Risk Factors for Silent Myocardial Ischemia in Type II Diabetic Patients

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Abstract

Background- Silent myocardial ischemia is more common in diabetic patients than others. Early detection plays an important role in the prevention of acute myocardial infarction and sudden cardiac death. Routine screening of all diabetics is costly. The aim of this study was to estimate the prevalence of silent myocardial ischemia in type 2 diabetes and define these high-risk patients by routine screening tests.

Methods- Between May 2004 and May 2006, this cross-sectional study was performed on 500 type 2 diabetic patients referred to Kerman internal medicine and cardiovascular clinics. Inclusion criteria were age between 35 and 70 years, absence of symptoms and resting electrocardiographic signs of ischemia, evidence of retinopathy or peripheral vascular disease, or at least one major atherogenic risk factor (except diabetes). All the patients underwent treadmill exercise test or thallium scintigraphy with exercise or dipyridamole injection. Data were analyzed with chi-square, t-test, and Mann-Whitney U tests.

Results- Five hundred patients, comprised of 232 men and 268 women, were evaluated. Screening tests were positive in 86 (17.2%) patients. There was a significant statistical relation between the duration of diabetes, low density lipoprotein cholesterol, family history of coronary artery disease (CAD), retinopathy, and peripheral vascular disease with silent myocardial ischemia ($P<0.05$). The prevalence of silent ischemia was not significantly different between the males and females ($P>0.05$). Among the patients with silent ischemia, body mass index was higher in the females and cigarette smoking was more common in the males ($P<0.05$).

Conclusion- With regard to the high frequency of silent myocardial ischemia in type 2 diabetes mellitus, routine silent ischemia screening by exercise stress test should be recommended in type 2 diabetes if any of these conditions are present: duration of diabetes more than ten years, family history of CAD, LDL cholesterol higher than 160 mg/dL, retinopathy, or peripheral vascular disease ***(Iranian Heart Journal 2008; 9 (2):37-42).***

Key words: type 2 diabetes ■ silent myocardial ischemia ■ coronary artery disease

Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with diabetes.[1]

More than half of all diabetic patients die from CAD.[2,3]

Diabetics have at least a two- to four-fold increased risk in cardiovascular events compared with age-matched controls.[4,5]

One of the late diagnostic signs of CAD is silent myocardial ischemia, where

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asymptomatic subjects show ischemia in resting electrocardiogram or exercise stress test.[6] For this reason and others, the occurrence of major cardiac events such as acute myocardial infarction, unstable angina, ischemic cardiomyopathy, and sudden death are often the first manifestations of CAD in diabetic patients.[4]

Silent myocardial ischemia is more frequent in diabetic patients than non-diabetics probably because of diabetic neuropathy.[6] Silent myocardial ischemia with ST-segment depression in treadmill exercise stress test is associated with an increase of five times in cardiovascular mortality risk.[7] Early diagnosis of myocardial ischemia can reduce morbidity and mortality in diabetes and improve quality of life.[8]

Different studies show conflicting data about the prevalence of silent myocardial ischemia in type II diabetes.[4,6,9] The role of major cardiovascular risk factors, micro- and macroangiopathy in the presentation of silent myocardial ischemia is also different.[10-13] On the other hand, routine screening tests for the detection of silent myocardial ischemia in all diabetics is costly. We sought to investigate the frequency of silent myocardial ischemia in type 2 diabetes in the city of Kerman. Furthermore, by determining the role of major atherogenic risk factors in silent myocardial ischemia, we tried to define the high-risk group of diabetic patients for whom screening tests would be helpful.

Methods

The present cross-sectional study included 500 patients with type 2 diabetes who were referred to the cardiovascular clinics between May 2004 and May 2006 in Kerman.

The inclusion criteria were a normal 12-lead resting electrocardiography, no history of CAD or congestive heart failure, and presence of at least one of the major atherogenic risk factors in addition to diabetes such as hypertension (blood pressure >140/90mmHg or antihypertensive treatment), dyslipidemia (serum total cholesterol >200mg/dL, triglycerides >150 mg/dL, LDL* >160mg/dL, HDL** <35mg/dL or lipid lowering treatment), cigarette smoking, obesity, family history of premature CAD (before 60 years in first-degree relatives), retinopathy, and peripheral artery disease.

The diagnosis of type 2 diabetes was based on the American Diabetes Association (ADA) criteria. Peripheral artery disease was diagnosed when peripheral pulses were abolished or weak and/or when previous history of vascular surgery and/or intermittent claudication was present.

Diabetic retinopathy was diagnosed if at least one microaneurysm or hemorrhage or exudate in one eye was found on fundoscopy.

All the blood samples were taken in the morning after at least 12 hours of fasting and measured by an automatic analyzer (Alcyon 300, Abbott, USA).

Written consent was obtained from each patient in accordance with the guidelines set by the ethical committee of Kerman University of Medical Sciences.

Each patient underwent a treadmill exercise test.

Before the exercise test, the patients were informed about the test and any drugs affecting the test results were discontinued before 48 hours. A maximal symptom-limited exercise protocol was used with a treadmill (Esaoate, DST 1000, Italy) according to the Bruce protocol. A twelve-lead electrocardiogram was recorded every minute, and blood pressure was measured at rest and at the end of each step during exercise.

The test was stopped when one of the following end-points was reached: target heart rate 85% of the predicted heart rate (220 beats/min minus age in years), severe fatigue, systolic blood pressure reduction more than 20mmHg from control-values, hypertensive response (BP>220/120 mmHg), severe chest pain, or serious cardiac arrhythmia.

* LDL: low density lipoprotein, ** HDL: high density lipoprotein

The exercise test was defined as maximal if the patient reached 85% of the predicted heart rate for the age. This test was positive for myocardial ischemia if horizontal or down sloping ST-segment depression of 1 mm or more calculated at 0.08 s after the J-point was present and was negative if the patient reached 85% of the predicted heart rate for age without change in the ST-segment. The test was considered not diagnostic or incomplete if the patient did not reach 85% of the predicted heart rate for age or the test was interrupted for any of the above-mentioned reasons.

If the patient had conditions that prohibited maximal exercise test (such as amputation, foot wound, severe obesity, intermittent claudication, serious cardiac arrhythmia, left bundle branch block at resting ECG, progressive valvular heart disease, and uncontrolled hypertension) or maximal exercise test was incomplete, we performed thallium myocardial scintigraphy in association with exercise testing and/or dipyridamole injection.

One mCi thallium 201 was injected for each 25kg body weight. Early imaging was performed at 5 to 10 minutes, and late imaging was carried out 4 hours after injection.

This test was positive if fixed or transient uptake defects were observed between stress and rest imaging (4 hours after the end of the dipyridamole test). Silent myocardial ischemia was defined as positive exercise test or positive thallium myocardial scintigraphy. The presence of left ventricular ejection fraction more than 50% in echocardiography ruled out heart failure.

Statistical analysis

The results are expressed as mean ± SD. The means of the two groups were compared using the student's t-test or Mann-Whitney U test. The rate of proportion was compared using the χ^2 test. P value < 0.05 was considered significant.

Results

Five hundred cases, comprised of 232 men and 268 women aged between 40 and 70 years, were studied. In total, 357 patients were able to perform the maximal exercise test, 312 of whom reached 85% of the predicted heart rate for age. Results were positive in 64 patients and negative in 248 patients. Thallium myocardial scintigraphy was carried out in 45 patients who could not complete the exercise test. Among them, six had positive and 39 had negative results. One hundred forty-three cases who were unable to perform exercise test had thallium myocardial scintigraphy carried out as a primary procedure. Results were positive in 16 patients and negative in 127 patients. All the patients were subdivided into those having ischemia and those having no ischemia. Of the 500 patients, 86 (17.2%) had silent myocardial ischemia and 414 (82.8%) patients did not have silent myocardial ischemia. The characteristics of the two groups are shown in Table I.

Table I. General characteristics of the patients with and without silent myocardial ischemia

	NO SMI**	SMI	P
N	414	86	
Age (yrs)*	51±10.1	52±10.6	NS
Male/Female	191/222	40/46	NS
Diabetes duration (yrs)*	8±5.2	15±7.2	<0.05
Systolic BP* (mmHg)	134±15	137±15	NS
Diastolic BP* (mmHg)	80±6	80±8	NS
Anti-HTN tx (%)	65	69	NS
Total chol* (mg/dl)	216±40	220±35	NS
HDL chol* (mmHg)	54±16	50±14	NS
LDL chol* (mg/dl)	124±35	138±33	<0.05
TG > 150 mg/dl (%)	38	37	NS
Lipid lowering drugs (%)	36	40	NS
BMI* (kg/m^2)	25.1±4.4	26.4±4.6	NS
Smokers (%)	73	68	NS
Retinopathy (%)	25	37	<0.05
PAD (%)	20	32	<0.05
Family hx of CAD (%)	12	26	<0.05
No. of CV risk factors (%):			
1	24	23	NS
2	55	50	NS
≥ 3	21	27	NS
Antidiabetic medications (no,%)			
Diet	18	20	NS
OHA	50	44	NS
Insulin/insulin + OHA	32	36	NS

* = Data are means ±SD; ** = SMI, silent myocardial ischemia; PAD = peripheral artery disease; HDL = high density lipoprotein; LDL = low density lipoprotein; BMI = body mass index; OHA = oral hypoglycemic agents

A significant association was found between silent myocardial ischemia and duration of diabetes, serum low density lipoprotein, retinopathy, peripheral vascular disease, and family history of CAD (P<0.05), but such a correlation was not found with age, gender, and other major atherogenic risk factors (Table I). Antidiabetic treatment between the two groups was not shown to have a significant difference (P>0.05). When correlation between the gender of the patients and occurrence of silent ischemia was considered, exercise test results were found positive in 41 (17.6%) males and 46 (17.1%) females (P> 0.05, Table II).

Significant differences were found between the female and male patients with respect to BMI and cigarette smoking. BMI was higher in the females (28.5±4.1 vs. 23.8±3.3 kg/m^2) and cigarette smoking was higher in the males (88.8% vs. 46.6%, P<0.05, Table II).

Table II. Distribution of the cases with silent myocardial ischemia according to gender

	Female	Male	P
N	46	40	
Age (years)*	52.5±8.8	52.3±9.6	
Duration of diabetes (years)*	14.7±6.9	15±7.2	
BMI (kg/m^2)*	28.5±4.1	23.8±3.3	
Patients with HTN (%)	72.1	70.4	
Total cholesterol* (mg/dl)	225±36	223±35	
TG > 150 mg/dl (%)	38	36.8	
LDL* (mg/dl)	140±30	136±32	
HDL* (mg/dl)	53±10	56±9	
Smokers (%)	46.6	88.8	
Retinopathy (%)	66.6	63.8	
PAD (%)	45	43.1	
Family history of CAD (%)	53.3	50.8	

* = Data are means ± SD; BMI = body mass index; LDL = low density lipoprotein; HDL = high density lipoprotein; PAD = peripheral artery disease; CAD = coronary artery disease

Discussion

In the 500 diabetic patients recruited during two years according to the inclusion criteria, the results of exercise tests were positive in 86 (17.2%) patients.

In some reports, the prevalence of silent myocardial ischemia in type 2 diabetes was similar to ours: 15.7% according to Janand-Delenne [6] and 18.4% according to Bacci et al.[14]

Although male sex and BMI are risk factors for CAD,[8] in our study this association was not observed. Perhaps this is because diabetes leads to the loss of female protection from cardiovascular disease and severe obesity was not seen in our population. These data were similar to some other reports in the literature.[11,12]

In our study, the correlation of diabetes duration, serum LDL cholesterol, family history of CAD, retinopathy, and peripheral artery disease with silent myocardial ischemia was stronger than the other risk factors.

In the Wackers et al. study, major atherogenic risk factors did not emerge as significantly predictive of silent myocardial ischemia; this may be due to the generally increased levels of these risk factors in their study population or might reflect the impact of treatment with statins, ACE inhibitors, and aggressive blood pressure and glucose control.[15]

A significant association between diabetes duration with silent myocardial ischemia has been seen in many studies,[15-17] which chimes in with our results. Various mechanisms have been explained for the premature onset of CAD in type 2 diabetes. Among them, the loss of normal endothelial function is an early warning sign of the atherogenic process. This event occurs concomitantly with hyperglycemia, hypertension, dyslipidemia, and hyperinsulinemia.[18] Endothelial dysfunction might thus be an explanation of the elevated proportion of patients with silent myocardial ischemia, as assessed by exercise test, but with non-significant coronary artery stenosis on coronary angiography.[17] Microangiopathy such as retinopathy is a sensitive marker of generalized endothelial dysfunction, which is common in diabetes.[17]

The association of macroangiopathy and microangiopathy with silent myocardial ischemia was significant in the Janand-Delenne study,[6] which is in agreement with our findings. In another study, however, this correlation was not seen probably because

severe retinopathy was considered to be an exclusion factor.[13]

BMI in the women with silent myocardial ischemia was higher than that in the men, because our women did not perform adequate regular exercise. Cigarette smoking in the male gender with this ischemia was significantly higher than that in the women, because smoking was an uncommon habit in our women. These results were similar to those in the Sargin study.[16] Antidiabetic treatment among our studied population did not reveal a significant difference, but in the Sargin study,[16] insulin usage was significantly higher in the silent myocardial ischemia group, probably because our patients did not like to take insulin injections.

Conclusion

In light of our results, we would advise routine screening for silent myocardial ischemia in type 2 diabetes in the following cases:

- retinopathy,
- family history of CAD (<60 years in first-degree relatives)
- peripheral vascular disease,
- LDL >160 mg/dl,
- diabetes duration ≥10 yrs (>5 yrs if additional risk factors are present).

Further studies with larger sample sizes are needed to investigate the role of new atherogenic risk factors such as high-sensitivity CRP, fibrinogen, lipoprotein (a), and homocysteine in silent myocardial ischemia in diabetes.

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