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: Sixty asymptomatic patients with type 2 diabetes were included in this study. Thirty (17 males, 13 females) with mean age of 54±8.3 years had microalbuminuria (Group-I) were compared with another thirty (21 males and 9 females) with a mean age of (52±7.8 years) who had normoalbuminuria (Group-II). A maximum symptom-limited treadmill exercise test was used to detect silent ischemia.

Results: In Group-I, 9 patients (30%) had SMI, with 6 patients showing SMI at higher work load and 3 at low work load. In Group-II, 2 patients (6.6%) showed SMI, one at high load and another at low load.

Conclusions: The prevalence of SMI in asymptomatic microalbuminuric and normalbuminuric type 2 diabetic patients were 30% and 6.6% respectively. Even with a maximum exercise, myocardial ischemia might be completely asymptomatic in type 2 diabetic patients.

KEY WORDS: Type 2 diabetic mellitus, silent myocardial ischemia, treadmill exercise test.

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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 dependant 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 dependant 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]

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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 sud den 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.[11-13] 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.

PATIENTS AND METHODS

Sixty patients with type 2 diabetes 30 (17 males, 13 females) with micro- albuminuria were compared with another 30 (21 males, 9 females) with normoalbuminuria, who were attended or admitted at Basrah Teaching Hospital during the period from February 2001-September 2001 for silent myocardial ischemia. The age of the microalbuminuric group ranged from 41-75 years (mean 54±8.3) and from 37-60 years (52.3±7.8) for the normoalbuminuric group. Twenty six patients with MA were on oral hypoglycemic agents and 4 on diet alone, while 27 normoalbuminuric patients were on oral hypoglycemic agents and 3 patients on diet therapy.

All the patients were asymptomatic, with normal resting ECG and had no contraindications for exercise stress test.

A detailed medical history was taken and

Table–I: Baseline characteristics of the microalbuminuric and normoalbuminuric patients (all figures are mean±SD unless stated otherwise).

Variables	*Microalbuminuria (Group-I)*	*Normoalbuminuria (Group-II)*	* *P-value*
No. of patients	30	30	
Age (years)	54 ± 8.3	52.3 ± 7.8	NS
Sex (male/female)	17/13	21/9	
Duration of diabetes (years)	7.6 ± 7	3.18 ± 3.4	HS
Body mass index (kg/m^2)	27.5 ± 6.3	27 ± 5.18	NS
Fasting blood glucose (mg/dl)	152.7 ± 26	131 ± 19.5	HS
Total cholesterol (mg/dl)	205 ± 40.8	181.4 ± 28.7	S
HDL (mg/dl) - male	47.6 ± 13	48.6 ± 14.7	NS
- female	50 ± 13.6	55 ± 14	NS
SBP(mmHg) - supine	135 ± 24.7	131 ± 18	NS
- erect	131.5 ± 34.6	128 ± 17	NS
DBP(mmHg) - supine	91.5 ± 18	82 ± 6.5	S
- erect	84.3 ± 11	83 ± 9	NS

* t-test

HDL: high density lipsprotein. S: significant.
SBP: systolic blood pressure. HS: highly significant.
DBP: diastolic blood pressure. NS: not significant.

Table–II: Comparison between the 2 studied groups in relation to risk factors and complications of Type-2 diabetes.

Risk factors	*Microalbuminuria*		*Normoalbuminuria*		**P-value*
	No.	*%*	*No.*	*%*	
Hypertension	9	30	8	26.6	NS
Diabetic retinopathy	11	36.6	7	23.3	HS
Formal alcoholism	9	30	3	10	HS
Smoking	6	20	6	20	NS
Family history of DM	19	63	18	60	NS

* z-test

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 (the only lipid profile available in our hospital laboratory), 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:[14]

1. At least 1mm horizental ST segment depression.
2. 1.5mm down sloping ST segment depression measured at the J point.

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 <2.5mg albumin/mmole creatinine in males and <4.5 mg/mmole in females. Above these values and up to 30 mg/mmole is considered as microalbuminuric range.

Patients with uncontrolled hyperglycemia, congestive heart failure, urinary tract infection, fever and pregnant women were excluded from the study.

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 60 patients, thirty each for micro abluminuria (Group-I) and normoalbuminuria (Group-II). Baseline characteristics, the risk factors and complications of diabetes in the two groups of patients are shown in Table I and II. 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, diastolic blood pressure in supine position, diabetic retinopathy and alcoholism. Smoking status was similar in both groups but HDL values were higher (not significantly) in Group-II.

Table-I shows that out of thirty patients in Group-I, nine patients (30%) 6 males and 3

Table –III: Treadmill exercise test (TET) results in both studied groups.

Patients with	*Total No.*	*Abnormal TET*		*Work load*	
		No. (M/F)	*%*	*High No.(%)*	*Low No. (%)*
Microalbuminuria	30	9(6/3)	30	6(66.6)	3(33.3)
Normoalbuminuria	30	2(0/2)	6.6	1(50)	1(50)

P-value < 0.01

females had silent myocardial ischemia (SMI). Six patients showed ischemia at high workload and three at low work load. In thirty patients in Group-II, two patients (6.6%) one male and one female showed SMI, one at a high load and the other at low load.

Table-II gives comparison between the two groups in this study as regards risk factors and complications of Type-II diabetes while Table-III gives Treadmill exercise test results in both groups.

Table-IV shows the baseline characteristics of the microalbuminuric patients with SMI and normoalbuminurea without SMI, most of the variables were more or higher among Group-1 than Group-II patients, the differences were statistically not significant except for DR and diastolic blood pressure in supine position.

Figure-1 shows that out of nine patients in Group-I with SMI, hypotension was detected in 6 (67%) patients during TET, while chest pain was the commonest symptom, present in 5 (55.5%) patients, other clinical manifestations were less frequent.

The electrocardiographic changes during TET shown in Figure-2: ST segment depression detected in 8 (89%) patients, and one patient (11%) demonstrated T wave pseudonor molization. The majority of the exercise induced ischemic changes 7 (78%) appeared in leads V4-V6. Premature ventricular contractions (PVCs) developed in 2 (22%) patients.

DISCUSSION

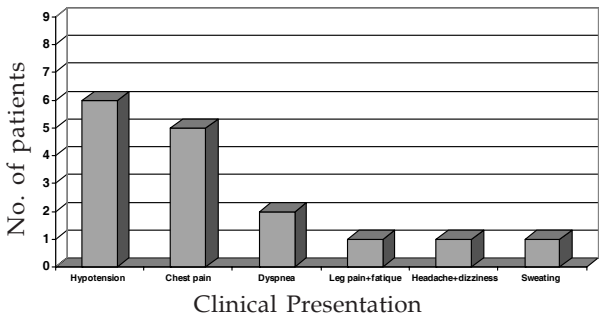
This study has detected SMI in 9 (30%) out of 30 microalbuminuric patients, 6 of them were males, the only one of the 9 patients who accepts referral for coronary angiography proved to have 3 vessels disease. Only 2 of 30 (6.6%) normoalbuminuric patients had SMI, this difference was highly significant statistically ($P<0.01$), this is in contrast to Rutter et al. Study (U.K),[15] which demonstrated SMI in 28 of 43 (65%) microalbuminuric patients and 17 of 43 (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 (54±8.3) years and with an approximate males-females numbers. On the other hand if we have

Table –IV: Baseline characteristics of microalbuminuric patients with and without silent myocardial ischemia (SMI) (all figures are mean ± SD unless stated otherwise).

Variables	*Microalbumuric patients with SMI*	*Normoalbumin-uric patients without SMI*	*P-value*
No. of patients	9	21	
Gender (male/female)	6/3	11/10	
Age (years)	55.3 ± 13	53.2 ± 6	*NS
Duration of diabetes (years)	5.75 ± 5.3	9 ± 7	*NS
Albumin : creatinine ratio	13.1 ± 7.3	14.6 -± 6.3	*NS
Total cholesterol (mg/dl)	208.2 ± 43.8	197.5 ± 44.5	*NS
HDL (mg/dl)	45 ± 11	50.3 ± 14	*NS
Fasting blood glucose (mg/dl)	156.2 ± 24.5	152 ± 27	*NS
Body mass index (kg/m^2)	28 ± 6.3	27.1 ± 6.6	*NS
SBP(mmHg) - Supine	142 ± 25	134.7 ± 26	*NS
- Erect	140 ± 22.4	131 ± 25	*NS
DBP(mmHg) - Supine	91 ± 12.6	84 ±11	*S
- Erect	89.4 ± 10	84 ±9.6	*NS
History of Hypertension No.(%)	3 (33.3%)	6 (26.5%)	**NS
Smoking status No. (%)	1 (11%)	4 (19%)	**NS
Diabetic retinopathy No. (%)	8 (88.8%)	6 (28.5%)	**S

* t-test .

** z-test .



Figure–I: Clinical presentations of microalbuminuric patients with SMI during TET.

included only those patients over 60 years of age, the prevalence of SMI would have been increased to (44.4%), 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.

Several authors[17,18] have reported the association between high systolic blood pressure and MA, supporting our finding of high systolic (and even diastolic) blood pressure among patients with 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 NA, 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 (Figure-I and II) demonstrated that, all the 9 patients with abnormal TET showed ischemic ECG changes in the form of ST segment depression (8 patients) and pseudonormalization of T wave (one patient), most of these ECG changes were accompanied by a clinical features like hypotension, shortness of breath and fatigue. Interestingly, we observed that inspite of a maximum exercise, 3 (33.3%) 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. 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 microal- buminuric patients and spared others?

In an attempt to answer this question, we divided the microalbuminuric patients into 2 groups (Table-IV): microalbuminuric patients with SMI vs. microalbuminuric patients without SMI. Using most of the variables applied in Table-I and II, 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 patients without SMI.

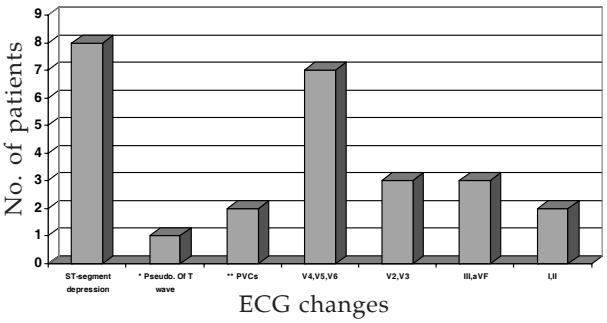


Figure –II: Electrocardiographic (ECG) changes during TET and distribution of the ischemia among ECG leads.

* Pseudo. of T wave : Pseudonormalization of T wave .

** PCVs : Premature ventricular contractions.

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 full lipid profile and angiographic confirmation of myocardial ischemia. However, with limited resources and prevailing conditions in Iraq, it has not been possible.

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