Silent Myocardial Ischemia in Patients With Diabetes

Who to screen

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OBJECTIVE — Silent myocardial ischemia (SMI) is more common in diabetic patients than in the general population. However, the exact prevalence of SMI is not known, and routine screening is costly. The purpose of this 1-year study was to estimate the prevalence of SMI and define a high-risk diabetic population by systematically testing patients with no symptoms of coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS — The criteria for inclusion in this study were age (between 25 and 75 years), duration of diabetes (>15 years for type 1 diabetes, 10 years for type 2 diabetes with no cardiovascular risk factors, and 5 years for type 2 diabetes with at least one cardiovascular risk factor), and absence of clinical or electrocardiogram (ECG) symptoms of CAD. For 1 year, 203 patients were screened, including 28 women and 45 men with type 1 diabetes (aged 41.5 ± 10.9 years, mean duration of diabetes 20.9 ± 7.7 years [mean ± SD]) and 61 women and 69 men with type 2 diabetes (aged 60.7 ± 8.7 years, duration of diabetes 16.5 ± 7.1 years). Exercise ECG was the first choice for screening method. If exercise ECG was not possible or inconclusive, thallium myocardial scintigraphy (TMS) with exercise testing and/or dipyridamole injection was performed. If any one of these tests was positive, coronary angiography was carried out and was considered to be positive with a stenosis of ≥50%.

RESULTS — Positive screening results were obtained in 32 patients (15.7%). Coronary angiography demonstrated significant lesions in 19 patients (9.3%) and nonsignificant lesions in 7 patients (1 false-positive result for exercise ECG and 6 false-positive results for TMS). Coronary angiography was not performed in six patients. All but 3 of the 19 patients (15 men and 4 women) in whom silent coronary lesions were detected presented with type 2 diabetes. The main differences between the 16 type 2 diabetic patients presenting with coronary lesions and the type 2 diabetic patients without SMI were a higher prevalence of peripheral macroangiopathy (56.2 vs. 15.1%, respectively, $P < 0.01$) and a higher prevalence of retinopathy ($P < 0.05$). No correlation was found between SMI and duration of diabetes, HbA_{1c} level, renal status, or cardiovascular risk factors except for family history of CAD.

CONCLUSIONS — The results of this study allowed us to determine a high-risk group for SMI in the diabetic population. SMI with significant lesions occurs in 20.9% of type 2 diabetic male patients who are totally asymptomatic for CAD. Based on these findings, we recommend routine screening for male patients in whom the duration of type 2 diabetes is >10 years or even less when more than one cardiovascular risk factor is present.

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Abbreviations: ALFEDIAM, Association de Langue Française pour l'Etude du Diabète et des Maladies Métaboliques; CAD, coronary artery disease; ECG, electrocardiogram; SMI, silent myocardial ischemia; TMS, thallium myocardial scintigraphy; WHO, World Health Organization.

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

Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with diabetes (1,2). More than half of all diabetic patients die from coronary artery insufficiency (3,4). CAD is usually more advanced at the time of diagnosis and has an unfavorable prognosis in diabetic patients (5,6). Late diagnosis of CAD may be explained by the presence of silent myocardial ischemia (SMI). Angiographically proved SMI is more frequent in patients with diabetes than in nondiabetic subjects (probably because of diabetic neuropathy). SMI has a reported prevalence ranging from 10 to 20% in diabetic populations versus from 1 to 4% in nondiabetic populations (7–14). There is no single definition of SMI because some authors include patients without clinical symptoms but with a resting electrocardiogram (ECG) that indicates a previous infarction or angina pectoris, some authors include patients with atypical clinical symptoms, and some authors restrict SMI to patients without any symptoms and with positive functional testing or angiographically documented CAD. In fact, by allowing early treatment, screening for SMI could lower the death rate from CAD in diabetic subjects.

Various screening methods for SMI are available, including continuous 24- or 48-h heart monitoring with the Holter technique, exercise ECG, and thallium myocardial scintigraphy (TMS) with exercise testing and/or dipyridamole injection. Although some controversy exists regarding stress ultrasound cardiography, evaluation of these techniques (15) has indicated that Holter monitoring is poorly sensitive, whereas exercise ECG is fairly specific and sensitive. TMS represents a satisfactory but costly alternative for patients who are not eligible for exercise ECG.

Routine screening for SMI in all patients with diabetes is debatable for several reasons. The prevalence of SMI is variable but low. There is no consensus concerning screening methods and interpretation of findings, so the cost-effectiveness of screening is then poor. But, although the benefits of appropriate treatment are not proven in people with diabetes, they are as likely as in

Table 1—*Clinical characteristics of the 203 patients*

Characteristics	Type 1 diabetes	Type 2 diabetes
n	73	130
Sex (M/F)	45/28	69/61
Age (years)	41.5 ± 10.9	60.7 ± 8.7
BMI (kg/m²)	23.8 ± 2.4	27.6 ± 4.6
Duration of diabetes (years)	20.9 ± 7.7	16.5 ± 7.1
Treatment		
Oral treatment (%)	—	46.2
Insulin (%)	100	53.8
HbA_{1c} (%)	8.9 ± 2.5	9.4 ± 1.5
Retinopathy (%)	68.5	50
Nephropathy (%)	24.6	39.3
Microalbuminuria (%)	13.7	27.7
Proteinuria (%)	10.9	10.8
Macroangiopathy (%)	0	20.9
Smokers (%)	31.5	31.2
Dyslipidemia (%)	17.8	62.8
Hypertension (%)	27.4	57.3
Family history of CAD (%)	12.3	8.6
≥1 CV risk factor (%)	63.0	96.1
≥2 CV risk factors (%)	30.1	53.1
≥3 CV risk factors (%)	2.8	9.2

Data are means ± SD or % of affected patients. CV, cardiovascular.

symptomatic CAD. Thus, based on current knowledge, it appears necessary to define a high-risk population in which screening is indicated. Current Association de Langue Française pour l'Etude du Diabète et des Maladies Métaboliques (ALFEDIAM) guidelines (16) recommend screening for SMI in diabetic patients who present with peripheral arterial disease, proteinuria, and/or major cardiovascular risk factors or are aged >65 years.

The purpose of this 12-month cross-sectional study, which was conducted according to ALFEDIAM criteria, was to further define a high-risk population requiring screening by assessing the prevalence of angiographically documented SMI in a group of totally asymptomatic diabetic patients. Screening was performed by using exercise ECG and TMS. Coronary angiography was performed when any noninvasive screening test was positive. Diagnosis of SMI was confirmed when coronary angiography demonstrated significant coronary artery stenosis.

RESEARCH DESIGN AND METHODS

Patients

Between May 1996 and April 1997, all patients meeting the following inclusion criteria (established on the basis of ALFEDIAM guidelines) were asked to undergo screening for SMI: type 1 diabetes (C-peptide negative, age at diagnosis <40 years, ketosis prone) or type 2 diabetes (according to World Health Organization [WHO] criteria [17]); age between 20 and 75 years; absence of clinical or ECG symptoms of CAD; duration of type 1 diabetes >10 years for patients >40 years of age and >15 years for patients <40 years of age; and duration of type 2 diabetes with or without insulin treatment >10 years for patients with no major cardiovascular risk factors or longer than 5 years for patients with at least one major cardiovascular risk factor.

Evaluation of complications included fundoscopy to detect retinopathy followed if necessary by fluorescein angiography and testing of creatinine clearance and 24-h albuminuria levels to detect nephropathy. Peripheral macroangiopathy was defined as stenosis of ≥40% detected by ultrasound visualization of the vessels of the neck and lower extremities or previous history of vascular surgery. Major cardiovascular risk factors including smoking, dyslipidemia, hypertension, and family history of CAD (aged <65 years) were recorded. Dyslipidemia was defined as a total serum cholesterol level >6.0 mmol/l and/or triglyceride level >2.5 mmol/l or hypolipemic treatment. Hypertension was defined according to WHO criteria (>160–195 mmHg) or treatment with an antihypertensive drug. Clinical findings are summarized in Table 1.

Methods

Screening for SMI (Fig. 1) was performed on clinically asymptomatic patients presenting with a normal resting ECG. First intention screening consisted of exercise ECG. If exercise testing was successfully completed and findings were negative, SMI was ruled out. If exercise testing was contraindicated or inconclusive, second intention screening was performed with TMS. If the findings of either exercise ECG or TMS were positive, coronary angiography was performed to confirm SMI.

Exercise ECG was performed by using a Marquette system with 12 standard leads

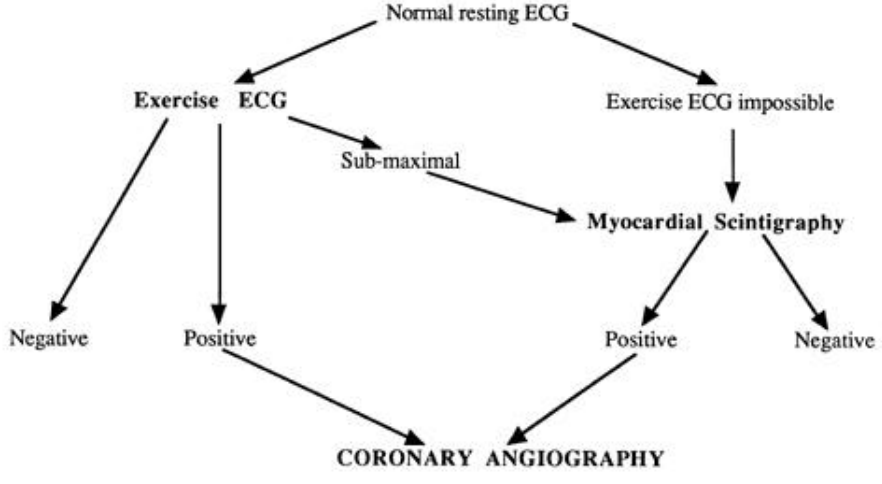

Figure 1—*Screening protocol.*

on an electrically braked bicycle with increments of 30 W every 3 min. In a few cases, testing was carried out on a treadmill with the modified Bruce protocol. The exercise test was considered positive if there was a horizontal downsloping or upsloping ST-segment depression of at least 1 mm occurring at least 0.08 s after the J point. The test was considered negative when the heart rate reached the maximal predicted exercise heart rate (calculated with the Astrand formula, 220 − age) without a change in the ST segment. The exercise test was submaximal and uninterpretable if the heart rate was <95% of the maximal predicted heart rate. The criteria for interrupting exercise testing were fatigue, precordial pain, dyspnea, decrease in heart rate or arterial pressure, exertional arterial hypertension, signs of insufficient cardiac output, major ventricular arrhythmia, conduction abnormalities, and downsloping ST segment.

TMS was performed in association with exercise testing and/or dipyridamole injection. Contraindications for dipyridamole injection were asthma and chronic obstructive bronchitis. Early imaging was made 5 min after injection of the radionuclide, and late imaging was made at 4 h. Five regions of the left ventricle were defined: anterior, apical, inferior/posterior, lateral, and septal. TMS was considered to be positive for SMI when scans showed fixed (suggestive of sequelae of myocardial infarction) or transient uptake defects on delayed imaging.

Exercise ECG and TMS were performed by the same observer for all subjects. Both tests were performed after complete discontinuation of medications that have potential antiangina effects (2 days for β-blockers, 1–3 days for calcium-channel blockers according to the medication).

Results of coronary angiography were interpreted by two observers who were unaware of the clinical presentation of the patients. Stenosis was scored in terms of percentage of cross-sectional narrowing. Coronary artery stenosis of ≥50% was considered significant.

Statistical analysis

Results are means ± SD. Means were compared with Student's *t* test, and percentages were compared with the χ^2 test. Differences with probability values <0.05 were considered significant.

RESULTS — By using our criteria, 203 patients were screened: 73 presenting with type 1 diabetes and 130 presenting with type 2 diabetes (including 70 insulin-treated patients).

First intention exercise ECG was feasible in 125 patients (61.5% overall), including 82% of patients with type 1 diabetes and 50% of patients with type 2 diabetes. The remaining 78 patients (38.5% overall), mainly patients with type 2 diabetes, were considered ineligible for exercise testing. Results of exercise ECG were positive in 12 of 125 (9.6%) patients. Exercise testing could not be completed in 27 of 125 (26.1%) patients, including 12 patients with type 1 diabetes and 15 patients with type 2 diabetes. In these 27 patients, second intention TMS was performed.

TMS was carried out in 105 patients, including 78 as a primary procedure and 27 as a secondary procedure. Results were positive in 20 patients (19%).

Thus, screening tests were suggestive of functional SMI in 32 patients (15.7%). Coronary angiography was performed in 26 of these patients, and the other 6 patients declined the procedure. Coronary stenosis was considered significant in 19 patients (9.6%) and not significant in 5 patients. In the remaining two patients, angiography was considered normal. No complications occurred during any of these 26 procedures. Patients who refused angiography did not differ appreciably from the overall population regarding severity of diabetes or cardiovascular risk factors.

The prevalence of positive screening tests and of angiographically documented SMI varied according to type of diabetes and sex (Table 2). In the type 1 diabetes group, 8 of 73 patients (10.9%), including 4 men and 4 women, had positive screening tests. Coronary angiography was performed in six patients and demonstrated significant coronary stenosis in three of these patients (4.2% overall). These patients included two women and one man, all with longstanding diabetes (duration of 25, 28, and 42 years) and severe retinopathy. In the remaining cases, angiography showed nonsignificant lesions in three cases. In the type 2 diabetes group, 24 of 130 patients (18.4%), including 18 men and 6 women, had positive screening tests. Coronary angiography demonstrated significant stenosis in 14 men and 2 women. Of the remaining patients, four presented nonsignificant lesions, and four refused to undergo angiography. Comparison of the four subgroups defined on the basis of type of diabetes and sex revealed that the prevalence of SMI was significantly higher among male patients with type 2 diabetes. Results were not affected by whether SMI was defined on the basis of functional or anatomical criteria (see Table 2).

Table 2—*Results of screening according to diabetes type and sex*

	Positive functional testing	Coronary artery stenosis
Type 1 diabetes (%)	10.9	4.2
Male	8.8 (4/45)	2.3 (1/44)
Female	14.3 (4/28)	7.4 (2/27)
Type 2 diabetes (%)	18.4	12.7
Male	26.1 (18/69)	20.9 (14/67)*
Female	9.8 (6/61)	3.4 (2/59)

*Significant difference between men with type 2 diabetes and other groups.

Table 3 compares patients presenting with type 2 diabetes with or without significant coronary stenosis. A significant correlation was observed between coronary stenosis and male sex, retinopathy, family history of CAD, and above all, arterial disease and a high number of major cardiovascular risk factors. Conversely, no difference was observed between the two groups regarding age, BMI, duration of diabetes, type of treatment, or HbA_{1c} level. The incidence of nephropathy was not significantly different in the two groups. A high number of risk factors was significantly associated with SMI.

The positive predictive value of screening tests can be estimated on the basis of the results of coronary angiography. Exercise ECG was positive in 12 of the 98 cases (12.2%) in which tests were successfully completed. TMS was positive in 20 of 105 patients (19%). Of 26 patients with positive screening tests, coronary angiography demonstrated significant lesions in 19 patients (76%). Thus, there were seven false-positive results, including one in the exercise ECG group and six in the TMS group (including two women). The positive predictive value was 90% for exercise ECG and 62.5% for TMS.

Table 3—*Clinical characteristics of patients with type 2 diabetes with or without silent coronary stenosis*

	With stenosis	*P* value	Without stenosis
n	16	—	110
Sex (M/F)	14/2	<0.01	53/57
Age (years)	62.3 ± 9.2	NS	60.3 ± 8.7
BMI (kg/m²)	26.4 ± 3.0	NS	27.6 ± 4.8
Duration of diabetes (years)	17.5 ± 7.1	NS	16.2 ± 6.9
Treatment			
Oral treatment (%)	43.7	NS	46.4
Insulin (%)	56.3	NS	53.6
HbA_{1c} (%)	9.6 ± 1.8	NS	9.4 ± 1.7
Retinopathy (%)	75	<0.05	45.4
Nephropathy (%)	50	NS	38.2
Microalbuminuria	37.5	NS	28.2
Proteinuria	12.5	NS	10
Macroangiopathy (%)	56.2	<0.01	15.1
Smokers (%)	43.7	NS	29.6
Hypertension (%)	56.2	NS	57.8
Dyslipidemia (%)	68.7	NS	63.3
Family history of CAD (%)	25	<0.05	5.5
≥2 CV risk factors (%)	56.2	NS	40.7
≥3 CV risk factors (%)	25	<0.05	7.2

Data are means ± SD or % of affected patients. CV, cardiovascular.

The positive predictive value of screening also varied according to the type of diabetes and sex. The positive predictive value was excellent for men with type 2 diabetes (87.5%). In comparison, the positive predictive value was 50% for men with type 1 diabetes, 66% for women with type 1 diabetes, and 50% for women with type 2 diabetes.

After the screening tests, patients with significant CAD were treated with angioplasty (with or without stenting) in 7 of 19 cases. In the remaining 12 patients, only medical treatment was performed because of various concurrent factors, including poor run-off, distal location of lesions, occlusion, and calcification. Coronary artery bypass was not performed for any patient in this study.

CONCLUSIONS — Screening tests via exercise ECG and TMS indicated that the prevalence of functional SMI was 15.7% in this series of 203 diabetic patients recruited consecutively during a 12-month period on the basis of wide inclusion criteria. The prevalence of angiographically confirmed SMI was 9.3%. A review of the literature shows prevalence rates ranging from 9 to 57% (8,14,18,19). This broad range is probably due to differences in the populations studied (e.g., age of patients, duration of diabetes, inclusion or exclusion of patients with high risk factors or symptoms of CAD, and definition of SMI). The broad range may be because of the screening techniques used (e.g., resting ECG, exercise testing, stress ultrasound, scintigraphy, or coronary angiography) and the diagnostic criteria (e.g., definition of positive exercise tests and confirmation by coronary angiography). In recent studies in which positive noninvasive screening tests were confirmed by coronary angiography, the prevalence of SMI with significant coronary stenosis was similar to our study: 9% according to Koistinen (8), 12% according to Naka et al. (12) in type 2 diabetes (which is the same as in our type 2 diabetes subgroup), and 13% according to Paillole et al. (11). On the other hand, the prevalence of positive noninvasive tests varies widely in the literature. Our positivity rate is similar to those of the Milan study (14) in which 12% of exercise tests were positive but lower than those of Koistinen (8) and Naka et al. (12), who reported 29% and 31% positive exercise tests, respectively. However, although we observed good concordance between noninvasive tests and coronary angiography (76% true positive), the predictive value of exercise testing in the two latter studies was low. A likely explanation for this difference is the choice of very strict criteria for positive tests.

The prevalence of angiographically documented SMI varied regarding type of diabetes and sex, with a significantly higher risk observed in men with type 2 diabetes. The difference in type 1 diabetic men may be related to the increased age of people with type 2 diabetes (59.9 ± 8 vs. 40.2 ± 10 years). Besides age, this group displays a more frequent association to other major cardiovascular risk factors. Because of the small number of patients in each subgroup, our results must be interpreted with caution. Comparison with previous studies is difficult because patients with type 1 and type 2 diabetes have often been mixed. However, in the Milan study (14), which involved only subjects with type 2 diabetes, the prevalence of positive exercise tests was similar to ours (12%), and a correlation was observed with male sex. Naka et al. (12) also found a higher prevalence in male patients with type 2 diabetes. Koistinen (8) reported no differences according to type of diabetes and sex. The positive predictive value of the screening test after excluding patients who declined coronary angiography was a satisfactory 76% overall and rose to 87% for male patients with type 2 diabetes. As expected, false-positive results were more likely with TMS. Two false-positive results were observed in women, and anterior defects have been related to mammary interposition (20). The four remaining false-positive results could be because of the presence of microvascular disease (21).

In type 2 diabetes, besides male sex, retinopathy, peripheral artery disease, and family history of CAD were predictive factors for SMI. The size of our population may have been too small to make conclusions about the other covariates studied. Correlation with retinopathy was not observed in the Milan study (14) probably because severe retinopathy was considered to be an exclusion factor. Conversely, such an association was noted by Naka et al. (12). Correlation of SMI with arterial disease involving the lower extremities or supra-aortic vessels is not surprising because both sites are common locations for the same disease. Our results confirm the high prevalence of SMI observed by Nesto et al. (18) in diabetic patients with arteriopathy. Concerning nephropathy, we could have expected to find a correlation because microalbuminuria and proteinuria are classic associations with cardiovascular mortality and symptomatic CAD (22–25), but in fact, four previous studies have evaluated the relationship between

SMI and nephropathy with conflicting results (13,14,26,27).

Regarding major cardiovascular risk factors, a correlation was noted with the total number of factors and family history of CAD. This has been poorly studied in the literature. Correlations with major cardiovascular risk factors are absent (12) or weak, with hypertension and hyperlipidemia associated with SMI in men only (14) or found in the population with peripheral vascular disease (18). An increased prevalence of SMI in patients with multiple cardiovascular risk factors was noted in this last study.

In conclusion, the results of this study (which was conducted in a large consecutively recruited population) show that one of five asymptomatic male patients with type 2 diabetes (20.9%) presents SMI with significant angiographically documented coronary stenosis. This finding, along with the high positive predictive value of functional testing, indicates that routine screening for SMI would be useful in this patient subgroup. For better cost-effectiveness, screening could be limited to patients with a duration of diabetes >10 years or even less when at least one major cardiovascular risk factor is present. Further studies are needed to define treatment modalities for patients with positive screening tests. In women with type 2 diabetes and patients with type 1 diabetes, selective rather than routine screening may be indicated in patients with a long duration of diabetes and severe retinopathy or peripheral artery disease associated with several major cardiovascular risk factors. Finally, the high prevalence of SMI in type 2 diabetic men emphasizes the need for a more active strategy to prevent CAD in these patients.

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