariate analysis demonstrated a nonsignificant relation between PHT and GFR impairment, which suggests that the alterations of renal function are a consequence, rather than a cause, of the high BP. The associations between PHT and the surrogate markers of insulin resistance were strong in the multivariate analysis. With a cross-sectional epidemiologic study we can describe associations only, rather than causal relationships. However these findings are clinically relevant, because preventing insulin resistance with diet and with reduction of overweight and sedentary lifestyle habits could reduce the progression from NT to PHT.

Nevertheless, our findings are in good agreement with previous reports⁶ that found a close relationship between increasing values of BP and insulin resistance, with both having an additive effect on small-vessel compliance.²⁴ This could also account for the high difference in mean BP found in subjects with MS as compared with subjects without MS. The triad of overweight, high triglycerides, and low HDL has been identified as an accurate surrogate marker of insulin resistance,⁹ and in our study this is the triad associated with a significant risk for BP values that correspond to PHT.

Renal function is centrally involved in the initiation and maintenance of HT. An initially impaired filtration pressure leads to an increased BP to maintain sodium balance.²⁵ Many reliable mechanisms have been proposed to clarify the association between MS and HT, apart from insulin resistance and renal dysfunction. The endothelial dysfunction associated with the presence of MS has been widely described; in daily practice, it can be clinically manifest by the presence of increased prevalence of microalbuminuria associated with MS.²⁰ Hypoadiponectinemia²⁶ and hyperleptinemia²⁷ have been described as markers of obesity and MS, and have recently been related to HT. The low prevalence of MS in subjects with NT could be explained by the low prevalence of obesity and the low levels of surrogate markers of insulin resistance and renal function impairment.

Hypertension, diabetes, and cardiovascular burden can directly affect renal function. Renal dysfunction can be evaluated by GFR or by the presence of any degree of proteinuria (either micro- or macroalbuminuria).²⁵ Hyperfiltration can be the initial effect of risk factors on renal function,^{2,3,25} which could explain the slightly higher GFR in individuals with diabetes compared with those with impaired fasting glucose. Presence of MS is a risk factor for any degree of chronic kidney disease evaluated with both parameters.²⁰ The MESYAS Registry has no access to urine samples, and therefore albuminuria could not be assessed. Restricting the diagnose of renal dysfunction, based on arbitrary limits, to a low estimated GFR is not very precise but helps to exclude possible associations. Our analysis cannot exclude any relationship between renal dysfunction and PHT, but at least we can state that lower GFR is not involved in such an association.

PHT, Lipid Levels, and Insulin Resistance

Subjects with PHT had a lower TG/HDL ratios than subjects with HT but had higher ratios than those with NT. This ratio has showed strong independent predictive power for myocardial infarction,²⁸ and has been proposed as a marker of insulin resistance.⁹ More recently, Davidson et al²⁹ have reported the association between an increased values in the triglycerides/HDL ratio and blunted diurnal BP variations. Our results demonstrate that the cluster of these two risk factors with a BMI >28.8 kg/m² increases the possibility of presenting with PHT. Although the differences in values of mean glycemia might not seem clinically relevant, increasing values of fasting glycemia are independent predictors of new-onset diabetes and a reduced probability of event-free survival.³⁰

Small dense LDL particles, greater than serum LDL levels, are a feasible explanation of the increased incidence of ischemic heart disease found in diabetes and MS.¹⁰ The size of LDL particles is inversely correlated with triglyceride-to-HDL ratio.³¹ Subjects with PHT showed intermediate values of both ratios between NT and HT, which demonstrates that prehypertension is an insulin-resistance state and highlights PHT as factor to be dealt with on a preventive basis.

Our results show that surrogate markers of insulin resistance are strong risk factors for the transition from NT to PHT. In particular, the triad of BMI >28.8 kg/m², hypertriglyceridemia, and low HDL increased threefold that difference (OR 3.2; 95% CI 1.4 to 7.1). Moreover, renal dysfunction showed no higher risk for such difference. Previous results demonstrated the strong predictive power of MS for new-onset diabetes¹² (OR 3.51, 95% CI 2.47 to 4.98) in univariate models. Our results amplify a subject of extreme importance in terms of prevention: the progression from NT to HT. These results also agree with recent data from the ATTICA study,³² that demonstrated that prehypertension is a pro-inflammatory state. In addition, MS has been largely described as a pro-inflammatory state.^{12–14}

Limitations of the Study

The main limitation of our analysis is our cohort may not be fully representative of current cardiac outpatients. Healthy active workers may have a lower cardiovascular risk, despite being a highly interesting group in terms of targeted prevention. We selected active workers for the MESYAS Registry because a large sample could be accessible by the annual health examinations. The age of this collective (mean 42 years) is highly suitable for preventive issues, as well as for incipient or subclinical cardiovascular diseases. Even more, the impact on disabilities or potentially lost working days and years have a huge social and health impact. The assessment of BMI instead of waist circumference is a well-validated modification of the ATP diagnostic criteria, although it underestimates the prevalence of MS.^{12,13,18} The highly significant differences found despite of this modification enhance our results. The only

parameter for the evaluation of renal function was GFR, and this could lead to an underestimation of renal insufficiency. The low prevalence of women could have decreased the prevalence of renal dysfunction, as most reports agree that women are at high risk for impaired renal function.^{2,3,23}

Conclusion

The main finding of this *MESYAS Registry* substudy is that prehypertension is an insulin resistance state, as assessed by the prevalence of metabolic syndrome and other surrogate markers, and not the result of initial renal dysfunction. The presence of MS was observed in almost one third of hypertensive but asymptomatic and otherwise healthy workers, and must be addressed as an important target for prevention.

References

1. Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 1996;334:374–381.
2. Fried LP, Kronmal RA, Newman AB, Bilb DE, Mittelmark MB, Polak JF, Robbins JA, Gardin JM, for the Cardiovascular Health Study Collaborative Research Group: Risk factors for 5-year mortality in older adults. *Cardiovascular Health Study. J Am Med Assoc* 1998;279:585–592.
3. Henry RMA, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CDA: Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn study. *Kidney Int* 2002;62:1402–1400.
4. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the Adult US Population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003;41:1–12.
5. Chobanian AV, Bakris GR, Black HF, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ, for the National Heart, Lung and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *J Am Med Assoc* 2003;289:2560–2572.
6. Kanauchi M, Kanauchi K, Hashimoto T, Saito Y: Metabolic syndrome and new category “pre-hypertension” in a Japanese population. *Curr Med Res Opin* 2004;20:1365–1370.
7. Wang Y, Wang QJ: The prevalence of prehypertension and hypertension among US adults according to the new Joint National Committee guidelines. *Arch Intern Med* 2004;164:2126–2134.
8. Greenland KJ, Croft JB, Mensah GA: Prevalence of heart disease and stroke risk factors in persons with prehypertension in the United States, 1999–2000. *Arch Intern Med* 2004;164:2113–2118.
9. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G: Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med* 2003;139:802–809.
10. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–1607.
11. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *J Am Med Assoc* 2002;287:356–359.
12. Sattar N, Gaw A, Scherbakova O, Ford I, O’Reilly DS, Haffner MS, Isles C, Macfarlane PW, Cobbe SM, Shepherd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 2003;108:414–419.
13. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: a 8-year follow-up of 14,719 initially healthy American women. *Circulation* 2003;107:391–397.
14. Grundy SM, Hansen B, Smith SC, Cleeman JJ, Kahn RA, for the Conference Participants: Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Circulation* 2004;109:551–556.
15. Schillaci G, Pirro M, Vaudo G, Gemelli F, Marchesi S, Porcellati, Mannarino E: Prognostic value of the metabolic syndrome in essential hypertension. *J Am Coll Cardiol* 2004;43:1817–1822.
16. Scuteri A, Najjar AS, Muller DC, Andres R, Hougaku H, Metter EJ, Lakatta EG: Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. *Am J Coll Cardiol* 2004;43:1388–1395.
17. Solymoss BC, Bourassa MG, Campeau L, Sniderman A, Marcil M, Varga S: Effect of increasing metabolic syndrome score on atherosclerosis risk profile and coronary artery disease angiographic severity. *Am J Cardiol* 2004;93:159–164.
18. Cheal KL, Abbasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES: Relationship to insulin resistance of the Adult Treatment Panel III diagnostic criteria for identification of the metabolic syndrome. *Diabetes* 2004;53:1195–1200.
19. Egan BM, Papademetriou V, Wofford M, Calhoun D, Fernandes J, Riehle JE, Nesbitt S, Michelson E, Julius S, TROPHY Sub-study Investigation Team: Metabolic syndrome and insulin resistance in the TROPHY sub-study: contrasting views in patients with high-normal blood pressure. *Am J Hypertens* 2005;18:3–12.
20. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004;140:167–174.
21. Grima A, Alegria E, Jover P: The prevalence of classic cardiovascular risk factors in a working Mediterranean population of 4,996 men. *Rev Esp Cardiol* 1999;52:910–918.
22. 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.
23. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1–S266.
24. Weinberger MH, Fineberg NS, Fineberg SE: The influence of blood pressure and carbohydrate tolerance on vascular compliance in humans. *Am J Hypertens* 2002;15:678–682.
25. Hall JE: The kidney, hypertension and obesity. *Hypertension* 2003;41:625–633.
26. Iwashima Y, Katsuyuta T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, Fu Y, Motone M, Yamamoto K, Matsuo A, Ohashi K, Kihara S, Funahashi T, Matsuzawa Y, Ogihara T: Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension* 2004;43:1318–1323.
27. Eikelis N, Schlaich M, Aggarwal A, Kaye D, Esler M: Interactions between leptin and the human sympathetic nervous system. *Hypertension* 2003;41:1072–1079.
28. Gaziano JM, Hennekens CH, O’Donnell CJ, Breslow JL, Buring JE: Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation* 1997;96:2520–2525.
29. Davidson MB, Vidt D, Hoogwerf BJ, Brotman DJ: Relation of diurnal blood pressure variation and triglyceride-to-high-density lipoprotein cholesterol ratio in patients without diabetes mellitus. *Am J Cardiol* 2005;95:123–126.

30. Verdecchia P, Reboldi G, Angeli F, Borgioni C, Gattobigio R, Filippucci L, Norgiolini S, Bracco C, Porcellati C: Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension* 2004;43:963–969.
31. Hanak V, Munoz J, Teague J, Stanley A, Bittner V: Accuracy of the triglyceride to high-density lipoprotein cholesterol ratio for the prediction of the low-density lipoprotein phenotype B. *Am J Cardiol* 2004;94:219–222.
32. Chrysoshoou C, Pitsavos C, Panagiostakos DB, Skoumas J, Stefanadis C: Association between prehypertension status and inflammatory markers related to atherosclerotic disease. *Am J Hypertens* 2004;17:568–573.

Appendix

The Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry investigators comprise the following:

Eduardo Alegría, Ignacio Ferreira, José Antonio Casanovas, Alfonso del Río, Alberto Cordero, Martín Laclaus-tra, Alberto Grima, Emilio Luengo, Montserrat León, Mónica Nájara, Beatriz Ordóñez, Clara Bergua, and Isaac Pascual Calleja.

Medical department of Corte Ingles, ASEPEYO, Valencia: Luis Francisco Camisa Jiménez, Eva María Costa Morant, Eugenia del Mar, Garcia-Vilanova Comas, and Joaquin Antoni Martínez.

Medical Department of Ford Factory, ASEPEYO, Almus-safes, Valencia: Francisco Orts Suarez, Francisco Iñiguez Albort, José Cruz Gisbert, Manuel Puchades Buendía, Concepcion Benaches Carcel, Agustin Baldovi Vercher, Jorge Grau Carmen, and Jorge Sanchis Botella.