Metabolic Syndrome in Patients With Coronary Heart Disease. Results of Using Different Diagnostic Criteria

Antonio Hernández Mijares,[a,b] Concepción Riera Fortuny,[a,c] María L. Martínez Triguero,[d] Carlos Morillas Ariño,[a,b] Pilar Cubells Cascales,[a] and María Morales Suárez-Varela[e]

[a]Sección de Endocrinología, Hospital Universitario Dr. Peset, Valencia, Spain.
[b]Departamento de Medicina, Universidad de Valencia, Valencia, Spain.
[c]Centro de Salud Xirivella, Valencia, Spain.
[d]Servicio de Análisis Clínicos, Hospital Universitario Dr. Peset, Valencia, Spain.
[e]Departamento de Medicina Preventiva y Salud Pública, Universidad de Valencia, Valencia, Spain.

A unified definition of metabolic syndrome, considered a common feature of cardiovascular risk, is lacking. The aim of this study was to compare the prevalence of this syndrome in patients with ischemic heart disease using two diagnostic criteria: the European Group of Resistance to Insulin and the National Cholesterol Education Program. We designed an observational, cross-sectional study of the factors that make up metabolic syndrome in subjects diagnosed with coronary heart disease.

A total of 169 patients aged 35 to 79 years were studied (129 men and 40 women). With the European group criterion the percentage of patients with metabolic syndrome was 43.7%, whereas the American group criterion yielded a prevalence of 40.8% (no significant difference). The prevalence of metabolic syndrome among patients with ischemic heart disease is high. The diagnostic criteria used are similar and do not differ significantly, although diagnostic concordance was only 50%.

Key words: *Risk factors. Diabetes mellitus. Obesity. Systemic hypertension. Hyperlipoproteinemia.*

Síndrome metabólico en pacientes con cardiopatía isquémica. Resultados obtenidos con la utilización de diferentes criterios

Carecemos de un criterio único para definir el síndrome metabólico, considerado como aglutinador del riesgo cardiovascular. Con objeto de comparar su prevalencia en pacientes con cardiopatía isquémica, utilizando los criterios del Grupo Europeo de Resistencia a la Insulina y los del National Colesterol Education Program, se diseñó un estudio observacional, transversal, de los factores integrantes del síndrome metabólico en pacientes con cardiopatía isquémica.

Se estudió a 169 pacientes (129 varones y 40 mujeres) con edades entre 35 y 79 años. La prevalencia del síndrome metabólico con los criterios del grupo europeo fue del 43,7% y con los del grupo americano, del 40,8% (sin diferencias significativas). La prevalencia del síndrome metabólico entre pacientes con cardiopatía isquémica es elevada. Los criterios diagnósticos utilizados son similares y sin diferencias significativas entre ellos, aunque la concordancia diagnóstica fue del 50%.

Palabras clave: *Factores de riesgo. Diabetes mellitus. Obesidad. Hipertensión arterial sistémica. Hiperlipoproteinemia.*

INTRODUCTION

The metabolic syndrome is the combination of a group of disorders. The more important of these disorders include insulin resistance with compensating hyperinsulinemia,[1] carbohydrate intolerance, or diabetes mellitus, dyslipidemia, obesity—mainly central, systemic hypertension, hyperuricemia, disorders of fibrinolysis, and endothelial dysfunction.[2] All these proces-

Correspondence: Dr. A. Hernández Mijares.
Servicio de Endocrinología. Hospital Universitario Dr. Peset.
Avda. Gaspar Aguilar, 90. 46017 Valencia. España.
E-mail: hernandez_antmij@gva.es

Received November 26, 2003.
Accepted for publication April 14, 2004.

ses, either simultaneously or sequentially, are associated and stimulate the development of arteriosclerosis.

No single criterion exists to define the metabolic syndrome. Proposed criteria include those of the World Health Organization (WHO) and the European Group for the Study of Insulin Resistance (EGIR).[3] Both organizations require the presence of insulin resistance and hyperglycemia, in association with 2 or more of the following: hypertension, dyslipidemia, and obesity. The WHO criteria also require the presence of microalbuminuria. More recent criteria from the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII)[4] require 3 or more of the following for the diagnosis of the metabolic syndrome: abdominal obesity (based on the waist circumference), dyslipidemia, hypertension, and hyperglycemia. Unlike the first 2 groups, the criteria of this third group approximate more closely to daily clinical practice, because they do not require measurement of insulin or calculation of insulin resistance.

The aim of this study was to calculate the prevalence of the metabolic syndrome in patients with ischemic heart disease, using the criteria of the EGIR and those of the NCEP-ATPIII. We also assessed the diagnostic concordance between the 2 sets of criteria.

PATIENTS AND METHODS

Study Design

We undertook an observational, cross-sectional study of the cardiovascular risk factors involved in the metabolic syndrome in an adult population, composed of men and women who had had at least one episode of acute myocardial infarction (documented clinically, enzymatically, and with changes on the electrocardiogram [ECG]) or angina (also documented clinically, by ECG and exercise stress test). Table 1 shows the diagnostic criteria for the metabolic syndrome according to the EGIR and the NCEP-ATPIII.

Study Protocol

During the course of one year all patients from the health center who fulfilled the required characteristics were recruited. Patients were excluded if fewer than three months had passed since their episode of ischemic heart disease or if sufficient clinical documentation was lacking. Each patient was informed of the characteristics and aims of the study. If the patients gave their consent, a medical history was obtained (personal and family history, and treatment followed) and anthropometric data were measured or calculated (weight, height, body mass index [BMI], and waist and hip measurements). Blood pressure was taken after a 10 minute supine rest. During the following week, blood was drawn after a 12 hour overnight fast. The plasma was separated immediately (3000 rpm for 10 minutes at 4ºC). The samples were processed either immediately or within the following 10 days and stored at –20ºC.

Measurements

Total cholesterol and triglycerides were measured by enzymatic methods (Roche/Hitachi 747 autoanalyzer).[5] The high density lipoprotein (HDL) cholesterol was measured by precipitation with dextran sulfate $MgCl_2$.[6] Low density lipoprotein (LDL) cholesterol was calculated from the Friedewald equation[7] (provided the triglycerides were <400 mg/dL). Apolipoprotein B (apo B) and apolipoprotein A-I (apo A-I) were measured by immunonephelometry,[8] glucose by an enzymatic method and insulin by immunochemiluminescence (Immulite analyzer). The homeostasis model assessment (HOMA), considered as an indirect index of insulin resistance, was calculated

TABLE 1. **Criteria Used for the Diagnosis of the Metabolic Syndrome***

WHO	EGIR	NCEP-ATPIII
GI/DM or IR, with 2 or more of:	Insulin >75th percentile, with 2 or more of:	3 or more of:
Microalbuminuria[a]	Baseline glycemia =110 mg/dL	Baseline glycemia ≥110 mg/dL
Blood pressure ≥140/90 mm Hg	Blood pressure ≥140/90 mm Hg	Blood pressure ≥130/85 mm Hg
TG≥150 mg/dL and/or	TG≥180 mg/dL and/or	TG≥150 mg/dL
HDL: men <35 mg/dL	HDL<40 mg/dL	HDL: men <40 mg/dL
women <39 mg/dL		women <50 mg/dL
Central obesity	Central obesity	Central obesity
BMI≥30 with waist to hip ratio:	Waist: men ≥94 cm	Waist: men ≥102 cm
men >0.9	Waist: women ≥80 cm	Waist: women ≥88 cm
women >0.8		

*DM indicates diabetes mellitus; HDL, high density lipoproteins; GI, glucose intolerance; BMI, body mass index; IR, insulin resistance; TG, triglycerides.
[a]Albuminuria =20 mg/min or albumin/creatinine ratio >30 mg/g.

according to the equation described by Matthews et al.[9] Hyperinsulinism and insulin resistance were defined by the 75th percentiles of insulin (12.75 μU/mL) and HOMA (3.03), as previously established.[10]

Statistical Study

The sample selection was undertaken by nonprobabilistic sampling of consecutive cases.[11] After verification of the normal distribution by the Kolmogorov-Smirnov method, the mean, standard deviation (SD), and 95% confidence interval were calculated for the descriptive analysis. Comparison of values between men and women was undertaken by calculating the differences in the means (Student's *t* test) for parametric variables and by the Mann-Whitney U test for nonparametric variables. Comparison of proportions was done with the χ^2 test. Concordance between the 2 sets of criteria for the definition of the metabolic syndrome was calculated with the κ test and the 95% confidence interval. The 95% statistical significance was evaluated.

RESULTS

The study included 169 patients with a personal history of ischemic heart disease (129 men and 40 women), aged between 35 and 79 years. Table 2 shows the characteristics of these patients. Significant differences were found between men and women in the BMI and waist to hip ratio. The women had significantly higher HDL-Cholesterol and apo A-I values than the men. The women also had higher figures for insulin and HOMA than the men.

Hyperinsulinism was present in 63 persons and insulin resistance in 80. The metabolic syndrome was present in 74 persons according to the EGIR criteria and in 69 according to the NCEP-ATPIII criteria (Table 3). Table 4 shows the classification of the metabolic syndrome in the patients with ischemic heart disease according to the EGIR and NCEP-ATPIII. The diagnostic concordance was only 50%.

The cardiovascular risk factors detected in the patients with ischemic heart disease were hypertension (67%), smoking (64.8%), dyslipidemia (64%), diabetes mellitus (43%), obesity (36.7%), central distribution of fat (39.4%), and a family history of ischemic heart disease (16.7%).

DISCUSSION

In this study we found that a high proportion of patients with established ischemic heart disease were obese, despite therapeutic measures, and had cholesterol levels above those acceptable for secondary prevention. An excessive number of the patients smoked, as well as having high levels of glycemia and insulinemia, an expression of insulin resistance.[12] However, we noted acceptable values for blood pressure and the remaining lipid fractions. These data reflect the true situation with regard to secondary prevention in our area.[13,14]

TABLE 2. **General Characteristics of the Patients With Ischemic Heart Disease***

	Patients With Ischemic Heart Disease		
	Men	Women	Total
Patients, n	129	40	169
Age, years	60.43±7.52	62.15±9.57	61.27±8.05
Systolic blood pressure, mm Hg	136.57±18.33	141.63±17.66	137.78±18.20
Diastolic blood pressure, mm Hg	79.06±10.36	80.87±12.08	79.49±10.79
Smokers/ex smokers	28/79	3/3	31/82
Total smokers, n (%)	107 (82.94)	6 (6.66)	73 (43.19)
Body mass index, kg/m^2	28.69±4.01	32.85±5.76*	29.67±4.89
Waist, cm	100.94±10.84	102.13±14.23	101.22±11.69
Waist to hip ratio	0.97±0.04	0.90±0.06*	0.95±0.05
Total cholesterol, mg/dL	199.64±38.89	204.73±42.92	200.84±38.33
Triglycerides, mg/dL	141.41±94.38	152.40±90.98	144.01±93.43
HDL-Cholesterol, mg/dL	42.01±9.98	50.55±12.32*	44.03±11.15
LDL-Cholesterol, mg/dL	128.92±34.67	123.60±36.68	127.65±35.12
apo B100, mg/dL	118.18±27.10	116.06±26.22	117.69±26.83
apo A-I, mg/dL	134.57±19.19	150.60±25.31*	138.39±21.83
Baseline glycemia, mg/dL	130.30±48.27	138.28±67.77	132.24±2.35
Baseline insulinemia, μU/mL	12.69±10.89	18.97±16.85*	14.19±12.78
HOMA	4.15±5.15	7.00±9.71*	4.83±6.60

The values of the quantitative parameters are expressed as the mean ± standard deviation. *apo A-I indicates apolipoprotein A-I; apo B100, apolipoprotein B100; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA, Homeostasis Model Assessment.
[a]*P*<.05 between men and women.

TABLE 3. **Prevalence of Hyperinsulinism, Insulin Resistance, and the Metabolic Syndrome in the Patients With Ischemic Heart Disease, According to the EGIR and NCEP-ATPIII Criteria (n=169)***

Hyperinsulinism (Insulin >12.7 mU/mL)			Insulin Resistance (HOMA>3.03)			Metabolic Syndrome EGIR			Metabolic Syndrome NECP-ATPIII		
n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
63	38.65	31.22-46.61	80	47.33	39.66-55.13	74	43.78	36.24-51.61	69	40.82	33.34-48.64

*95% CI indicates, 95% confidence interval. The difference between the proportion of EGIR and ATPIII was not statistically significant (*P*=.581); κ=0.503 (*P*=.001).

TABLE 4. **Analysis of the Diagnostic Concordance Between the EGIR and the NCEP-ATPIII Criteria for the Metabolic Syndrome in Patients With Ischemic Heart Disease**

		ATPIII	
		MS	No MS
EGIR	MS	51	23
	No MS	18	77

*MS indicates the metabolic syndrome. κ=0.503.

Women with ischemic heart disease had a notable increase in weight compared with similar-aged men with ischemic heart disease. The women tended to have an android (central) body fat distribution, with an even greater mean waist circumference than the men and very close to that included in the definitions of the metabolic syndrome used in this study. This situation may well be the origin of the high levels of insulin and insulin resistance in the women. We also detected the known increases in HDL-Cholesterol and apo A-I in the women, despite their age.

Insulin resistance and hyperinsulinism have been associated with a greater cardiovascular risk.[15-18] Hyperinsulism is considered to be present when baseline insulin levels are 12-20 μU/mL.[19,20] In our study we used an insulin value >12.7 μU/mL (75th percentile)[10] and found that 38.6% of the subjects had hyperinsulinism. These figures are indicative of the established association between hyperinsulinism and coronary heart disease in different communities.[21,22]

Because HOMA has a good correlation with the glucose clamp method,[23] which is considered the reference technique for the study of insulin resistance, use of the HOMA to measure insulin resistance has enabled its prevalence to be determined in large study groups. These data agree with previously published reports, to the extent that they relate this measurement of insulin resistance with the cardiovascular risk.[24,25]

Evaluation of the prevalence of the metabolic syndrome according to the EGIR criteria showed a prevalence of 43.78% for the population with ischemic heart disease, more than 4 times greater than the figure for the general Spanish population, which these same criteria situate at 15.5%.[5] These data indicate a clear association between ischemic heart disease and the presence of the metabolic syndrome, and highlight the risk these patients have, in spite of receiving therapy.

Use of the NCEP-ATPIII criteria for the diagnosis of the metabolic syndrome gave a prevalence of 40.82%, which was 3% lower than the figure obtained with EGIR criteria, though the difference was not statistically significant. However, study of the diagnostic concordance between the 2 methods led to the metabolic syndrome being diagnosed with both sets of criteria in just 50% of the patients. This lack of concordance could be related with the pharmacological therapy given or even with the response of these patients to the particular drug used. Future studies are worthwhile to examine this difference in diagnostic concordance between individuals whereas no differences are appreciated when these persons are grouped together.

The advantages of the diagnostic criteria according to the American group are related with the ease with which the clinician can use them, because they do not require insulin measurements, which are not always available in daily clinical practice, and they limit the tests to a few simple anthropometric and laboratory measurements which are readily available. However, as we have seen, this can limit their diagnostic usefulness in certain patients.

The high prevalence of the metabolic syndrome could be determined to a certain extent by the high mean age of the study population, as the prevalence of the metabolic syndrome increases with the increasing age of the population. Nevertheless, as the study contained no exclusion criteria for age, these patients are representative of the true age of patients with ischemic heart disease.

In conclusion, the patients with established ischemic heart disease included in this study did not attain all the accepted objectives in secondary prevention, especially concerning weight and LDL-Cholesterol. The high prevalence of the metabolic syndrome detected in these patients with ischemic heart disease was similar with the 2 methods used. These findings mean that the

diagnosis of the metabolic syndrome can be done easily in daily clinical practice.

REFERENCES

1. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
2. Kohler HP. Insulin resistance syndrome: interaction with coagulation and fibrinolysis. Swiss Med Wkly 2000;132:241-52.
3. Balkau B, Charles MA, Drivsholm T, Borch-Johnsen K, Wareham N, Yudkin JS, et al. European Group For The Study Of Insulin Resistance (EGIR). Frecuency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. Diabetes Metab 2002;28:364-76.
4. Ford ES, Giles WH, Dietz WH. Prevalence of the Metabolic Syndrome Among US Adults. Findings From the Third National Health and Nutrition Examination Survey. JAMA 2002;287:356-9.
5. Bachorik PS. Measurement of total cholesterol, HDL-cholesterol, and LDL-cholesterol. Clin Lab Med 1989;9:61-72.
6. Finley PR, Schifman RB, Williams RJ, Lichti DA. Cholesterol in high-density lipoprotein: use of Mg2+/dextran sulfate in its enzymic measurement. Clin Chem 1978;24:931-3.
7. Friedewald WT, Levy RI, Freddrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-02.
8. Maciejko JJ, Levinson SS, Markyvech L, Smith MP, Blevins RD. New assay of apolipoproteins A-I and B by rate nephelometry evaluated. Clin Chem 1987;33:2065-9.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Teacher DF, Turner RC. Homeostasis model assessment: insulin resistance and B cell function from fasting plasma glucose and insulin resistance concentration in man. Diabetologia 1985;28:412-9.
10. Hernández Mijares A, Riera Fortuny C, Solá Izquierdo E, Oliver Oliver MJ, Martínez Triguero ML, Morillas Ariño C, et al. Prevalencia del SM en pacientes con cardiopatía isquémica. Med Clin (Barc) 2003;121:204-8.
11. Silva LC. Muestreo para investigación en ciencias de la salud. Madrid: Díaz de Santos, 1993.
12. Bueno H. Prevención y tratamiento de la cardiopatía isquémica en pacientes con diabetes mellitus. Rev Esp Cardiol 2002;55:975-86.
13. López-Mínguez JR, Fuentes ME, Doblado M, Merchán A, Martínez A, González RE, et al. Papel pronóstico de la hipertensión arterial y de la diabetes mellitus en los pacientes con angina inestable tratados con *stents* coronarios. Rev Esp Cardiol 2003;56: 987-94.
14. Gutiérrez Fuentes JA, Gómez-Jerique J, Gómez de la Cámara A, Ángel Rubio M, García Hernández A, Aristegui I. Dieta y riesgo cardiovascular en España. Descripción de la evolución del perfil de riesgo cardiovascular. Med Clin (Barc) 2000;115:738-9.
15. Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Ekfeldt JH. A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 1997;20:935-42.
16. Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men. The 22-year follow-up results of the Helsinki Policemen Study. Circulation 1998;98:398-04.
17. Ruige JB, Assendelft JJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease. A meta-analysis. Circulation 1998;97:996-1001.
18. Conget I. Diagnóstico, clasificación y patogenia de la diabetes mellitus. Rev Esp Cardiol 2002;55:528-38.
19. Fontbonne A, Charles MA, Thibult N, Richard JL, Claude JR, Warnet JM, et al. Hyperinsulinaemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15-year follow-up. Diabetologia 1991;34:356-61.
20. Zavaroni I, Bonini L, Gasparini P, Barilli AL, Zuccarelli A, Dall'Aglio E, et al. Hyperinsulinemia in a normal population as a predictor of non-insulin-dependent diabetes mellitus, hypertension, and coronary heart disease: the Barilla Factory Revisted. Metabolism 1999;48:989-94.
21. Chien KL, Lee YT, Sung FC, Hsu HC, Su TC, Lin RS. Hyperinsulinemia and related atherosclerotic risk factors in the population at cardiovascular risk: a community-based study. Clin Chem 1999;45:838-46.
22. Sheu WH, Jeng CY, Young MS, Le WJ, Chen YT. Coronary artery disease risk predicted by insulin resistance, plasma lipids, and hypertension in people without diabetes. Am J Med Sci 2000;319:84-8.
23. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MA, et al. Homeostasis model assesment closely morrors the glucose clamp technique in the assessment of insulin sensitivity. Diabetes Care 2000;23:57-63.
24. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio heart study. Diabetes Care 2002;25:177-84.
25. Hedblad B, Nilsson P, Engström G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diabet Med 2002; 19:470-5.