

# Microalbuminuria Accounts for the Increased Vascular Disease Risk in Diabetic Patients With Metabolic Syndrome

José A. Gimeno-Orna,<sup>a</sup> Edmundo Molinero-Herguedas,<sup>a</sup> Luis M. Lou-Arnal,<sup>a</sup> Beatriz Boned-Juliani,<sup>b</sup> Tomás Labrador-Fuster,<sup>a</sup> and Miguel Guiu-Campos<sup>a</sup>

<sup>a</sup>Sección de Medicina Interna, Hospital Comarcal de Alcañiz, Teruel, Spain

<sup>b</sup>Sección de Bioquímica, Hospital Comarcal de Alcañiz, Teruel, Spain

The aim of this study was to determine the impact of the metabolic syndrome on vascular disease risk in patients with type-2 diabetes. A prospective cohort study was carried out. The main dependent variable was the combination of coronary disease, stroke, and lower leg amputation. Cox regression modeling was used. In total, 317 patients were followed for a mean of 7.7 years. The prevalence of metabolic syndrome was 87%. Multivariate analysis identified the following as predictors of incident vascular disease: age (relative risk [RR]=1.06, 95% confidence interval [CI], 1.02-1.1;  $P=0.0003$ ), baseline cardiovascular disease (RR=1.8; 95% CI, 1.1-3.0;  $P=0.017$ ), and the simultaneous presence of four metabolic risk factors (RR=5.8; 95% CI, 1.8-18;  $P=0.003$ ). The most predictive factor was microalbuminuria ( $\chi^2=5.9$ ;  $P=0.015$ ). Microalbuminuria accounts for the increased risk of vascular disease in patients with metabolic syndrome. In evaluating vascular disease risk in patients with type-2 diabetes, it is more important to consider the total number of metabolic risk factors than the presence of metabolic syndrome alone.

**Key words:** Syndrome X. Diabetes mellitus. Cardiovascular disease.

## La microalbuminuria explica el incremento de riesgo vascular en pacientes con diabetes y síndrome metabólico

El objetivo fue evaluar la importancia pronóstica del síndrome metabólico (SM) en el riesgo vascular en diabetes mellitus tipo 2 (DM2). Se realizó estudio de cohortes prospectivo. La variable dependiente, enfermedad cardiovascular (ECV), fue una combinación de eventos coronarios, cerebrovasculares y amputación de extremidades inferiores. Se utilizó modelo de regresión de Cox. Se incluyó a 317 pacientes seguidos durante 7,7 años. La prevalencia de SM fue del 87%. Los predictores de ECV incidente en análisis multivariable fueron: edad (riesgo relativo [RR] = 1,06; intervalo de confianza [IC] del 95%, 1,02-1,1;  $p = 0,0003$ ), ECV prevalente (RR = 1,8; IC del 95%, 1,1-3;  $p = 0,017$ ), y presentar simultáneamente 4 factores de riesgo metabólicos (RR = 5,8; IC del 95%, 1,8-18;  $p = 0,003$ ). El componente más predictivo fue la microalbuminuria ( $\chi^2 = 5,9$ ;  $p = 0,015$ ). La microalbuminuria explica el poder predictivo del SM para la aparición de ECV. Es más importante considerar el número de factores de riesgo metabólico que el SM al evaluar el riesgo vascular del paciente con DM2.

**Palabras clave:** Síndrome X. Diabetes mellitus. Enfermedad cardiovascular.

## INTRODUCTION

There are a number of definitions of metabolic syndrome (MS),<sup>1</sup> an entity that nearly doubles the risk of cardiovascular disease (CVD).<sup>2</sup> Nevertheless, the utility of identifying diagnostic criteria for MS in patients who

have already developed type 2 diabetes mellitus (DM2), and even MS itself, has recently been questioned.<sup>3-5</sup>

In a previous article,<sup>6</sup> we demonstrated that the simultaneous presence of all the components of MS, defined according to the World Health Organization (WHO),<sup>7</sup> was related to an increase in the cardiovascular risk of patients with DM2. In the present report, we attempt to validate the utility of diagnosing MS in patients with DM2 and to determine whether all its components have the same prognostic value.

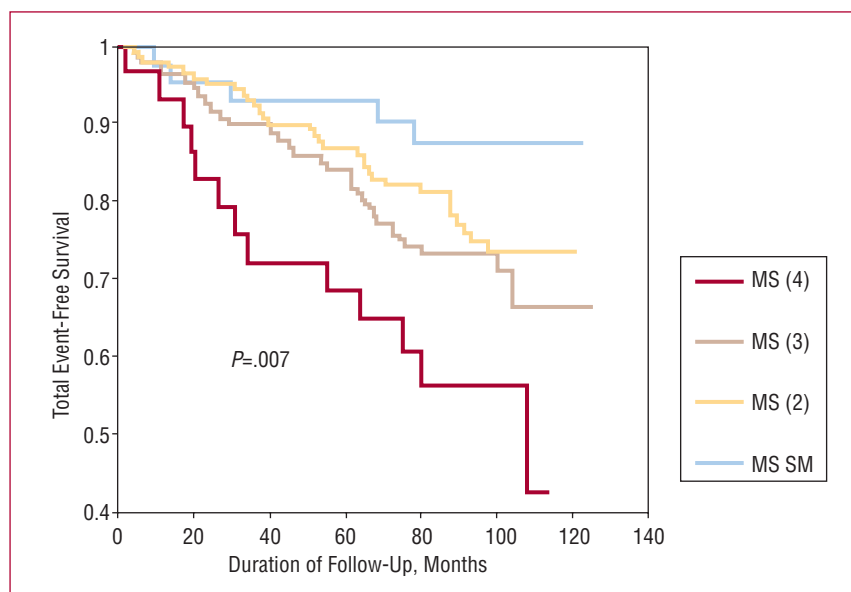
## METHODS

A prospective cohort study was carried out in a previously defined population.<sup>6</sup> Between June 1, 1994 and June 1, 1998, DM2 patients were selected from the out-patient

Correspondence: Dr. J.A. Gimeno-Orna. Bielsa, 27, 6.ºA. 50014 Zaragoza. España. E-mail: jagimeno@salud.aragon.es

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**Figure 1.** Cardiovascular event-free survival curve according to the number of metabolic risk factors present. The difference in the incidence rates (16.4/1000 without metabolic syndrome [MS], 33.3/1000 with 2 metabolic risk factors in addition to diabetes, 42.8/1000 with 3 factors, and 80/1000 with 4 factors) was significant ( $P=.007$ ).



endocrinology clinic of the Regional Hospital in Alcañiz, Teruel, in eastern Spain. The present study involves 317 of the 318 patients of the original cohort.<sup>6</sup>

The definition of MS was based on that provided by the WHO,<sup>7</sup> according to which a person with diabetes has MS if he or she meets 2 or more of the following criteria: hypertension (systolic pressure  $\geq 140$  mm Hg and/or diastolic pressure  $\geq 90$  mm Hg, and/or receiving hypotensive agents), dyslipidemia (triglyceride levels  $\geq 150$  mg/dL and/or high-density lipoprotein level  $< 35$  mg/dL in men, or  $< 39$  mg/dL in women), obesity (body mass index  $> 30$  and/or waist-to-thigh ratio  $> 0.9$  in men, or  $> 0.85$  in women), and microalbuminuria (albumin excretion rate  $> 30$  mg/24 hours).

The follow-up of the cohort was prospective in all the patients until their death or until the end of the study, on February 14, 2005. The development of clinical events and causes of death were obtained from the hospital records or through the attending primary care physician, as described in our previous article.<sup>6</sup>

The numbers of events per 1000 person-years were compared using Kaplan-Meier analysis and the log-rank test. The independent contribution of MS was evaluated by means of multivariate analysis with the Cox model of proportional hazard regression. The main dependent variable analyzed was the incidence of CVD, defined as a combination of new-onset angina, fatal or nonfatal acute myocardial infarction (AMI), transient ischemic attack (TIA), fatal or nonfatal stroke, sudden death, or lower extremity amputation. The attempt was made to evaluate the contribution of the different metabolic risk factors to the prognostic significance of MS by means of their sequential inclusion. The statistical significance of the improvement in the plausibility of the models when new variables are

introduced progressively is analyzed by means of the  $\chi^2$  test. A  $P$  value less than .05 was considered to indicate statistical significance.

## RESULTS

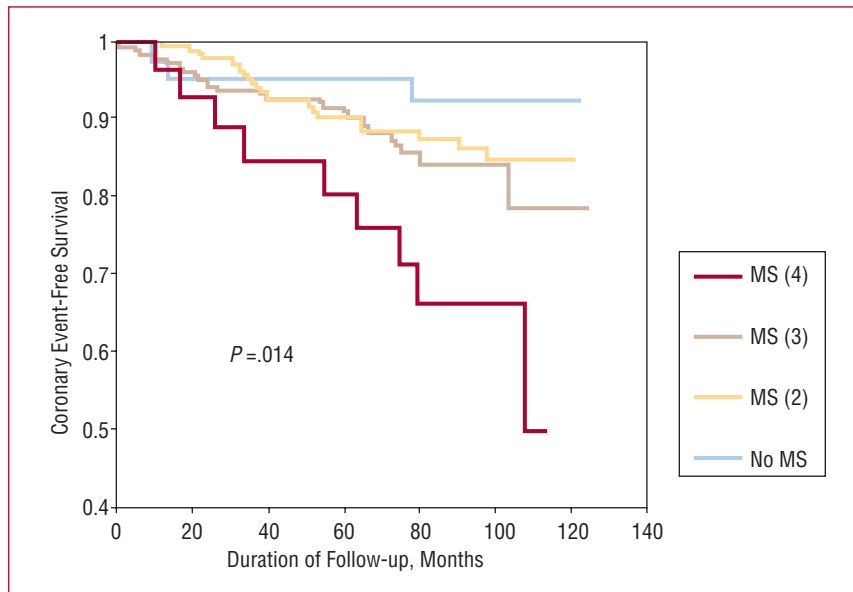
The study included 317 patients (129 men and 188 women), with a mean age (standard deviation [SD]) of 64.6 (9) years and a duration of diabetes of 10.8 (7.7) years. The prevalence of MS was 87%.

The mean duration of follow-up in event-free patients was 7.7 years, with a total of 2151 patient-years. There were 15 new-onset anginas (4.7%), 18 nonfatal AMI (5.7%), 9 fatal AMI (2.8%), 12 TIA (3.8%), 16 nonfatal strokes (5%), 2 fatal strokes (0.6%), 5 sudden deaths (1.6%), and 4 above-knee amputations (1.3%). The incidence rates of CVD and coronary artery disease increased as the number of metabolic risk factors grew ( $P=.002$  in a linear trend for CVD and  $P=.01$  for coronary events; Figures 1 and 2).

The univariate predictors of CVD and coronary artery disease with a  $P < .1$  appear in Table 1.

In the multivariate analysis, with adjustments for age, sex, duration of diabetes, smoking, glycohemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), and prevalent CVD, MS did not significantly increase the risk of incident CVD, (relative risk [RR]=2.5; 95% confidence interval [CI], 1-7.1;  $P=.07$ ) or of coronary events (RR=2.7; 95% CI, 0.6-11;  $P=.18$ ).

The significant predictors of incident CVD in the multivariate analysis were: age (RR=1.06; 95% CI, 1.02-1.1;  $P=.0003$ ), prevalent CVD (RR=1.8; 95% CI, 1.1-3;  $P=.017$ ), and the simultaneous existence of 4 metabolic risk factors (RR=5.8; 95% CI, 1.8-18;  $P=.003$ ). For



**Figure 2.** Coronary event-free survival curve according to the number of metabolic risk factors present. The difference in the incidence rates (9.8/1000 without metabolic syndrome [MS], 18.7/1000 with 2 metabolic risk factors, 23.5/1000 with 3 factors, and 55.4/1000 with 4 factors) was significant ( $P=.014$ ).

coronary artery disease, they were: LDL-C (RR=1.01; 95% CI, 1-1.02;  $P=.03$ ), prevalent CVD (RR=2.3; 95% CI, 1.2-4.3;  $P=.01$ ), and the simultaneous existence of four metabolic risk factors (RR=7.4; 95% CI, 1.5-36;  $P=.013$ ).

In an additional analysis, according to the ATP-III definition,<sup>1</sup> MS was not related to an increase in total cardiovascular risk (RR=1.22; 95% CI, 0.7-2.1;  $P$  not significant) or coronary risk (RR=1.016; 95% CI, 0.49-2.28;  $P$  not significant).

**TABLE 1. Predictive Variables for the Onset of Total Cardiovascular and Coronary Events With  $P<.1$  in Univariate Analysis**

Variable	Total CVD			Coronary Artery Disease		
	RR	95% CI	P	RR	95% CI	P
Age (1 year)	1.05	1.02-1.08	.0002	1.03	1-1.07	.07
Prevalent CVD	2.3	1.4-3.6	.0005	2.9	1.6-5.2	.0003
Current smoking	1.7	0.9-3.2	.08	2.9	1.3-6.4	.03
LDL-C (1 mg/dL)	—	—	—	1.01	1-1.02	.05
Metabolic syndrome	2.5	1-6.2	.047	—	—	—
3 metabolic RF	2.6	1-6.7	.04	—	—	—
4 metabolic RF	4.8	1.7-13	.003	5.5	1.5-20.5	.01

CI indicates confidence interval; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; RF, risk factors; RR, relative risk (unadjusted) conferred by each variable.

**TABLE 2. Improvement in the Plausibility of the Cox Regression Models for Predicting the Onset of Total Cardiovascular and Coronary Events When the Different Components of the Metabolic Syndrome (MS) Were Introduced Progressively, and, Finally, MS Itself**

Variable	Total CVD			Coronary Artery Disease		
	-2LL	$\chi^2$	P	-2LL	$\chi^2$	P
Initial model <sup>*</sup>	831.75	—	—	472.12	—	—
Obesity	830.70	1.05	.3	472.09	0.03	.86
Dyslipidemia	829.35	1.35	.24	471.03	1.06	.3
Hypertension	826.00	3.35	.07	467.65	3.38	.07
Microalbuminuria	820.06	5.94	.015	464.06	3.59	.05
Metabolic syndrome	819.95	0.12	.5	464.01	0.05	.82

CVD indicates cardiovascular disease; -2LL, plausibility of the Cox regression models.

<sup>\*</sup>Constituted by age, sex, duration of diabetes, smoking, glycohemoglobin, low-density lipoprotein cholesterol, and prevalent CVD.

## DISCUSSION

In the present report, we have confirmed<sup>6</sup> the fact that there is an increase in total cardiovascular risk and coronary risk in patients with DM2 who present the largest number of metabolic risk factors, and that microalbuminuria was the factor with the greatest predictive power.

Type 2 diabetes mellitus is associated with insulin resistance and a high prevalence of MS.<sup>8,9</sup> The advisability of performing diagnostic tests for MS in patients with DM2 is a matter of controversy,<sup>4</sup> with inconsistent results reported in the medical literature with regard to its ability<sup>8,10</sup> or inability<sup>11</sup> to predict cardiovascular events. Other findings of these studies are that the risk increases as the number of metabolic risk factors grows<sup>10,12</sup> and that microalbuminuria is the component with the greatest predictive power.<sup>8,11</sup>

In our study, MS did not significantly increase vascular risk, probably because of the limited number of subjects. Given the high prevalence of MS in DM2,<sup>13</sup> in these patients, we consider it to be of greater interest to take into account the total number of metabolic risk factors than whether or not they have MS. The fact that the greatest part of the risk conferred by MS was due to the inclusion of microalbuminuria, a marker of generalized endothelial dysfunction,<sup>14</sup> in its definition was also very interesting. In fact, when the ATP-III definition was applied, MS was related to a lesser increase in vascular risk (1.22 vs 2.5) than when the WHO definition was employed. Thus, we consider the elimination of microalbuminuria from the recent definitions of MS to be the right move.<sup>15</sup>

In conclusion, we think it is more important to consider the number of metabolic risk factors than MS in the evaluation of the vascular risk of the patient with DM2.

Given that microalbuminuria is a marker of endothelial dysfunction, we feel that its exclusion from the definition of MS to be the proper approach.

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