

The Natural History of Patients With Isolated Metabolic Syndrome

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Abstract

Objectives: To define the natural history of patients with isolated metabolic syndrome (MS).

Patients and Methods: Metabolic syndrome is associated with increased risk of cardiovascular mortality. Patients with isolated MS are a subset of patients with MS who do not meet the diagnostic criteria of hypertension (HTN) and diabetes mellitus (DM). Data were collected prospectively on a population-based random sample of 1042 Olmsted County, Minnesota, residents aged 45 years or older who underwent clinical evaluation, medical record abstraction, and echocardiography (visit 1: January 1, 1997, to December 31, 2000). The cohort was subdivided into healthy controls, those with isolated MS, and those with MS with HTN and/or DM groups. After 4 years, patients returned for visit 2 (September 1, 2001, to December 30, 2004). After visit 2, we have a median of 8.3 years of follow-up.

Results: There was a higher incidence of HTN, DM, and obesity in the isolated MS group at visit 2 ($P < .001$) than in healthy controls. Patients with isolated MS did not have significantly higher rates of cardiovascular mortality (hazard ratio [HR], 0.85; 95% CI, 0.23-3.13; $P = .80$) or development of heart failure (HR, 1.29; 95% CI, 0.58-2.73; $P = .53$) compared with healthy controls over 8 years of follow-up after visit 2. However, patients with MS with HTN and/or DM had higher rates of cardiovascular mortality (HR, 2.40; 95% CI, 1.00-5.83; $P = .02$) and heart failure (HR, 2.24; 95% CI, 1.16-4.32; $P = .02$) compared with healthy controls over 8 years of follow-up after visit 2.

Conclusion: Isolated MS was associated with increased risk for the development of HTN, DM, and obesity, but not increased mortality or heart failure over an 8-year period compared with healthy controls. Future studies should determine whether aggressive management of risk factors in isolated MS will prevent progression to MS.

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Metabolic syndrome (MS) is associated with significant cardiovascular morbidity and mortality.¹ It is defined per current Adult Treatment Panel-National Cholesterol Education Program III criteria as the presence of more than 3 of the following 5 characteristics: (1) *abdominal obesity*, defined as a waist circumference of 102 cm (40 in) or more in men and 88 cm (35 in) or more in women; (2) serum triglyceride (TG) level of 150 mg/dL (1.7 mmol/L) or more or drug treatment for elevated TG levels; (3) serum high-density lipoprotein cholesterol (HDL-C) level of less than 40 mg/dL (1 mmol/L) in men and less than 50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C level; (4) blood pressure (BP) value of 130/85 mm Hg or more or drug treatment for elevated BP; and (5) fasting blood

glucose level of 100 mg/dL (5.6 mmol/L) or more or drug treatment for elevated blood glucose level.²

Isolated MS is defined as a subset of patients with MS who do not meet the diagnostic criteria for hypertension (HTN) or diabetes mellitus (DM) and are not on drug treatment for them either.³ Previously, a cross-sectional study in the same cohort as our study found that the prevalence of isolated MS was 21.7% in men and 16.7% in women. Left ventricular (LV) mass index was higher and LV diastolic dysfunction was more prevalent in women with isolated MS than in women without MS.³ No such difference was found in men. However, that study did not delineate long-term mortality and cardiovascular outcomes in patients with isolated MS.



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Our aim for this study was to delineate the natural history, the long-term mortality, and cardiovascular outcomes of patients with isolated MS in the same cohort.

METHODS

This study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center before data collection. In 1997, a random sample of Olmsted County residents aged 45 years or older (predominantly Caucasian) was identified by applying a sampling fraction of 7% within each sex- and age-specific (5 years) stratum. Of the 4203 residents invited, 2042 residents participated at visit 1, which made up the cohort for this study.⁴ These patients underwent clinical evaluation, medical record abstraction, and echocardiography during visit 1 (January 1, 1997, to September 30, 2000). After 4 years, 1402 patients returned for visit 2. Our study cohort included 1042 of the patients (after excluding those who did not have MS and did not meet the criteria for healthy controls) who returned for visit 2 (September 1, 2001, to December 30, 2004).

Subgroup Classification

The study patients were classified into 1 of 3 categories at visit 1: (1) 576 healthy controls, (2) 225 patients with isolated MS, and (3) 241 patients with MS with HTN and/or DM. Metabolic syndrome was defined per current Adult Treatment Panel-National Cholesterol Education Program III criteria by the presence of any 3 of the following 5 characteristics: (1) *abdominal obesity*, defined as a waist circumference of 102 cm (40 in) or more in men and 88 cm (35 in) or more in women; (2) serum TG level of 150 mg/dL (1.7 mmol/L) or more or drug treatment for elevated TG level; (3) serum HDL-C level of less than 40 mg/dL (1 mmol/L) in men and less than 50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C level; (4) BP value of 130/85 mm Hg or more or drug treatment for elevated BP; and (5) fasting blood glucose level of 100 mg/dL (5.6 mmol/L) or more or drug treatment for elevated blood glucose level.² Because we were interested in studying patients with MS with HTN and/or DM, we included only those patients with MS in this group who had BP values of more than

130/85 mm Hg and had HTN diagnosis or were taking antihypertensives for BP criterion and fasting blood glucose (FBG) level of more than 100 mg/dL and had DM diagnosis for elevated FBG criterion.

Isolated MS was defined as a subset of patients with MS with same criteria as MS for central obesity, elevated TG level and low HDL-C level, and BP of more than 130/85 mm Hg but no HTN diagnosis nor taking antihypertensives for BP criterion and FBG level of more than 100 mg/dL and no DM diagnosis for elevated fasting glucose criterion. Healthy controls were patients who (1) did not meet criteria for MS, (2) did not have any cardiovascular disease, and (3) were not taking any cardiovascular medications.

Echocardiography

Two-dimensional, M-mode, and tissue Doppler echocardiography was performed for all patients.⁴ All echocardiograms were interpreted by a single echocardiologist. M-mode echocardiography, quantitative 2-dimensional (biplane Simpson) method, and semiquantitative 2-dimensional visual estimate method were used to quantitate ejection fraction.⁴ Because there was a high correlation between these 3 methods, visual estimate ejection fraction was used in the final interpretation.⁴ To quantitate the LV mass, standard formulas based on M-mode measurement of diastolic dimension and wall thickness were used. Pulsed-wave Doppler examination of mitral flow (before and during Valsalva maneuver) and pulmonary venous inflow, as well as by Doppler tissue imaging of the mitral annulus, was used to measure diastolic dysfunction as previously described.⁵ A 4-point ordinal scale was created to grade diastolic dysfunction as follows: (1) normal; (2) *mild diastolic dysfunction*, defined as abnormal relaxation without increased LV end-diastolic filling pressure (peak early (E) to peak late [atrial] (A) diastolic filling velocity ratio <0.75); (3) *moderate* or "*pseudonormal*" *diastolic dysfunction*, defined as abnormal relaxation with increased LV end-diastolic filling pressure (E/A ratio of 0.75-1.5, deceleration time >140 ms, and 2 other Doppler indices of elevated LV end-diastolic filling pressure); and (4) *severe diastolic dysfunction*, defined as advanced reduction in compliance with restrictive filling (E/A ratio >1.5,

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