ISSN 2304-2354
Number 2, Volume 44, 2013

SILENT MYOCARDIAL ISCHEMIA AND MICROALBUMINURIA IN ASYMPTOMATIC TYPE 2 DIABETIC PATIENTS

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Abstract

Objectives: To detect silent myocardial ischemia (SMI) in asymptomatic type 2 diabetic patients with or without microalbuminuria, and the importance of microalbuminuria as a predictor for diabetic cardiovascular complications.

Methods: Forty asymptomatic patients with type 2 diabetes were included in this study. The patients were divided into two groups as regard the presence of microalbuminuria: group I of twenty patients (12 males, 8 females, with a mean age of 52±8.5 years) with microalbuminuria and group II of twenty patients (14 males and 6 females, with a mean age of 52±7.6 years) without microalbuminuria. A maximum symptom-limited treadmill exercise test was used to detect silent ischemia.

Results: In group I, 7 patients (35%) had SMI, with 5 patients showing SMI at higher work load and 2 at low work load. In group II, 2 patients (10%) showed SMI, one at high load and another at low load.

Conclusions: The prevalence of SMI in asymptomatic microalbuminuric and normoalbuminuric type 2 diabetic patients were 35% and 10% respectively. Even with a maximum exercise, myocardial ischemia might be completely asymptomatic in type 2 diabetic patients.

Key words: ype 2 diabetes mellitus, silent myocardial ischemia, treadmill exercise test.

Introduction

Diabetic nephropathy (DN) is an important cause of morbidity and mortality and is among the most common causes of end stage renal failure (ESRF) in developed countries (1). However, not all patients with diabetes develop serious renal complications.

Microalbminuria (MA) is defined as urinary albumin excretion rate of 30-300 mg/24 hours (20-200 microgram/minute), and results from glomerular hyperfiltration and elevated intraglomerular pressure (2). Microalbuminuria in non insulin dependent diabetes mellitus (NIDDM) reflects an underlying predisposition to developing progressive kidney disease as well as serving as a marker of predilection for generalized cardiovascular disease. The progression of the renal complications in NIDDM generally follows the same course as for insulin dependent diabetes mellitus (IDDM) (3).

Two forms of silent myocardial ischemia are recognized. The first and less common form, designated Type-I silent ischemia, occurs in patients with obstructive coronary artery disease (CAD), who do not experience angina at any time.

The second and much more frequent form, designated Type-II silent ischemia, occurs in patients with the usual forms of chronic stable angina, unstable angina, and Prinzmetal's angina. These patients exhibit some episodes of ischemia associated with chest discomfort and others without pain (2).

Irrespective of the mechanism (s) responsible for silent ischemia, it is reasonable to assume that asymptomatic ischemia has a significance similar to symptomatic ischemia and that their diagnosis and management with respect to coronary angiography and revascularization should be similar (4).

The possible explanations for the association of microalbuminuria with (CVD) are more or less related to the following factors, endothelial dysfunction, hypertension, dyslipidemia, insulin resistance, smoking, (5) hyperhomocysteinemia, (6,7) and advanced glycated proteins (8). In addition, left ventricular hypertrophy, which occurs early in the course of diabetic nephropathy, is an independent risk factor for myocardial ischemia and sudden death (9).

Cardiovascular disease (CVD) is a leading cause of death among individuals with type 2 diabetes.[10] Coronary artery disease is more common in diabetes and is more extensive and diffuse. Relative risk of acute

myocardial infarction is (50%) higher in diabetic males and 150% more in diabetic females, therefore coronary artery disease in diabetic patient is associated with increase immediate and long term morality (11,12,13). These facts should make the clinicians more serious about early detection of silent myocardial ischemia in an attempt to abort any sudden or hidden catastrophic events.

Our study aimed to detect silent myocardial ischemia (SMI) in asymptomatic type 2 diabetic patients with or without microalbuminuria, and the importance of microalbuminuria as a predictor for diabetic cardiovascular complications.

Pantients and methods

The patients were divided into two groups as regard the presence of microalbuminuria: group I of twenty patients (12 males, 8 females, with a mean age of 52±8.5 years) with microalbuminuria and group II of twenty patients (14 males and 6 females, with a mean age of 52±7.6 years) without microalbuminuria. The patients were attended or admitted at University Hospital Center "Mother Teresa", "Hygeia"Hospital, Diagnostic Center "IKEDA-Euromedica" and Diagnostic Center "Med. al" during the period September 2010 – August 2011 for silent myocardial ischemia. The mean age of the microalbuminuric group was 52±8.5 and 52.4±7.6 for the normoalbuminuric group. Fifteen patients with MA were on oral hypoglycemic agents and 5 on diet alone, while 18 normoalbuminuric patients were on oral hypoglycemic agents and 2 patients on diet therapy. Patients with uncontrolled hyperglycemia, congestive heart failure, urinary tract infection, fever and pregnant women were excluded from the study. All the patients were asymptomatic, with normal resting ECG and had no contraindications for exercise stress test.

A detailed medical history was taken and proper clinical examination with particular attention to the cardiovascular system was performed for every patient. Laboratory investigations in the form of: fasting blood glucose (mg/dl), fasting cholesterol, high density lipoprotein in mg/dl, low density lipoprotein in mg/dl, fasting triglycerides, chest X ray, ECG, urine examination, and fasting urine sample to measure albumin creatinine ratio by using bromocresol Green (BCG) method with some modifications, was done for every patient.

An informed written consent was obtained from each patient before performing a maximum symptom-limited Treadmill Exercise Test (TET) according to Bruce protocol. Heart rate and blood pressure were measured at the end of each stage and every 2 minutes up to 10 minutes during the recovery phase. Hypotension was considered if there was a decrease in systolic blood pressure (3) 10mm Hg or below the rest value (13).

An ischemic ECG response to exercise test was defined as at least 1 mm horizontal ST segment depression and 1.5 mm down sloping ST segment depression measured at the J point (14).

Table nr.1. Baseline characteristics of the microalbuminuric and normoalbuminuric patients

Variables	Microalbuminuria Group I	Normoalbuminuria Group II	P-value
No.of patients	20	20	NS
Age (years)	52 ± 8.5	52 ± 7.6	
Sex (male/female)	12 / 8	14 / 6	0.001
Duration of diabetes (years)	7.4 ± 7	3.8 ± 4	NS
Body mass index (kg/m^2)	27.5 ± 8.2	27 ± 6.3	0.001
Fasting blood glucose (mg/dl)	167.5 ± 18	135 ± 15.5	0.01
Total cholesterol (mg/dl)	217 ± 35.5	190 ± 17.5	NS
HDL (mg/dl) - male	45 ± 14	50 ± 15.5	NS
- female	52 ± 15.5	58 ± 16.7	NS
LDL (mg/dl) - male	185.5 ± 12.5	196 ± 13.3	NS
- female	162 ± 13,4	171,5 ± 11	NS
Triglycerides (mg/dl) - male	178 ± 15	169 ± 17	NS
- female	168 ± 12	165 ± 11,8	NS
SBP (mmHg) - supine	134 ± 19.2	131 ± 17.4	NS
- erect	130.6 ± 28.2	127 ± 21.5	0.01
DBP (mm Hg) - supine	92 ± 15	82 ± 8.5	NS
- erect	85.5 ± 9.5	84 ± 11	

HDL: high density lipoprotein; **LDL**: low density lipoprotein; **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure; **S**: significant; **HS**: highly significant; **NS**: not significant.

Treadmill exercise test was considered positive at low and high work load, if the abnormalities appear in the first 2 stages or the 3rd and subsequent stages respectively. The normal value for albumin/creatinine ratio (ACR) is <2.5 mg albumin/mmole creatinine in males and <4.5 mg/mmole in females. Above these values and up to 30 mg/mmol is considered as microalbuminuric range.
Statistical analysis was done by using a student's t-test and Chi-square test. Significance was taken for $p<0.05$.

Results

The study included 40 patients, 20 each for microalbuminuria (group I) and 20 for normoalbuminuria (group II). Baseline characteristics of the microalbuminuric and normoalbuminuric patients are shown in Table nr.1.

The mean age in the two groups was similar. However, there were significant to highly significant differences of higher values in group I, for the following parameters: duration of diabetes, fasting blood glucose, total cholesterol and diastolic blood pressure in supine position. HDL values were higher (not significantly) in group II. LDL and triglycerides values were higher (not significantly) in group I. Table nr.2 gives comparison between the two groups in this study, as regards risk factors and complications of Type 2 diabetes.

Table nr.2. Comparison between the 2 studied groups in relation to risk factors and complications of Type 2 diabetes

Risk Factors	Microalbuminuria No.	%	Normoalbuminuria No.	%	P-value
Hypertension	6/20	30	5/20	25	NS
Diabetic retinopathy	8/20	40	3/20	15	0.001
Formal alcoholism	5/20	25	2/20	10	0.001
Smoking	8/20	40	7/20	35	NS
Family history of DM	13/20	65	12/20	60	NS

Hypertension, smoking status and family history for DM in the two groups were similar. There were significant to highly significant differences of higher values in group I, for diabetic retinopathy and alcoholism.
Table nr.3 gives Treadmill exercise test results in both groups.

Table 3. Treadmill exercise test (TET) results in both studied groups

Patients with	Total No.	Abnormal TET No. (M/F)	%	Work load High No. (%)		Low No. (%)	
Microalbuminuria	20	8/20 (6/2)	40	5/8	(62.5)	3/8	(37.5)
Normoalbuminuria	20	2/20 (1/1)	10	1/2	(50)	1/2	(50)

Table nr.3 shows that out of twenty patients in group I, 8 patients (40%): 6 males and 2 females had SMI. Five patients showed ischemia at high workload and three at low work load. In twenty patients in group II, two patients (10%), one male and one female showed SMI, one at a high load and the other at low load.
Table nr.4 shows the baseline characteristics of the microalbuminuric patients with or without SMI.
The differences between the differences were statistically not significant, except for diabetic retinopathy and diastolic blood pressure in supine position.
According to clinical manifestations of microalbuminuric patients with SMI during TET, in group I with SMI, hypotension was detected in 4 patients (66.6%) during TET, while chest pain was present in 3 patients (50%). Other clinical manifestations as dyspnea, palpitations and swealling were less frequent.

Conclusions

In our study, the prevalence of SMI in asymptomatic microalbuminuric and normoalbuminuric type 2 diabetic patients were 35% and 10% respectively.

Table nr.4. Baseline characteristics of microalbuminuric patients with or without silent myocardial ischemia (SMI) (all figures are mean ± SD unless stated otherwise)

Variables	Microalbuminuric patients with SMI	Microalbuminuric patients without SMI	P value
No. of patients	8	12	NS*
Gender (male/female)	6//2	7//5	NS*
Age (years)	54.7 ± 12	52.4 ± 8	NS*
Duration of Diabetes (years)	4.45 ± 7.2	6 ± 4.5	NS*
Albumin:creatinine ratio	13.7 ± 8.3	14.8 ± 5.8	NS*
Total cholesterol (mg/dl)	212 ± 44	201 ± 47	NS*
HDL (mg/dl)	47 ± 14	53.2 ± 12	NS*
LDL (mg/dl)	144 ± 11,3	152 ± 13	NS*
Triglycerides (mg/dl)	175 ± 6,3	165 ± 11,2	NS*
Fasting blood glucose (mg/dl)	159 ± 27	154 ± 23	NS*
Body mass index (kg/m^2)	29 ± 4.5	28 ± 6.2	NS*
SBP (mmHg) - supine	144 ± 23	135 ± 27	NS*
- erect	142 ± 24	134 ± 25	NS*
DBP (mm Hg) - supine	90 ± 13	83 ± 10	S*
- erect	88.8 ± 11	82 ± 9.8	NS*
History of Hypertension No. (%)	4 (50%)	5 (41.6%)	NS*
Smoking status No. (%)	2 (40%)	4 (33.3%)	NS*
Diabetic retinopathy No. (%)	7 (87.5)	4 (33.3%)	S*

*t-test; **z-test; **S**: significant; **NS**: not significant.

Important factors as total cholesterol, fasting blood glucose, systolic and diastolic blood pressure, body mass index and history of systemic hypertension were more or higher among patients with SMI, while HDL level was higher in patients without SMI.

Diabetic retinopathy (DR) was more statistically significant in patients with SMI than in patients without SMI.

Duration of diabetes and smoking habits were more associated with patients without SMI (although not significant statistically).

According to clinical presentation and ECG changes during TET, all the patients with abnormal TET showed ischemic ECG changes in the form of ST segment depression and pseudo normalization of T wave. Most of these ECG changes were accompanied by a clinical feature like hypotension, shortness of breath and fatigue.

Interestingly, we observed that inspite of a maximum exercise 33.3% of these patients developed neither chest pain nor any significant complaints, emphasizing a crucial note that: myocardial ischemia in type 2 diabetics might be asymptomatic even with a maximum exercise.

Discussion

This study has detected SMI in 8 patients (40%) out of 20 microalbuminuric patients, 6 of them were males and two were females. Only 2 of 20 patients (10%) normoalbuminuric patients had SMI, this difference was highly significant statistically ($P<0.01$). This is in contrast to Rutter et al. Study (UK), (15) which demonstrated SMI in 28 of 43 patients (65%) microalbuminuric patients and 17 of 43 patients (40%) normoalbuminuric patients. This difference could be explained by the fact that the majority of patients in Rutter et al. Study were males, in their sixties and recruited from hospital diabetic clinics located is an area known for its high prevalence of CHD, while our study included patients who were attending a general hospital, younger age group and with an approximate males-females numbers. On the other hand if we have included only those patients over 60 years of age, the prevalence of SMI would have been increased, reflecting the high prevalence of SMI among elderly diabetics. Similar results was obtained by Inoguchi T et al. (Japan), (16) who recorded a prevalence of (45.3%) SMI in their

studied asymptomatic type 2 diabetic patients above 60 years of age.

Our finding of high systolic (and even diastolic) blood pressure among patients with MA support the reports of several authors (17,18) for the association between high systolic blood pressure and MA.

A high total cholesterol level showed a significant association with MA ($P<0.05$). A similar figure was recorded by Juan-Manuel Guizar et al. study (19). On the other hand, HDL level was higher among patients with MA, these risk factors are relevant for the high cardiovascular mortality rate found in type 2 diabetics (20,21).

Smoking is a recognized cardiovascular risk factors, and it may also be related to MA(19). Juan-Manuel Guizar et al., stated that smoking habit was more among microalbuminuric patient (31.6%) than normoalbuminuric patients (21.1%), while Charles T et al (22) mentioned that smokers were more in patients with NA (46.1%) than microalbuminuric patients (44%). However our study documented no difference between both studied groups (20% vs. 20%). Observations of the studied patients regarding clinical presentation and ECG changes during TET demonstrated that all the 10 patients with abnormal TET showed ischemic ECG changes in the form of ST segment depression (8 patients) and pseudonormalization of T wave (two patients), most of these ECG changes were accompanied by a clinical feature like hypotension, shortness of breath and fatigue. Interestingly, we observed that inspite of a maximum exercise 3 patients (33.3%) developed neither chest pain nor any significant complaints, emphasizing a crucial note that: myocardial ischemia in type 2 diabetics might be asymptomatic even with a maximum exercise. In addition to that we noticed that (78%) of the ECG ischemic changes appeared in leads V4-V6, a similar figure (75-80%) reported by Bernard R. Chaitman (13).

Why SMI developed in some microalbuminuric patients and spared others?

In an attempt to answer this question, we divided the microalbuminuric patients into 2 groups (Table nr.IV): microalbuminuric patients with SMI vs. microalbuminuric patients without SMI. Using most of the variables applied in Table nr.1 and nr.2, for statistical comparison, we noticed the following:

1. The following factors: total cholesterol, fasting blood glucose, systolic and diastolic blood pressure, body mass index and history of systemic hypertension were more or higher among patients with SMI while HDL level was higher in patients without SMI, these factors might explain susceptibility of some microalbuminuric patients to SMI.

2. Diabetic retinopathy (DR) was more statistically significant (P-value = 0.010) in patients with SMI than in patients without SMI. Joon Kee Yoon, et al. (23) reported that DR is helpful in predicting the occurrence of myocardial perfusion defects, and in a study investigating SMI, a significantly higher prevalence was found in patients with DR (24).

3. Against our provisional expectation, duration of diabetes and smoking habits were more associated with patients without SMI (although not significant statistically) which remain unexplained.

Limitations of the Study: It would have been ideal to have angiographic confirmation of myocardial ischemia. However, with limited resources and prevailing conditions in Albania, it has not been possible.

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