

Brief Report

Metabolic Syndrome and Cardiovascular Mortality in Older Type 2 Diabetic Patients: A Longitudinal Study

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Background. Although age does not seem to modify the association of the metabolic syndrome (MS) with cardiovascular risk in middle-aged individuals, no comparison of risks associated with MS between old and middle-aged persons has been reported so far.

Methods. An observational study was performed on a consecutive series of 1716 type 2 diabetic outpatients (age range: 28–96 years). The diagnosis of MS was made following either the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATPIII) or the International Diabetes Federation (IDF) criteria.

Results. The difference in cardiovascular mortality between patients with and without MS was significant up to the age of 70 years. After adjusting for age and sex, hazard ratios of MS for cardiovascular mortality were 3.03 (95% confidence interval, 1.45–6.29), 1.56 (0.91–2.68), and 1.17 (0.42–3.22) in patients ≤ 70 , 71–80, and > 80 years old, respectively.

Conclusions. MS is associated with increased cardiovascular risk in middle-aged type 2 diabetic patients, and the clinical utility of this category in older diabetic individuals is questionable.

Key Words: Diabetes mellitus—Advanced age—Cardiovascular mortality—Metabolic syndrome.

METABOLIC syndrome (MS), which is the association of abdominal adiposity, hyperglycemia, reduced high-density lipoprotein (HDL) cholesterol, elevated triglyceride, and increased arterial blood pressure (1,2), is known to increase cardiovascular morbidity and mortality in diabetic (3–10) as well as in nondiabetic (6,9–18) individuals.

The prevalence of MS increases progressively with age, up to approximately 70 years (12). In older persons, the prevalence of MS could actually be lower, as a possible effect of selective mortality. The predictive value of MS for cardiovascular morbidity and mortality has been assessed in one study only (19). Although age does not seem to modify the association of MS with cardiovascular risk in middle-aged individuals (19), no comparison of risks associated with MS between old and middle-aged persons has been reported so far. The present analysis was aimed at assessing the effect of age on the association of MS with cardiovascular mortality in a cohort of type 2 diabetic patients in a wide age range.

METHODS

Patients and Baseline Assessment

An observational cohort study was performed on a consecutive series of 1716 outpatients (age range: 28–96 years), with an established diagnosis of type 2 diabetes, who

were visited at the Diabetes and Metabolic Diseases Clinic of the Geriatric Unit of the University of Florence between January 1, 1998, and December 31, 2003.

Demographic and clinical data were collected from clinical records and included a medical history with detailed information on duration of diabetes, any current pharmacological treatment, cardiovascular risk factors, and associated medical conditions. At first visit, patients underwent a physical examination that included measurement of body weight and height, waist circumference, and blood pressure following World Health Organization (WHO) recommendation (20). A standard 12-lead electrocardiogram (ECG) was recorded as well.

After an overnight fast, blood was sampled for determining HbA_{1c} (high pressure liquid chromatography, Menarini Diagnostici, Italy; upper normal limit 6.2%) and creatinine, total cholesterol, HDL cholesterol, and triglyceride (all measured with an automated method Aeroset; Abbott Laboratories, Milan, Italy).

Diagnostic Criteria

Patients were considered hypertensive if they were on antihypertensive medication and/or if blood pressure was $\geq 140/90$ mmHg (20). Renal failure was defined as serum creatinine > 1.5 mg/dL. Ischemic heart disease was diagnosed when patients reported previous myocardial infarction, angina (or when ECG showed unequivocal signs

Table 1. Baseline Characteristics of Type 2 Diabetic Patients Enrolled

Principal Parameters	Whole Sample	Age, y				
		<50	51–60	61–70	71–80	>80
<i>N</i> (% women)	1716 (44.7)	187 (29.9)	350 (40.9)	638 (49.8)	448 (49.8)	93 (58.1)
Age, y	65.5 ± 11.0	43.8 ± 5.4	55.6 ± 2.9	65.6 ± 2.9	74.7 ± 2.8	84.1 ± 2.5
BMI, kg/m ²	28.0 ± 4.8	28.7 ± 5.9	29.1 ± 4.8	28.3 ± 4.7	27.0 ± 4.4*	25.9 ± 3.9 [†]
Duration of diabetes, y	11.9 ± 10.5	7.1 ± 8.5	9.5 ± 9.1	12.3 ± 9.8*	14.6 ± 11.2 [†]	15.6 ± 15.2 [†]
HbA _{1c} , %	7.9 ± 1.9	8.1 ± 2.1	8.0 ± 2.0	7.9 ± 2.1	7.8 ± 1.7	8.0 ± 1.9
Total cholesterol, mg/dL	212.8 ± 44.6	206.4 ± 43.1	216.5 ± 43.5	213.6 ± 44.7	212.2 ± 45.5	209.8 ± 41.3
Systolic BP, mmHg	143.5	138.7	139.1	141.9	143.9	145.5*
Diastolic BP, mmHg	84.8	82.3	84.4	85.1	79.1	78.7
Charlson's index	2.5 ± 1.6	1.8 ± 1.1	2.1 ± 1.4	2.6 ± 1.7*	3.0 ± 1.8 [†]	3.2 ± 1.7 [†]
CVD at enrolment, %	28.1	20.2	25.1*	27.8 [†]	28.6 [†]	30.1 [†]
Diabetes treatments						
Insulin-secretagogue, %	54.5	43.3	52.3*	44.4	60.3 [†]	49.5
Metformin, %	39.2	34.8	41.1*	40.6*	39.5	29.0*
Insulin, %	33.9	31.0	29.7	35.1	35.0	41.9*
Diet only, %	18.8	24.6	24.3	17.7*	14.1*	16.1*
Other treatments						
Antihypertensive, %	47.5	43.4	44.9	48.5	52.3*	43.7
Statins, %	18.1	14.8	16.0	15.3	24.7*	21.1*
Antiplatelet, %	40.3	43.4	38.0	40.0	45.8	47.2
MS components						
Hypertension, %	58.5	44.9	57.4*	62.2 [†]	60.3 [†]	55.9
HDL cholesterol, %	43.9	51.9	45.4	43.4	41.3*	37.6 [†]
Triglycerides, %	50.3	54.5	56.0	50.3	45.5*	44.1*
Waist						
NCEP-ATPIII, %	53.1	47.1	56.0*	56.1*	51.3	43.0
IDF, %	80.2	67.4	82.0*	83.5*	80.4*	76.3

Notes: Data are expressed as mean ± standard deviation or percent.

* $p < .05$, [†] $p < .01$; the reference category is the group aged <50 y.

BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; MS = metabolic syndrome; HDL = high-density lipoprotein; NCEP-ATPIII = National Cholesterol Education Program-Adult Treatment Panel; IDF = International Diabetes Federation.

of current or previous infarction or ischemia according to the Minnesota coding system) (21). A history of stroke or transient ischemic attack was used to make the diagnosis of cerebrovascular disease. Chronic comorbidity was assessed using the Charlson index (22). The diagnosis of MS was made following either the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATPIII) (1) or the International Diabetes Federation (IDF) criteria (2). According to both sets of criteria, MS is present when at least three of five conditions (abdominal adiposity, hyperglycemia, reduced HDL cholesterol, elevated triglyceride, and increased arterial blood pressure) are satisfied, but IDF criteria established lower thresholds for abdominal adiposity and hyperglycemia, and considered elevated waist circumference as a mandatory condition for the diagnosis.

Follow-Up

Information on all-cause mortality and of causes of death up to December 31, 2005, was obtained by the City of Florence Registry Office, which contains complete and updated records of all persons living within city boundaries. For persons who had moved away, queries were sent to the Registry Office requesting the new city of residence. Following the International Classification of Diseases (ICD), cardiovascular causes of death were coded as 410–414 (ischemic heart disease), 420–429 (other heart diseases), or

798–799 (sudden death) for cardiac diseases, and as 430–434 or 436–438 for cerebrovascular disease. Codes 140–239 were used to identify cancer-related deaths.

Statistical Analysis

Normally distributed data were expressed as mean ± standard deviation. Unpaired Student's *t* test and Mann-Whitney U-test were used to compare continuous variables whenever appropriate. Chi-square test was used for between-group comparisons of categorical variables. Kaplan-Meier analysis of survival was performed with definition of hazard ratios (HR) and 95% confidence intervals (CI), and a stepwise Cox regression was carried out for multivariable analysis. The absence of variations over time of hazards associated with age or MS was checked to verify the proportionality of hazards assumed in the Cox models. All analyses were carried out with the SPSS 12.0.1 statistical package (Chicago, IL, USA), and $p < .05$ was considered statistically significant.

RESULTS

The characteristics of patients enrolled are summarized in Table 1. MS was present in 67.1% and 80.2% of patients using either NCEP-ATPIII or IDF criteria, respectively. During an average follow-up of 4.7 ± 2.1 years, 404 deaths were recorded, with a yearly rate of 4.2, 1.4, and 1.0 for

all-cause, cardiovascular, and cancer-related mortality, respectively. After adjusting for age and sex, MS defined with NCEP-ATPIII criteria was associated with a significant increase in all-cause and cardiovascular mortality (HR 1.36, 95% CI, 1.10–1.69 and 1.82, 95% CI, 1.24–2.68, respectively; both $p < .001$), but not in cancer-related mortality (HR 1.11, 95% CI, 0.72–1.70; $p = .63$). When chronic comorbidity and duration of diabetes were entered as covariates into the same Cox regression model, the association of NCEP-ATPIII-defined MS with all-cause and cardiovascular mortality retained its statistical significance (HR 1.23, 95% CI, 1.01–1.53, $p = .048$; and HR 1.69, 95% CI, 1.13–2.54, $p = .011$, respectively). Conversely, IDF-defined MS was not associated with increased mortality after first adjustment for age and sex (data not shown).

Using NCEP-ATPIII criteria, the prevalence of MS was significantly lower in patients ≥ 70 years old than in younger individuals (62.5% vs 69.3%; $p = .005$). Cardiovascular mortality as a function of age in patients stratified for MS status is reported in Figure 1. Cardiovascular mortality increased significantly with age (p for trend $< .001$ for groups with and without MS). The difference in cardiovascular mortality between patients with and without MS was statistically significant up to the age of 70 years. After adjusting for age and sex, HR values of MS for cardiovascular mortality were 3.03 (1.45–6.29), 1.56 (0.91–2.68), and 1.17 (0.42–3.22) ($p = .003$, .11, and .62) in patients ≤ 70 , 71–80, and > 80 years old, respectively. In an alternative model, after adjustment for age group (≤ 70 , 71–80, and > 80 years), sex, and MS, the interaction term Age group \times MS was not significantly associated with all-cause or cardiovascular mortality (data not shown). Similar results were obtained when the two genders were examined separately (data not shown). Among patients ≤ 70 , 71–80, and > 80 years old, HRs of MS for all-cause mortality were 1.36 (0.98–1.90), 1.33 (0.99–1.83), and 1.27 (0.89–2.28), respectively.

DISCUSSION

The present study confirmed the negative impact of MS on cardiovascular risk in a homogeneous population of type 2 diabetic patients (3–10), with an effect possibly greater than that observed in nondiabetic individuals (9). NCEP-ATPIII criteria were superior to IDF criteria in identifying diabetic type 2 patients at increased cardiovascular risk (7).

Compared to middle-aged individuals, the predictive value of MS for cardiovascular mortality appeared to be reduced in persons older than 70 years. This phenomenon cannot be attributed to an inadequate sample size: Indeed, the absolute number of events observed was actually larger at older ages, and the distribution of patients between those with and without MS was more balanced in older than in younger participants, which are both factors potentially improving statistical power. A previous study of older diabetic women detected an increased cardiovascular mortality associated with MS (5). This discrepancy from our results might be due to different characteristics of the background population (North American vs Southern European), whereas our data do not support the hypothesis of gender

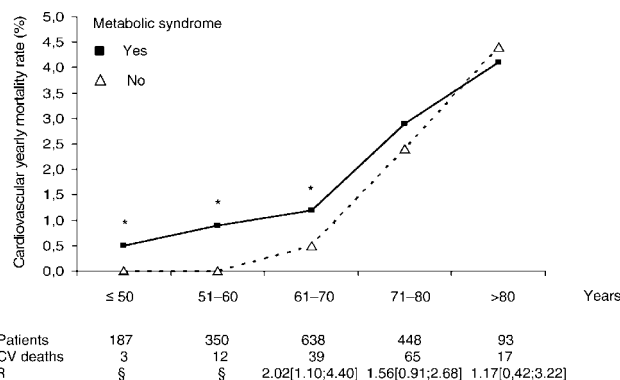


Figure 1. Yearly cardiovascular mortality rate for decades. CV = cardiovascular; HR = hazard ratio at multivariate analysis, after adjusting for age and sex. * $p < .05$; §Not calculable.

differences in the predictive value of MS for cardiovascular mortality.

It could be speculated that individuals with greater genetic susceptibility to the effect of metabolic risk factors on cardiovascular disease have a lower life expectancy, and they could therefore be under-represented in the oldest decades. Furthermore, higher blood pressure levels in older persons without MS, in comparison with younger individuals without MS, could attenuate the independent effect of MS on cardiovascular risk in this age group. It also could be speculated that abdominal adiposity, which is one of the key components of MS, could have a smaller effect on cardiovascular morbidity in old, compared to younger persons (23). In fact, overweight and obesity are well-known risk factors for cardiovascular disease and cancer in young and middle-aged individuals; conversely, the ability to accumulate excess body fat could be a marker of adequate health status in older persons, for whom malnutrition can represent a more relevant threat. Furthermore, older individuals had, on average, lower abdominal adiposity than did younger individuals.

Conclusion

Although MS is associated with increased cardiovascular risk in middle-aged type 2 diabetic patients, the clinical utility of this category in older individuals is questionable.

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