Endocrine, *vol. 27, no. 3, 213–217, August 2005* 0969–711X/05/27:213–217/$30.00

Silent Myocardial Ischemia Is Associated with Autonomic Neuropathy and Other Cardiovascular Risk Factors in Type 1 and Type 2 Diabetic Subjects, Especially in Those with Microalbuminuria

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The prevalence of silent myocardial ischemia (SMI) seems to be above average in diabetic subjects. As routine screening is costly, identifying high-risk populations is mandatory. This study aimed to estimate the prevalence of SMI in diabetic subjects and in controls and to define the diabetic population at risk. We studied 353 asymptomatic caucasian subjects (217 with diabetes and 136 controls matched by age, sex, and cardiovascular risk factors) with normal resting ECG. The diabetic group included 39 type 1 and 178 type 2 diabetics (age 57 ± 11 yr, 162 males/55 females). Subjects performed the Treadmill Test (TT) and, when abnormal, underwent single-photon emission computed tomography (SPECT) with exercise testing or dipyridamole injection. Coronary angiography was performed if the SPECT was suggestive of ischemia. TT was positive in 16 (8.5%) diabetics: 3 with type 1 and 13 with type 2. No controls had positive TT. SPECT was performed in 13 subjects and was positive in 10; angiography was performed in 7 and identified significant lesions in all cases. Patients with SMI were older and had a higher prevalence of autonomic neuropathy, hypertension, and dyslipidemia than those without. Microalbuminuria was also higher in the SMI group (613 ± 211 vs 72 ± 245 mg/d; $p < 0.05$). We conclude that diabetic patients aged over 60 with autonomic neuropathy and other cardiovascular risk factors should be screened for the presence of SMI especially if they have increased microalbuminuria.

Key Words: Silent myocardial ischemia; coronary heart disease; diabetic complications; autonomic neuropathy; microalbuminuria.

Introduction

Coronary heart disease (CHD) is the main cause of mortality in both type 1 and type 2 diabetes. This is because the prevalence of coronary atherosclerosis is higher in diabetic subjects, the mortality related to myocardial infarction is also higher than in non-diabetics and, in addition, the symptomatology of CHD is often not typical or absent. Silent myocardial ischemia (SMI) seems to be more prevalent in diabetics than in non-diabetics *(1)*, and the presence of autonomic neuropathy has been hypothesized as a possible explanation *(2)*. Owing to the difficulty of screening all diabetic subjects for the presence of SMI, it is very important to establish subgroups of patients with a high risk of SMI. Stress myocardial perfusion imaging has been postulated as the best technique for SMI screening *(3)*. However, the technique is complex and expensive for large populations. On the other hand, the classic Treadmill Test (TT), easier to implement and cheaper, has not shown optimal sensitivity and specificity for CHD diagnosis *(4)*. The objectives of the present study were first, to determine the prevalence of SMI in a caucasian population of Spanish type 1 and type 2 diabetic subjects compared with that observed in a non-diabetic control group with the same prevalence of classic risk factors for CHD; second, to identify the distinctive features of subjects with diagnoses of SMI in order to define a high-risk subpopulation; and third, to assess the real utility of TT in SMI screening in diabetic patients.

Results

One hundred and eighty-eight subjects with diabetes and 130 controls achieved at least 85% of the theoretical maximal heart rate predicted for their age (the threshold required for the TT to be valid) so, 29 diabetics (13.3%) and 6 controls (4.4%) were excluded from the study. All controls (100%) had negative TT. However, 16 diabetic patients (8.5%): 3 type 1 (8%) and 13 type 2 (8.6%) had an electrically positive TT, in all cases without chest pain or other symptoms. A myocardial SPECT was performed in only 13 subjects, 3 of whom were considered normal in the absence of perfusion defects; in the other 10, myocardial ischemia

Received April 28, 2005; Revised May 24, 2005; Accepted June 8, 2005.
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Table 1
Blood Pressure and Biochemical Differences Found Between Controls and Diabetic Subjects

	Diabetic subjects (n = 217)	Type 1 (n = 39)	Type 2 (n = 178)	Control subjects (n = 136)
Glucose (mg/dL)	153 ± 52	174 ± 79	149 ± 43*	90 ± 10**
HbA_{1c} (%)	7.1 ± 1	7.4 ± 1	6.8 ± 1	—
Cholesterol (mg/dL)	202 ± 34	209 ± 38	201 ± 33	213 ± 40**
HDL-c (mg/dL)	54 ± 17	66 ± 18	52 ± 15*	53 ± 14
LDL-c (mg/dL)	125 ± 33	126 ± 35	125 ± 32	136 ± 33**
Tryglicerides (mg/dL)	122 ± 70	87 ± 80	130 ± 65*	121 ± 79
Systolic BP (mmHg)	134 ± 16	125 ± 13	137 ± 16*	129 ± 15**
Diastolic BP (mmHg)	79 ± 9	75 ± 8	80 ± 8*	79 ± 9

*$p < 0.05$ between type 1 and type 2 diabetic subjects. **$p < 0.05$ between whole group of diabetic patients and the control group.

was confirmed. In other words, 77% of subjects who had SPECT were positive, suggesting that 23% of the TT results were false positives [positive predictive value (PPV) 77%]. In the seven cases with severe perfusion defect, subjects underwent a coronary angiography, which confirmed the presence of significant coronary lesions in all cases. In fact, five of these subjects were scheduled for revascularization surgery and the two others remained under medical treatment when revascularization surgery was ruled out. Of the three patients with abnormal TT who did not undergo myocardial SPECT, one died (non-cardiac death) and two had a normal second TT and decided not to continue the study.

Table 1 shows the biochemical differences between controls and diabetics. Surprisingly, the lipid profile was better in the diabetes group (higher concentrations of total cholesterol and LDL-c) probably due to the more intense therapeutic approach. However, systolic blood pressure, and, obviously, fasting glucose values, were higher in the group with diabetes.

Comparisons of patients with positive and negative TT are shown in Table 2. Patients with positive TT were older and had higher systolic blood pressure and microalbuminuria. In addition, the prevalence of microangiopathic complications (retinopathy, nephropathy, peripheral neuropathy) was higher, as was the prevalence of peripheral vascular disease, autonomic neuropathy, dyslipidemia, and hypertension. No differences were found related to sex, lipid profile, diabetes duration and treatment, type of diabetes, glycated hemoglobin concentrations, diastolic blood pressure, or smoking habit. The presence of hypertension (OR 1.4, 95% CI 2.6–12), dyslipidemia (OR 0.5, 95% CI 1.3–5.9), autonomic neuropathy (OR 6.5, 95% CI 1.3–7.9), and peripheral vascular disease (OR 0.96, 95% CI 1.2–9) were independently associated with positive TT in the multivariate analysis ($p < 0.05$) (Table 3). Patients in the highest quartile of microalbuminuria (>23.7 mg/24 h) were more likely to have a positive TT (OR 3.2, 95% CI 2.0–8.0) than those in the middle or lowest quartiles.

Discussion

In our study the prevalence of SMI screened using the TT was 8% in type 1 and 8.6% in type 2 diabetics consecutively attended at our clinic. The global prevalence was 8.5%. The prevalence of angiographically confirmed SMI was 3.7%. Reports of SMI prevalence in the literature range from 9% to 57% *(5–7)*. This broad range is the consequence of differences in study populations, in techniques used for the screening, the diagnostic criteria used, and the type of diabetes analyzed *(8,9)*. In general, our prevalence is lower than that reported elsewhere. In the Milan study the prevalence of SMI using the TT was 12% *(5)* and in other studies it was as high as 29% or 31%. Possible explanations are the relatively low rate of diabetic complications in our population, the good metabolic control, and the relatively good control of blood pressure and lipids. Another explanation may be the strict criteria applied for regarding the TT and the angiographic coronary exam as positive. We considered stenosis ≥70% as significant, whereas other series use a threshold of ≥50% *(7)*. In our study, the TT presented false positive results, while the SPECT had a PPV of 77%, slightly higher than the figure of 60% published in the literature *(7)*.

None of our controls had a positive TT. SPECT and angiography were not performed, so the true prevalence of SMI is unknown, but our findings suggest that SMI is indeed more frequent in diabetic subjects. Some reports have found a higher prevalence of SMI induced by exercise in diabetics than in non-diabetics *(10)*. However, a relatively recent meta-analysis concluded that the excess of SMI in diabetic subjects is the result of the global excess of CHD in these patients *(11)*. An interesting aspect of the present study, and one that supports the hypothesis of a higher SMI in the dia-

Table 2
Differences Observed Comparing Diabetic Subjects with a TT Suggesting Myocardial Ischemia and Those with a Normal TT

	Diabetic subjects with positive TT (n = 16)	Diabetic subjects with negative TT (n = 172)	p
Age (yr)	64 ± 7	57 ± 11	<0.05
Males/females	13/3	133/39	ND
Type of diabetes (1/2)	3/13	34/138	ND
Insulin/oral drugs (%)	8/8	74/98	ND
Diabetes duration (yr)	18 ± 13	14 ± 10	ND
HbA1c (%)	6.7 ± 1	6.9 ± 1	ND
Cholesterol (mg/dL)	199 ± 36	203 ± 34	ND
HDL-c (mg/dL)	50 ± 14	55 ± 17	ND
LDL-c (mg/dL)	126 ± 26	125 ± 33	ND
Tryglicerides (mg/dL)	120 ± 46	122 ± 72	ND
Microalbuminuria (mg/d)	613 ± 211	72 ± 245	<0.01
Retinopathy (%)	50	33.7	<0.01
Nephropathy (%)	31.2	19.1	<0.05
Peripheral neuropathy (%)	50	31.3	<0.01
Autonomic neuropathy (%)	33.3	4.7	<0.01
Peripheral vascular disease (%)	37.5	12.8	<0.05
Hypertension (%)	68.7	53.4	<0.05
Dyslipidemia (%)	62.5	47.6	<0.05
Active smokers (%)	23	26	ND
Systolic BP (mmHg)	141 ± 13	134 ± 16	<0.05
Diastolic BP (mmHg)	78 ± 8	79 ± 9	ND

Table 3
Multiple Regression Analysis of Factors Associated with the Presence of a Positive TT

	Odds ratio (95% CI)	p value
Autonomic neuropathy	6.5 (1.3–7.9)	<0.05
Hypertension	1.4 (2.6–12)	<0.05
Dyslipidemia	0.5 (1.3–5.9)	<0.05
Peripheral vascular disease	0.96 (0.89–9)	<0.05

betic population, is that our control group was of the same age and had the same prevalence of other risk factors (hypertension and dyslipidemia) as the diabetic group. And, curiously, the control group includes more active smokers, which increases the risk for CHD in this group.

No differences were found between sexes with regard to TT results. The data on this subject are inconsistent: some studies found a correlation between SMI and male sex *(5, 12)*, but others found no sex-related differences *(13)*. In our study, patients with positive TT had a higher prevalence of complications such as retinopathy, nephropathy, peripheral neuropathy, and also autonomic neuropathy. No differences were found in diabetes duration or HbA1c levels. In summary, the more complications, the higher the level SMI, regardless of the duration of diabetes. The patients with greater complications may have had poorer metabolic control during the disease. We cannot confirm this, because the HbA1c levels were recorded for the last time before the TT, but multivariate analysis associated the classic risk factors (hypertension and dyslipidemia), autonomic neuropathy, microalbuminuria, and peripheral vascular disease with positive TT. Some studies have found associations of SMI and retinopathy and others have not *(5,12)*, but it is well known that patients with established nephropathy and those with early stages of microalbuminuria are a high-risk population for cardiovascular disease independently of the classical cardiovascular risk factors. However, our association of SMI and microalbuminuria has been reported only in a few studies *(14–16)*. Our findings are consistent not only because patients with abnormal TT had higher microalbuminuria but also because those with higher microalbuminuria had a greater risk of a positive TT than those with lower concentrations.

The association between SMI and autonomic neuropathy has often been hypothesized *(17,18)*. Recently, the DIAD Study *(11)* found a strong association between abnormal Valsalva test results and SMI *(19)*. In our series, patients with SMI had a higher prevalence of autonomic neuropathy, whether or not they had other diabetic complications. The relationship between SMI and peripheral vascular disease is well described in the literature—not surprisingly,

Table 4
Clinical Differences Found Comparing
the Group of Diabetic Subjects with the Control Group

	All diabetic subjects (n = 217)	Type 1 (n = 39)	Type 2 (n = 178)	Control subjects (n = 136)
Age (yr)	57 ± 11	43 ± 10	61 ± 8	55 ± 8
Males/females	162/55	23/16	139/39	102/34
Hypertension (%)	54	15	64	50
Dyslipidemia (%)	48	31	51	47
Smokers (%)	24	26	25	39
BMI (kg/m^2)	27 ± 3	25 ± 3	28 ± 3	27 ± 4
Diabetes duration (yr)	18 ± 11	23 ± 11	13 ± 10	—

because both sites are common locations for the same disease *(20)*. Another interesting finding in our study was the association between SMI and classic risk factors for cardiovascular disease such as hypertension and dyslipidemia. In some studies this association has been found only in men *(5)* or only in patients with peripheral vascular disease *(21)*. Other studies only found a higher SMI prevalence in patients with multiple cardiovascular risk factors *(7,22)*. The relationship with hypertension is supported also by the finding of a higher systolic blood pressure in subjects with positive TT.

In summary, our study supports the hypothesis that SMI is more frequent in diabetic population. As it is impossible to screen all diabetic patients, we recommend screening in those with multiple diabetic complications (especially those with autonomic neuropathy and peripheral vascular disease) and other risk factors for CHD. Special attention should be paid to subjects with microalbuminuria, which was the only analytical parameter associated with SMI. The TT could be a good first-step method for screening, although its PPV is suboptimal *(23)*. SPECT proved its high specificity in this study, and appears to be the best screening technique available. It should also be applied in subjects who do not achieve the heart rate needed for a valid TT.

Material and Methods

Three hundred and fifty-three subjects were screened for the presence of SMI. This group comprised 217 diabetic patients (39 type 1 and 178 type 2) attended at our clinic and enrolled consecutively, and a control group of 136 nondiabetic subjects matched by age and sex obtained from the periodical health check-ups carried out by companies. The prevalence of classic risk factors for CHD (hypertension, dyslipidemia) was the same in the two groups with the exception of smoking, which was higher in controls. The inclusion criteria were absence of CHD symptoms and normal resting ECG. Subjects with a previous history of CHD were excluded. Subjects with blood pressure >130/80 mmHg or under antihypertensive treatment were defined as hypertensive, dyslipidemia was defined in those with total cholesterol >200 mg/dL, LDL-c >100 mg/dL, triglycerides >150 mg/dL, HDL-c <40 mg/dL, or under lipid-lowering therapy. Table 4 shows the clinical features and differences between the groups. Clinical data (age, BMI, blood pressure immediately prior to the TT, presence of classic risk factors), data concerning diabetes in the diabetic group (type and treatment, diabetes duration, micro/macroangiopathic complications), and also biochemical data obtained in the month before the TT (glucose, glycated hemoglobin, lipid profile, microalbuminuria) were recorded. The presence of retinopathy was confirmed by an ophthalmologist after an eye revision in the month before the TT. Nephropathy was defined as the presence of microalbuminuria >30 mg/24 h in at least two examinations in the absence of urinary infection in the month before TT. Peripheral neuropathy was defined as the presence of an abnormal nerve conduction study, or an abnormal clinical examination (in the month before TT) which included vibratory threshold perception, pain and light touch assessed with a 128 Hz tuning fork, a pin, and 10-g monofilament. Cardiovascular autonomic neuropathy was evaluated with the Cardionomic system, 1 mo before TT and defined as the presence of at least two abnormal scores on the study's three tests: heart rate variability during deep breathing, blood pressure response to standing up, and lying to standing R-R variability. Peripheral vascular disease (PVD) was defined as previous revascularization surgery, an abnormal Doppler or angiographic exam, or when the patient was taking medication prescribed by a vascular surgeon.

All subjects performed a Treadmill Test (TT) following the Bruce protocol and were evaluated in all cases by the same cardiologist. The TT was considered suggestive of ischemia when ST experimented a horizontal or downsloping depression ≥1 mm at 0.08 s after the J point. The TT was considered unevaluable when the patient scored below 85% of the theoretical maximal heart rate calculated with the Astrand formula (220–age).

The subjects with positive TT suggesting ischemia underwent a SPECT (single–photon-emission computed tomography) myocardial scintigraphy with exercise testing or dipyridamole injection and those with abnormal SPECT underwent coronary angiography. The angiography was considered to be positive when stenosis ≥70%.

The SPSS (v 11.5.1) package program was used for data analysis. Data are presented as mean ± SD. Bivariate associations were tested using *t* test, χ^2 test, and Fisher's exact test. A p value <0.05 was considered significant. Multivariate analysis was performed including all the variables identified in the bivariate analysis with $p < 0.05$. When required, continuous variables were categorized into quartiles for multivariate logistic regression analysis. Odds ratio (OR) for the variables associated with SMI was calculated.

Acknowledgment

This work was supported by a grant from the Instituto de Salud Carlos III, GDM (G03/212). Madrid, Spain.

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