Med. J. Cairo Univ., Vol. 62, No.1 March (Suppl.): 219-226, 1994

Silent Myocardial Ischemia in Patients with Diabetes Mellitus During Exercise Tolerance Testing

LAILA RAMADAN, M.D.; WAFAA EL-BARBARY, M.D. and FATMA EL-MOGY, M.D.

The Departments of Internal Medicine and Chemical Pathology, Faculty of Medicine, Cairo University.

Abstract

50 patients with diabetes were compared with 20 non-diabetic subjects, with respect to the prevalence of silent myocardial ischemia, by means of treadmill exercise testing. Results of treadmill exercise testing showed ischemia in 14 of the 50 diabetic patients (mean age 49.2 ± 1.3) and in 2 of 20 non-diabetic control subjects (mean age 49 ± 6 y.) (28%VS 10%, $P < 0.05$). Diabetics with "positive treadmill" had a higher serum total cholesterol and lower serum high density cholesterol than "negative treadmill" diabetics. Diabetic patients with retinopathy had a higher prevalence of silent myocardial ischemia (40%) than those who did not (25%, $p < 0.05$). Diabetics above the age of 40 years should be screened with treadmill exercise testing.

Introduction

SILENT coronary artery disease defined as exercise induced ST. Segment depression without chest pain has been recoginzed for 20 years, but there is controversy regarding its mechanism and prognostic significance [1]. Chon [2] has proposed a three type classification for silent myocardial ischemia. Type I are totally asymptomatic subjects, type II occurs in patients asymptomatic after a myocardial infarction and type III are patients with angina who have additional episodes of myocardial ischemia that are silent. Little is known about the prognosis of type I. The Norwegian study [3], however, confirms that asymptomatic patients with exercise induced silent myocardial ischemia develop angina or infarction, and they recommended angiography for these asymptomatic patients, especially in the presence of multiple coronary risk factors.

Patients with diabetes mellitus have an increased risk for cardiovascular disease and myocardial infarction [4]. Acute myocardial infarction in diabetics may present without pain or with acute acidosis, sudden hypotension, syncope, vomiting or cerebrovascular accident [5].

The prevalence of painless myocardial ischemia in diabetics compared with non-diabetics was found to be increased by some investigators [6] but not by others [7].

Detection of diabetic patients with silent myocardial ischemia is important, as physical exercise is encouraged in diabetics, as it increases insulin sensitivity [8]. Silent myocardial ischemia is a contraindication for strenuous exercise.

Moreover, it is important to identify such patients, because asymptomatic persons with a positive ST segment response to exercise are at increased risk for developing coronary events in the ensuing years [9]. We, therefore, investigated the prevalence of silent myocardial ischemia among asymptomatic diabetic and non-diabetic control subjects with the use of treadmill exercise testing.

Material and Methods

This study was carried out on 50 diabetics (18 insulin dependent and 32 non-insulin dependent) and 20 non diabetic control subjects. Diagnosis of diabetes was based on criteria of the World Health Organization [10]. Control subjects were matched for age, sex, body mass index (BMI), serum cholesterol level and blood pressure with the diabetic patients (Table 1). BMI was calculated as weight in Kg/ height square meters.

All patients and control subjects had no history of chest pain or previous history of myocardial infarction, congenital and rheumatic heart disease and none were receiving digitalis. Resting ECG was normal in all cases.

Funduscoping examinations of the retina were performed for all diabetics. Symptom limited exercise testing was carried out in the fasting state with the Bruce protocol [11]. Throughout the exercise testing the ECGs were monitored on an oscilloscope and blood pressure was measured every minute. ECGs were recorded (using 12 leads) on paper every minute during exercise and immediately after exercise, and then every minute during the recovery period. Exercise was continued until 90% of the predicted maximal heart rate for age was achieved. The exercise test was interrupted if there was dyspnea, fatigue, or multiple ventricular ectopics. Stress testing was terminated within one minute when ischemic ST segment response was detected. A positive test result was defined as horizontal or downsloping ST segment depression of at least 2mm [12].

Autonomic function tests were performed for all diabetic cases [13]. Coefficient of variation for 100 consecutive R.R. intervals on the ECG (CV R.R) in the resting supine position was measured. Expiration/ Inspiration ratio (E/I) was calculated as the ratio of the mean of the longest R.R. interval during expiration and the shortest R.R. interval during inspiration, the patient took 6 deep breaths per minute. Serum cholesterol level, high density lipoprotein cholesterol (HDLC) and proteins in 24 hour urine were measured for all cases, by conventional methods.

Results

Treadmill exercise test showed ischemic ST segment depression in 14 out of 50 diabetics (28%) [mean age 49.2 ± 1.3] and in only 2 (10%) out of the 20 non diabetics [mean age 49 ± 6] (p value < 0.05), although none of them had chest pain or related cardiac symptoms during exercise testing. Leg pain during exercise occurred in four diabetics with positive exercise test.

The age, type of diabetes, duration of diabetes, B.M.I., the prevalence of hypertension, and the values of cardiac autonomic function tests did not differ significantly between the treadmill positive diabetic group and the treadmill negative diabetic group. (Table 2). However, the positive treadmill diabetic group had a higher meal

Table (1) Clinical Treadmill Exercise Test and Laboratory Data of Diabetic and non Diabetic Subjects

	Diabetics	Nondiabetics	*P* Value
No. of subjects	50	20	
Age (years)	48.7 ± 0.7	48.8 ± 1.5	NS +
Sex	Males 12	Males 14	NS + +
	Females 12	Females 6	
EMI (kg / m2)	26.1 ± 0.34	26.2 ± 0.5	NS +
Hypertension	18 (36%)	5 (25%)	NS +
Serum total cholestrol (mg / dl)	198 .14 ± 4.4	195 ± 11.7	NS +
Result of treadmill test.	Positive 14 (28%) Negative 36 (72%)	Positive 2 (10%) Negative 18 (90%)	Sign + + $p < 0.05$

+ Students *t* test.

++Chi square test.

Table (2) Results of 50 Diabetic Patients with Positive and Negative Exercies Treadmill Test.

	Positive treadmill	Negative treadmill	*P* Value
No. of patients	14 (28%)	36 (72%)	NS
Age	49.2 ± 1.3	48.5 ± 0.9	NS
Therapy			
Sulphoryl urea (32)	9 (28%)	23 (72%)	NS
Insulin (18)	5 (28%)	13 (72.%)	
Duration (years)	10.6 ± 1.4	10.3 ± 0.6	
Hypertension	5 (35%)	13 ± (36.1%)	NS
BMI	26.3 ± 0.8	26.07 ± 0.4	NS
S. total cholesterol (mg / dl)	236.7 ± 4.8	183.7 ± 3.4	NS
Serum HDLC (mg / dl)	33.4 ± 1.6	46.2 ± 2.7	+ < 0.001(Signif.)
.Retinopathy			
+ 10	4 / 10 (40%)	6 / 10 (60%)	+ < 0.05 (Sign.)
- 40	10 / 40 (25%)	30 / 40 (75%)	
Proteins in 24h.			
Urine in gms.	1 ± 0.08	0.48 ± 0.02	< 0.05 + + (Sign.)
Cv R - R (%)	2 ± 1	2.4 ± 0.8	< 0.05 + (Sign.)
E / I Ratio.	1.29 ± 0.2	1.65 ± 0.13	NS+

+ Students *t* test.

++Chi square test.

total serum cholesterol level and a decreased mean HDL-C level than the treadmill negative diabetic group.

Patients with diabetic retinopathy had a higher prevalence of silent myocardial ischemia (40%) than those without retinopathy (25%), $p < 0.05$.

Discussion

Although much recent attension has focused on the detection of silent myocardial ischemia in patients with known coronary artery disease, there remains considerable controversy concering the prevalence and prognosis of silent ischemia in asymptomatic populations [9]. The best estimate

to date of prevalence comes from an extensive Norwegian study [7] using exercise ECG and angiography, silent ischemia was detected in 2.5%. Fleg et al. [9] detected silent myocardial ischemia by exercise ECG and thallium scintigraphy in 6.2% of asymptomatic volunteers, 50% of them developed clinical manifestations of coronary artery disease during 4.6 year mean follow up.The investiators concluded that screening with exercise ECG or thallium scintigraphy, is not an effective strategy for the early diagnosis of coronary artery disease in unselected asymptomatic subjects, however, exercise screening may be considerably more effective in patients with multiple coronary risk factors [13].

Several studies have evaluated the hypothesis that painless myocardial ischemia is more common among diabetics with coronary artery disease (CAD) than nondiabetics with CAD. Smith et al. [14] found no difference in the prevalence of silent myocardial ischemia between diabetics and nondiabetics undergoing exercise testing after myocardial infarction. Aronow et al. [15] found that the prevalence of silent myocardial ischemia was similar in both diabetics and non diabetics with CAD, using Holter ECG monitoring.

By contrast Nesto et al. [6] found that painless myocardial ischemia was significantly higher in diabetics (72%) than non diabetics (25%) with CAD, using exercise thallium scintigraphy. Ranjadaylalan et al. [16] showed that among diabetic patients with symptomatic CAD, the perception of angina after the onset of exercise induced ST segment depression was significantly delayed than non diabetic patients, which may deprive them of the warning symptoms to stop exercise, thus intensifying the ischemia and worsening the prognosis.

Data are particularly scarce regarding the association of diabetes with painless myocardial ischemia in asymptomatic diabetics without previous history of CAD, although clinical studies have drawn attension to this coincidence [13].

We reported in this study an increased prevalence of silent myocardial ischemia (14%) in diabetics compared to normal controls (10%). Patients with retinopathy had a higher prevalence of silent myocardial ischemia than those without it (Table 2). Our findings are compatible with recently reported data that the presence of angiographically proven CAD reflects the severity but not the age of onset or duration of diabetes [17].

Accordingly we consider the development of silent myocardial ischemia to be associated with the severity of diabetes, long standing hyperglycemia, per se, might be a risk factor for silent mycoardial ischemia. The mean serum total cholesterol levels in our patients with silent myocardial ischemia, were elevated above the optimal

level of 200mg/dl recommended by the European atherosclerosis society [18], which also recommended a cut-off point of 35 mg/dl for a low plasma HDLC.

The recent findings that lowering serum cholesterol reduces both the incidence and progression of symptomatic CAD [19], coupled with the recent advances in percutaneous transluminal angioplasty make detection of early asymptomatic CAD an important clinical goal, particularly for older diabetics starting a program of aerobic exercises.

The reason for the high prevalence of painless myocardial ischemia in our diabetic patients is not known. Painless myocardial ischemia has not yet been clearly related to autonomic neuropathy [20].

Autonomic neuropathy has been shown in diabetics with atypical myocardial infarction [21]. There may be a subset of patients who consistently and repeatedly do not sense pain with ischemia because of a defect in the anginal warning system, generalised decreased pain sensitivity [22] or an increased endogenous opiate concentration [23].

In our study, some patients fail to have chest pain because they perceive more intense exercise related discomfort in their legs. Some patients with evidence of peripheral ischemia may be at increased risk for painless myocardial ischemia [7].

From our data we concluded that diabetics over the age of 40 years should be carefully screened by exercise ECG for silent myocardial ischemia before prescribing exercise therapy. Coronary angiography should be done for the positive treadmill test cases, as coronary bypass surgery was associated with improved survival in a subgroup of diabetics with silent myocardial ischemia. This subgroup had 3-vessel CAD with either preserved or abnormal left ventricular function [24]. Diabetics with multivessel disease are at increased risk for serious cardiac events and should be treated aggressively even in absence of symptoms [24]. Antianginal medications such as nitrates, β-blockers, and calcium channel blockers are also effective in treatment of silent myocardial ischemia [25].

References

1. WEINER, D.A.; RYAN, R. and McCABE, C.: Significance of silent myocardial ischemia during exercise testing in patients with coronary artery disease. Am. J. Cardiol., 59: 726, 1987.

2. COHN, P. F.: Silent mycoardial ischemia: Classification, prevalence and prognosis. Am. J. Med., 79:2, 1985.

3. REISMAN, S.; LANDHEIM, M. and STAMLOG, H.: Asymptomatic patients with exercise Thallium 201 hypoperfusion: Identification of high risk subset. Circulation, 72: 45, 1985.

4. KANNEL, W.: Diabetes and cardiovascular disease. JAMA, 214: 2035, 1979.

5. NIAKAN, E.: Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy autonomic neuropathy. Arch. Irtern. Dem., 146: 2229, 1986.

6. NESTO, R.; PHILIPS, R. and HILL, T.: Angina and exertional myocardial ischemia in diabetic and non diabetic patients: assessment by thallium scintigraphy 1988. Ann. Intern. Med., 108: 170, 1988.

7. CHIPKIN, S.; TRID, D.; ALPERT, J.: Frequency of painless myocardial ischemia during exercise tolerance testing in patients with and without diabetes. Am. J. Cardiol., 59: 61, 1987.

8. De TRANZO, R.: Effect of physical training on insulin action in obesity. Diabetes, 36: 1379, 1987.

9. FLEG, J.; LEWIS, C.; COSTA, J.and EDWARD, G.: Prevalence and prognositc significance of exercise induced silent myocardial ischemia detected by thallium scintigraphy and ECG in asymptomatic volunteers. 81: 428, 1990.

10. WHO EXPEPT COMMITTEE ON DIABETES: SECOND REPORT. GENEVA: WHO Technial report series, N. 646, 1980.

11. BRUCE, R.A: Stress testing in screening for cardiovascular disease. Bull NY. Acad. Med., 45: 1288, 1969.

12. EWING, D.: Assessment of cardiovascular effects in diabetic autonomic neuropathy. Ann. Int. Med., 92: 308, 1980.

13. NAKA, M.; HIRAMATSU, K. and AIZAWA, T.: Silent myocardial ischemia in patients with dependent diabetes as judged by treadmill exercise testing and angiography. Am. Heart J., 123:46, 1992.

14. SMITH, J.; BUCKELS, L.; MARCUS, F.: Clinical characteristics and results of non-invasive tests in 60 diabetics after myocardial infarction. Am. J. Med., 75: 217, 1983.

15 ARONOW, W.; ANTHONY, D. and SPSTEIN, S.: Prevalence of silent myocardial ischemia detected by 24-hour ambulatory ECG, and its association with new coronary events at 40 month follow up in elderly diabetic and non-diabetics with coronary artery disease. Am. J. Cardiol., 69:555, 1992.

16. RAN JADAYALN, K.; UMACHANDRAN, V. and MILL, G.: Prolonged anginal perspceptual threshold in diabetes, effects on exercise capacity and myocardial ischemia. J. Am. Coll. Cardiol., 16: 120, 1990.

17. LEMP, G.; ZWAAG, R. and HUGHES, J.: Association between the severity of diabetes and coronary atherosclerosis. Am. J. Cardiol., 60: 1015, 1987.

18. EUROPEAN ATHEROSCLESOSIS SOCIETY STUDY ON OPTIMAL LEVEL OF SERUM CHOLESTEROL: Lipid Review. Vol. 1, P. 11, 1987.

19. NIKKILA, E.: Prevention of progression of coronary atherosclerosis by treatment

of hyperlipidemia. A seven year prospective angiographic study. B.M.J., 284: 220, 1984.

20. ACHARY, U.; SKE KHAR, C. and ANAND, S.: Lack of pain during myocardial infarction in diabetics. Is autonomic dysfunction responsible? Am. J. Cardiol., 68: 793, 1991.

21. FAERMAN, L.: Autonomic neuropathy and painless myocardial infarction in diabetic patients: histological evidence of their relationship. Diabetes, 26: 1147, 1977.

22. COHN, P.: Silent myocardial ischemia in patients with a defective anginal ovarning system. Am. J. Cardiol., 45:697, 1980.

23. VAN RIJN: Effect of naloxone, a specific opioid antagonist on exercise induced angina. Circulation, 64 Suppl., IV: 149, 1981.

24. WEINER, D.; THOMAS, J.; PARSONS, L. and BERNARD, F.: Significance of silent myocardial ischemia during exercise testing in patients with diabetes. A report from the coronary artery surgery study registry. Am. J. Cardiol., 68: 729, 1991.

25. GOTIEB, S.: Asymptomatic myocardial ischemia in angina. Clinical implications. Cardiology Clinic. Vol. 9 No. 1. 49, 1991.