Risk Factors for Silent Myocardial Ischemia in High-Risk Type 1 Diabetic Patients

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Coronary artery disease (CAD) is the leading cause of mortality in people with type 1 diabetes. Silent myocardial ischemia (SMI) is common in this population (1), and a large body of evidence attests to the high diagnostic yield of stress myocardial perfusion imaging (MPI) for the prediction of major coronary events (2,3). However, screening all patients with stress MPI is not practical and should be limited to those with a high-risk profile (4). No such profile has been determined in type 1 diabetic patients.

We thus evaluated the clinical and biological variables associated with silent coronary stenosis to determine a high-risk profile of asymptomatic type 1 diabetic patients who should benefit from stress MPI screening.

RESEARCH DESIGN AND METHODS

— All asymptomatic type 1 diabetic patients admitted to our department between January 1999 and June 2002 were considered for SMI screening, using dipyridamol (0.75 mg/kg) combined with exercise on an ergometer bicycle (when feasible) and stress-gated single-photon emission computed tomographic ^{99}Tcm-MIBI imaging if they had at least one of the following conditions: one other major cardiovascular risk factors, age ≥60 years, or peripheral arterial disease (PAD). Patients with known CAD, age ≥80 or <30 years, and dipyridamole contraindications were excluded. Participants were considered to have type 1 diabetes if they had a history of ketosis and started insulin treatment in the 2 years following the diagnosis. SMI was diagnosed in the case of a positive MPI (mean activity <70% of the maximal myocardium activity in at least 3 of 20 segments) and/or a positive exercise electrocardiogram (horizontal or descending ST segment depression >1 mm). None of the patients experienced the clinical symptoms of CAD during the test.

Albuminuria was examined in a 24-h urine sample. Patients also had an eye examination administered by an ophthalmologist within less than a year from the study date. PAD was considered when one or more peripheral arterial pulse was abolished at clinical examination and/or when intermittent claudication and/or a past history of revascularization of the lower limbs was present. None of the patients were receiving either hormonal replacement therapy or oral contraceptives.

Patients with SMI were recommended coronary angiography. Patients with ≥50% narrowing in the luminal diameter for one of the three major epicardial coronary arteries or for the left main coronary artery were considered to have hemodynamically significant coronary artery stenosis (CAS).

We used χ^2 tests, Mann-Whitney *U* tests, and Student's unpaired *t* test for univariate analyses. Because triglycerides had skewed distribution, the variable was dichotomized into normal and elevated levels (≥150 mg/dl). Multivariate analysis was performed using logistic regression analysis, entering those variables found to be statistically significant ($P \leq 0.05$) at the univariate level of analysis while adjusting for sex, age, and diabetes duration.

RESULTS

— A total of 135 type 1 diabetic patients (mean age 52 ± 10 years, 98 men, and mean HbA_{1c} 9.1 ± 1.6%) were included. Thirty of the 135 patients (22%) had SMI (23 had positive MPI, 1 had positive exercise tolerance test, and 6 had both positive MPI and positive exercise tolerance test). Of 30 patients with SMI (80%), 24 underwent coronary angiography. CAS was found in 16 of 24 patients (67%): 1 had three-vessel disease, 6 had two-vessel disease, and 9 had one-vessel disease.

A significant association was found between SMI and family history of CAD, PAD, sex, LDL cholesterol, microangiopathy, and non-HDL cholesterol (Table 1). In multivariate analysis, family history of CAD (odds ratio [OR] 6.9, $P = 0.003$), PAD (3.6, $P = 0.023$), and microangiopathy (3.4, $P = 0.018$) were found to be significant independent predictors for SMI.

The respective positive predictive values (95% CI) of family history of CAD, PAD, and microangiopathy for SMI were 0.50 (0.26–0.74), 0.44 (0.24–0.64), and 0.37 (0.22–0.50), respectively. The negative predictive values (95% CI) were 0.82 (0.75–0.79), 0.83 (0.76–0.90), and 0.87 (0.79–0.94), respectively. For SMI, the positive and negative predictive values of having at least one of these three conditions (74 of 135 patients) were 0.36 (0.26–0.48) and 0.95 (0.90–1.00), respectively. Testing only these 74 patients

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Received for publication 25 February 2004 and accepted in revised form 12 April 2004.

Abbreviations: CAD, coronary artery disease; CAS, coronary artery stenosis; MPI, myocardial perfusion imaging; PAD, peripheral arterial disease; SMI, silent myocardial ischemia.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Comparison of patients without and with SMI*

	No SMI	SMI	*P*
n	105	30	—
Age (years)	52.6 ± 10.1	53.6 ± 10.8	0.660
Men (%)	68	90	0.015
Diabetes duration (years)	24.2 ± 12.8	24.9 ± 11.6	0.803
HbA_{1c} (%)	9.2 ± 1.7	8.9 ± 1.3	0.552
BMI (kg/m^2)	24.1 ± 3.4	25.3 ± 3.6	0.074
Patients reaching 85% of MHR (%)	46	57	0.289
Total cholesterol (mg/dl)	204 ± 40	218 ± 35	0.108
HDL cholesterol (mg/dl)	63 ± 19	59 ± 17	0.316
LDL cholesterol (mg/dl)	122 ± 35	136 ± 33	0.047
Non-HDL cholesterol (mg/dl)	142 ± 38	159 ± 38	0.034
Ratio of total to HDL cholesterol	3.54 ± 1.33	4.03 ± 1.43	0.086
Subjects with triglycerides >150 mg/dl (%)	17	17	0.951
Lipid-lowering medication (%)	14	23	0.237
Systolic blood pressure (mmHg)	133 ± 16	136 ± 16	0.309
Diastolic blood pressure (mmHg)	76 ± 9	76 ± 8	0.805
Antihypertensive treatment (%)	49	67	0.080
Microangiopathy (%)*	31	63	0.001
Retinopathy (%)	21	43	0.019
PAD (%)	13	37	0.004
Family history of CAD (%)	9	30	0.003
Smokers (%)	40	30	0.319
Number of cardiovascular risk factors (%)†			
≤1	24	23	0.343
2	55	43	—
≥3	21	33	—

Data are means ± SD, unless noted otherwise. *Nephropathy and/or retinopathy; †risk factors included family history of CAD, smoking, dyslipidemia (lipid-lowering therapy and/or LDL cholesterol >130 mg/dl and/or triglycerides >150 mg/dl and/or HDL cholesterol <40 mg/dl), and hypertension (antihypertensive treatment and/or blood pressure >130/80 mmHg). MHR, maximal predicted heart rate for age.

would have increased the yield of the screening procedure (the number of tests that need to be done to detect a "true case") from 1 in 4.5 to 1 in 2.7, but would have left three patients with SMI undiagnosed.

CONCLUSIONS — This study allows us to determine a high-risk profile for SMI in type 1 diabetic patients. Family history of CAD, PAD, and microangiopathy were associated with SMI. Family history of CAD was the strongest predictor, increasing the relative odds for SMI sevenfold and confirming the link between hereditary factors and CAD (5,6). PAD also increased the relative odds of SMI by a factor of 3.6. The correlation of SMI with arterial disease involving the lower extremities is a common finding, even in asymptomatic diabetic patients (4,7), and is not surprising because both sites are a common location for the same disease.

Microangiopathy, as assessed by the presence of retinopathy and or nephropathy, was the third factor that was associated with SMI (OR 3.4). Microangiopathy is a sensitive marker for generalized endothelial dysfunction (8), which is known to be associated with thallium scintigraphic defects, suggestive of myocardial ischemia, even in the in the absence of CAS (9). Endothelial dysfunction might thus be an explanation of the elevated proportion of patients with SMI, as assessed by stress MPI, but with nonsignificant CAS at the time of coronary angiography, as was observed in the present study.

In addition, in our population of high-risk but asymptomatic type 1 diabetic patients, the presence of at least one of the above conditions (family history of CAD, PAD, and microangiopathy) showed a high negative predictive value in ruling out SMI (95%), making SMI unlikely in patients who have none of these conditions.

In summary, early identification of diabetic patients with SMI is very important because a significant reduction of mortality and morbidity for cardiovascular diseases can be achieved by the early identification of patients with CAD, for whom revascularization is appropriate (10). The present investigation suggests that family history of CAD, PAD, and microangiopathy could contribute effectively and inexpensively to the identification of asymptomatic diabetic patients, who should benefit from screening by stress MPI. Based on our results, we believe that patients who have none of these conditions have very low chances of benefiting from SMI screening by stress MPI.

Acknowledgments— We thank Prof. J.P. Daures (Laboratory of Epidemiology and Biostatistics, Montpellier, France) for his assistance with statistical analysis.

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