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Original Research Article

Prevalence of silent myocardial ischemia in type 2 diabetes mellitus with microalbuminuria

Sonu Chauhan[1]*, Mrinmay Ghosh[2], Pramod Kumar Agrawal[3], Mrityunjay Pratap Singh[4], Wasim Alam[5]

[1]Junior Resident, [2]Professor, [3]Professor and Head, [4]Associate Professor, [5]Junior Resident, Department of General Medicine, Katihar Medical College, Katihar, Bihar, India

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***Correspondence:**
Dr. Sonu Chauhan,
E-mail: sonuprachi3008@gmail.com

ABSTRACT

Background: The study was designed to assess the prevalence of silent myocardial ischemia (SMI) in asymptomatic patients of type 2 diabetes mellitus (T2DM) with and without microalbuminuria, by the exercise electrocardiography and to assess the role of microalbuminuria as a marker for detecting silent coronary artery disease (CAD) and role of other conventional CAD risk factors in diabetic patients in development of SMI.
Methods: A total of 60 patients with type 2 diabetes mellitus who were dipstick negative for macroalbuminuria and had no history suggestive of CAD or ECG abnormality were taken. Out of 60 patients 30 patients were positive for microalbuminuria by Micral Test® II sticks and 30 were tested negative for microalbuminuria. Subsequently, they were divided into case and control groups.
Results: The risk of undetected CAD was increased in male Type 2 diabetics ($p < 0.05$) and in the presence of Microalbuminuria ($p < 0.05$). A positive correlation was found between exercise time and amount of work performed during treadmill test (TMT). A positive TMT with angiographically proven significant coronary stenosis is higher in male and in patients having microalbuminuria.
Conclusions: Patients with T2DM and microalbuminuria have significant association with SMI as proven by TMT and coronary angiography. Patient have SMI with severe disease might benefit from revascularization. Patients with less severe disesase may benefit from drug and lifestyle interventions.

Keywords: Coronary artery disease, Diabetes mellitus, Microalbuminuria, Silent myocardial ischemia, Treadmill test

INTRODUCTION

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia.[1] It results from a defect in insulin secretion and/or insulin action, which results in hyperglycemia with disturbances of carbohydrate, fat and protein metabolism.[2] Diabetes is one of the commonest chronic non-communicable disease affecting the society at large both in developing and developed countries. It is generally classified as type 1, type 2 or other specific types.[3] Type 1 diabetes is caused by autoimmune destruction of insulin producing cells (β cells) in the pancreas, resulting in absolute insulin deficiency, whereas type 2 diabetes is characterized by resistance to the action of insulin and an inability to produce sufficient insulin to overcome this ‘ insulin resistance’.[4] Globally, all types of diabetes are on the increase, type 2 diabetes in particular.[5] While diabetes has been known for many centuries, the prevalence has reached epidemic level proportion only recently.[6] The rise of prevalence has been more alarming in developing countries than in developed countries (69% versus 20%). There has also been a trend towards a shift in the mean age of onset of type 2 diabetes to a much younger age.[7]

As per the 6th edition of International Diabetes Federation Atlas, it is estimated that there are currently 387 million people with diabetes worldwide and this number is set to increase to 592 million by the year 2035. The major proportion of this increase will occur in developing countries of the world like India.[8] India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "Diabetes Capital of the World". According to ICMR-INDIAD (Indian Council of Medical Research - India Diabetes) National diabetes study, currently there are an estimated 62.4 million individual with diabetes in India.[9] This is further expected to increase to 101 million in 2030, unless urgent preventive steps are taken.[10] The first national study on the prevalence of type 2 diabetes in India was done from 1972 and 1975 by the Indian Council Medical Research (ICMR, New Delhi).[13] The prevalence was 2.1% in urban population and 1.5 % the rural population while in those above 40 years of age, the prevalence was 5 % in urban and 2.8% in rural areas.

Silent myocardial ischemia is common in diabetic patients and may delay or mask the diagnosis of coronary artery disease (CAD), particularly in its early stages.[11] CAD is one of the microvascular complication accounting for as many as 80% of death in diabetic patients, furthermore the prevalence of silent myocardial ischemia (SMI) among the individuals with DM is high ranging from 20% to > 50%.[12]

In diabetes, myocardial ischemia tend to be more extensive and have a poorer survival rate than in age, weight and sex matched individuals without diabetes.[13] The prevalence of SMI is 10-20% in diabetic patients versus 1-4% in non-diabetic patients.[14] Because of the prevalence in the diabetic population and its overwhelming burden of early mortality, careful evaluation of coronary artery disease risk is crucial. By 2020 it is estimated that CAD will be the major cause of death in all regions of the world.[15]

Microalbuminuria is now recognised as a marker of endothelial dysfunction.[16] Endothelial dysfunction is considered to be one of the most important pathophysiological precursor to the development of cardiovascular disease. Thus the presence of microalbuminuria can be an important clue to identify asymptomatic diabetic patients with underlying cardiovascular disease.

Aim of the study was to study the prevalence of silent myocardial ischemia (SMI) in asymptomatic patients of type 2 diabetes mellitus (DM), with and without microalbuminuria (case vs. control), by exercise electrocardiography (ECG) and thus to assess the role of microalbuminuria as a marker for detecting silent CAD, to assess the role of other conventional CAD risk factors in diabetic patients in development of SMI, to further confirm and then analyze the pattern of CAD by coronary angiography in subjects with positive stress test.

METHODS

The study was a case control study conducted over a period of February 2015 to January 2016; involving type 2 diabetic subjects attending diabetic clinic or medicine OPD and indoor department of Katihar Medical College and Hospital, Katihar, Bihar, India were selected.

A total of 60 patients with Type 2 diabetes mellitus in the age group of 30 - 60 years, who were dipstick negative for macroalbuminuria and had no history suggestive of coronary artery disease or ECG abnormality were taken. Out of 60 patients 30 patients were positive for microalbuminuria by Micral Test® II sticks and 30 were tested negative for microalbuminuria. Subsequently, they were divided into case and control groups.

30 patients who were positive for microalbuminuria were taken as case group and these 30 patients tested positive for microalbuminuria on repeat testing by Micral Test® II sticks in a time interval of 6 months. 30 controls from the normoalbuminuria group were matched for age, gender, diabetes duration and smoking status with microalbuminuria cases and were enrolled for the study.

The following parameters were evaluated in all cases and controls.

- Fasting plasma glucose
- HbA1c level
- Known diabetes duration
- Treatment
  a) Oral treatment
  b) Insulin±oral treatment.
- History of smoking
- Family history of premature CHD
- Body mass index (BMI)
- Waist circumference
- Hypertension
- Dyslipidemia
- A 12 lead electrocardiogram
- Treadmill test (TMT).

Inclusion criteria

- Diabetes was diagnosed according to ADA[17] criteria
- A urinary albumin level of 20-200mg/L as detected by semi-quantitative Micral test® II sticks (equivalent to 30-300 mg/ 24 hours) was considered as microalbuminuria
- Age between 30 to 60 years.

Exclusion criteria

- History of acute coronary syndromes (unstable angina, NSTEMI, STEMI)
- History of angina
- History of CVA

- Heart failure, significant valvular disease, cardiomyopathy
- Any history of uncontrolled cardiac arrhythmia or AV block
- Pregnancy
- Liver disease
- Severe chronic obstructive pulmonary disease
- Kidney disease, urinary tract infection
- History of peripheral vascular disease
- Conditions which will not permit exercise ECG (amputation, foot wound, severe obesity etc.)
- Patient on digitalis therapy
- Patients with abnormalities in resting ECG were excluded from the study
- Contraindication of TMT 18
- Contraindications of Angiography 19.

RESULTS

The success of the matching was demonstrated by no significant differences in age, gender, known diabetes duration or smoking status between the case and control groups. The body mass index (BMI) and waist circumference of the two groups were also similar. The case and control groups did not have statistically significant difference with respect to their systolic and diastolic blood pressure (For SBP P value = 0.253; for DBP P value = 0.356). There was also no statistically significant difference in the presence of family history of premature coronary artery disease (CAD) between the two groups. The two groups were also similar with respect to their fasting plasma glucose (FPG), HbA1c and lipid profile (LDL, HDL, Triglyceride, total cholesterol).

Table 1: Summary of patient characteristics in case and control groups.

Characteristics	Microalbuminuric	Normoalbuminuric	P value
Number	30	30	1
Age (years)	49.56±6.68	49.06±7.51	0.786
Male/female	13/17	13/17	1
Known DM duration (years)	6.45±3.51	6.38±3.74	0.944
Family history	14 (46.7%)	10 (33.3%)	0.292
Smoking	11 (36.7%)	10 (33.3%)	0.787
SBP (mmHg)	139±19.09	134.2±18.46	0.253
DBP (mmHg)	85.47±12.49	82.47±10.91	0.356
BMI	25.32±4.4	26.47±4.13	0.303
Central obesity	12 (40%)	13 (43.3%)	0.793
FPG (mg/dl)	157.17±40.95	159.2±36.393	0.84
HbA1c (%)	7.85±0.87	8.05±0.91	0.390
Total cholesterol (mg/dl)	207.72±32.83	208.62±32.32	0.915
Triglyceride (mg/dl)	194.2±48.38	195.02±46.74	0.947
LDL (mg/dl)	126.12±33.17	125.38±30.41	0.929
HDL (mg/dl)	42.76±8.15	44.24±9.89	0.532

Table 2: Exercise ECG results in case and control groups.

		Exercise ECG		
		Positive	**Negative**	**Non diagnostic**
Cases	N	14	14	2
	%	46.7%	46.7%	6.6%
Controls	N	7	21	2
	%	23.3%	70%	6.7%
Total	**N**	**21**	**35**	**4**
	%	**35%**	**58.3%**	**6.7%**

Table 3: Clinical parameter during exercise ECG test.

		n	Mean	SD	P-value
% of target heart rate	Cases	30	90.7	4.75	0.065
	Controls	30	94	8.32	
Exercise time (mins)	Cases	30	5.93	1.41	0.001
	Controls	30	7.61	2.24	
Work done (METS)	Cases	30	7.15	1.17	0.001
	Controls	30	8.75	2.14	

Coronary angiography results

Exercise ECG was positive in 14 cases and 7 controls. Coronary angiography was done in all of these 21 patients. 12 out of 14 patients with microalbuminuria had more than 50% stenosis which is suggestive of significant coronary artery disease. 3 out of 7 patients in the control group were found to have more than 50% stenosis.

Overall prevalence of silent CAD (> 50% stenosis in major coronary arteries or their major branches) in the study group as adjudged by angiography was 25% (15 out of 60 type 2 diabetics).

Table 4: True and false positvity rates in case and control groups.

		Exercise ECG		
		True positive	**False positive**	**Total**
Cases	n	12	2	14
	%	85.7%	14.3%	100%
Controls	n	3	4	7
	%	42.9%	57.1%	100%
Total	**n**	**15**	**6**	**21**
	%	**71.4%**	**28.%**	**100%**

71.4% of the patients (15 of 21) who had a positive exercise ECG test were found to have significant CAD.

Pearson chi square test P value = 0.04 (Significant).

There was statistically significant association between a true positive stress ECG result and presence of microalbuminuria.

There was statistically significant difference in true positivity rate of stress ECG result among males and females (P value = 0.018).

Table 5: True and false positivity rates in males and female.

		Exercise ECG		
		True positive	**False positive**	**Total**
Males	n	11	1	12
	%	91.7%	8.3%	100%
Females	n	4	5	9
	%	44.4%	55.6%	100%
Total	**n**	**15**	**6**	**21**
	%	**71.4%**	**28.6%**	**100%**

SMI and microalbuminuria

The overall prevalence of SMI in the study group was 25% (n = 15).

40% (n = 12) of patients with microalbuminuria had SMI, whereas 10% (n = 3) of normoalbuminuria patients had SMI. Pearson chi square test P value = 0.007 (Significant) There was statistically significant association between SMI and microalbuminuria.

Table 6: Clinical characteristics of patients with or without silent CAD.

Characteristics	SMI present	SMI absent	P value
Number	15	45	-
Microalbuminuria	12 (80%)	18 (40%)	0.007
Age (years)	50.93±6.50	48.77±7.22	0.786
Male/Female	11/4	15/30	0.007
Known DM duration (years)	6.80±3.76	6.28±3.57	0.944
Family history	6 (40%)	18 (40%)	1
Smoking	4 (26.7%)	17 (37.8%)	0.435
SBP (mmHg)	137.33±18.93	136.88±19.01	0.938
DBP (mmHg)	83.06±12.80	84.26±11.48	0.735
BMI	25.77±4.04	25.93±4.39	0.899
Central obesity	4 (26.7%)	21 (46.7%)	0.174
FPG (mg/dl)	154±37.20	159.57±39.13	0.633
HbA1c (%)	7.86±0.88	7.98±0.90	0.644
Total cholesterol (mg/dl)	220.46±39.88	204.07±29.53	0.089
Triglyceride (mg/dl)	205±42.87	191.14±48.47	0.329
LDL (mg/dl)	133.46±39.88	123.18±28.32	0.278
HDL (mg/dl)	46±8.01	42.66±9.26	0.218

When males ≥ 45 years and females ≥ 55 years were considered, a significant association was found between SMI and patients belonging to age group above the said limits (P value = 0.05).

Table 7: Age group and SMI.

SMI		Age group (years)	
		Males (≥ 45) or Females (≥ 55)	Males (< 45) or females (< 55)
Yes	N	10	5
	%	66.7%	33.3%
No	N	17	28
	%	37.8%	62.2%
Total	N	27	33
	%	45.0%	55.0%

TMT variables and SMI

Besides the conventional parameters, the following exercise stress ECG variables like percentage of target heart rate achieved, exercise time and work performed (METS) were analyzed for any significant association with SMI.

Exercise time and amount of work performed during exercise stress test were found to have significant statistical association with presence of SMI (P values = 0.007 and 0.005 respectively).

However, percentage of target heart rate achieved failed to show any significant statistical association with presence of SMI (P value = 0.791).

Table 8: Exercise ECG parameters and SMI.

	SMI	N	Mean	SD	P value
% of target heart rate	Yes	15	91.93	3.51	0.791
	No	45	92.48	7.76	
Exercise time (mins)	Yes	15	5.51	1.53	0.007
	No	45	7.19	2.02	
Work done (METS)	Yes	15	6.84	1.28	0.005
	No	45	8.32	1.92	

Table 9: Angiographic characteristics of patients with significant CAD.

Angiographic characteristics	Percentage (number)
Single vessel disease (SVD)	33.3 (5)
Double vessel disease (DVD)	40 (6)
Triple vessel disease (TVD)	26.67 (4)
Severe stenosis	73.3 (11)
Eccentric lesions	100 (15)

DISCUSSION

In this study, 30 patients of microalbuminuria positive by Micral test ® II sticks were taken. In the UKPDS study group 20, at diagnosis of diabetes 7.3% of patients had microalbuminuria or worse, which increased to 17.3% after 5 years, 24.9% after 10 years and 28% after 15 years. Gupta et al reported a prevalence of 26.6% in 65 type 2 diabetic North Indian patients.[21]

The prevalence rate for positive exercise ECG response in this study group was 35% (21/60). The prevalence rate for positive exercise test in patients with microalbuminuria was 46.7% (14/30) and that in patient without microalbuminuria was 23.3% (7/30). In a study by Delenne J et al, 203 of type 1 and type 2 DM patients were screened for SMI by exercise ECG.[22] Positive screening results were obtained in 32 patients (15.7%). The positivity rate in Milan study was 12% but lower than those in studies by Koistinen and Naka et al, who reported 29% and 31% positive exercise tests respectively.[23-25] Exercise time and amount of work performed during exercise stress test were found to have significant association with presence of SMI (P values = 0.007 and 0.005 respectively). However, percentage of target heart rate achieved failed to show any significant association with presence of SMI (P value = 0.791).

In meta-analysis of 147 studies, mean sensitivity and specificity of exercise testing was reported as 68% and 77% respectively.[26] In this study, 71.4% of patients who had a positive exercise ECG response had CAD, as defined by > 50% stenosis of major coronary artery or its major branches on angiography. A true positive result to a positive exercise ECG response was present in 85.7% of patients with microalbuminuria. However, a true positive result to a positive exercise ECG was present in 42.9% of the patients with normoalbuminuria (p=0.04).

Male patients also had a higher true positivity rate of 91.7% compared with 44.4% of that for females (p = 0.018). In the study by Delenne J et al, the positive predictive value of screening test after excluding patients who declined coronary angiography was 76% overall and rise to 87% for male patients with type 2 DM.[22]

Overall prevalence of silent CAD (>50% stenosis in major coronary arteries or their major branches in the absence of clinical or electrocardiographic evidence of CAD) in the study group as adjudged by angiography was 25% (15 out of 60 type 2 diabetics). 40% (n = 12) of patients with microalbuminuria had SMI, whereas only 10% (n = 3) of normoalbuminuric patients had SMI.In recent studies in which positive noninvasive screening tests were confirmed by coronary angiography, the prevalence of SMI with significant coronary artery stenosis was 9.3% according to Janand-Delenne et al, 9% according to Koistinen, 12% according to Naka et al in type 2 diabetes.

In our study, beside microalbuminuria the factor which was predictive of SMI was male sex. When patients in the age group considered to be at risk for CAD were considered (males ≥ 45 years and females ≥ 55 years) a significant risk of SMI was found to be present in those belonging to the higher age group (p = 0.05). No other clinical variable like duration of diabetes, diabetic control, family history of premature CAD, smoking status, SBP and DBP, presence of central obesity or lipid profile were found to have a significant association with presence of SMI.

In the study by Delenne J et al, involving both type 1 and type 2 diabetics, a significant correlation was observed between coronary stenosis, male sex, and family history of CAD and above all, arterial disease and high number of major cardiovascular risk factors. In a study in Spain, involving 353 asymptomatic Caucasians of which 217 were diabetic, subjects with SMI were found to be older and had a higher prevalence of autonomic neuropathy, hypertension and dyslipidemia. Microalbuminuria was also higher in the SMI group ($p<0.05$).[27] In our study, microalbuminuria, male sex, treatment with insulin and age higher than 45 years in males and 55 years in females have been found to be predictive of presence of SMI.

CONCLUSION

Patients with T2DM and microalbuminuria were more likely to have SMI. Prevalence of angiographically proven SMI in type 2 diabetic Indian population is 25% and is higher than that reported in western literature. The likelihood of positive exercise ECG test to correlate with angiographically proven significant coronary stenosis is higher in male patients and in patients having microalbuminuria. A positive correlation was found between exercise time and amount of work performed during exercise stress test and presence of SMI. The study reveals the need for more intensive work up for detecting silent CAD in Indian diabetic patients, especially in the presence of microalbuminuria. Patients identified to have SMI with severe disease might benefit from some form of coronary revascularization. Patients with less severe disease may benefit from pharmacological and lifestyle interventions.

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