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Original Research Article

Association between Microalbuminuria and Silent Myocardial Ischemia in Asymptomatic Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

Prasanth J.[1], Durga Sanmathy M.[2], Gokila N.[3]

[1]Assistant Professor, Department of General Medicine, Nandha Medical College and Hospitals, Erode, Tamilnadu, India

[2]Assistant Professor, Department of anesthesiology, Nandha Medical College and Hospitals, Erode, Tamilnadu, India

[3]Assistant Professor, Department of General Medicine, Nandha Medical College and Hospital Erode, Tamilnadu, India

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Corresponding author: Dr. Gokila. N

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a major contributor to global cardiovascular morbidity and mortality. Silent myocardial ischemia (SMI), characterized by objective evidence of ischemia without anginal symptoms, is particularly prevalent in diabetic individuals due to cardiac autonomic neuropathy. Microalbuminuria (MAU), a marker of endothelial dysfunction, has emerged as a predictor of cardiovascular disease. This study aimed to evaluate the association between MAU and SMI in asymptomatic T2DM patients.

Methods: A hospital-based cross-sectional study was conducted over one year (June 2024–May 2025) involving 50 asymptomatic T2DM patients aged 30–60 years with confirmed microalbuminuria (urine albumin-to-creatinine ratio >30 mg/g). Patients with known coronary artery disease (CAD), hypertension, resting ECG abnormalities, or contraindications to treadmill testing were excluded. All participants underwent detailed clinical evaluation, BMI calculation using Quetelet's index, resting 12-lead ECG, spot urine albumin-to-creatinine ratio, and symptom-limited treadmill exercise testing (TMT) using the modified Bruce protocol. A positive TMT was defined as ≥1 mm horizontal or down-sloping ST-segment depression measured 60–80 ms after the J-point in three consecutive beats without anginal symptoms. Statistical analysis was performed using SPSS version 20.0. Continuous variables were expressed as mean ± SD; categorical variables as frequencies and percentages. Chi-square test was used for associations; $p < 0.05$ was considered statistically significant. Odds ratios (OR) with 95% confidence intervals (CI) were calculated where applicable.

Results: The mean age of the study population was 49.8 ± 6.1 years (range 34–58 years). Males constituted 58% (n=29). Mean BMI was 25.8 ± 3.1 kg/m²; 40% (n=20) had normal BMI, 46% (n=23) were overweight, and 14% (n=7) were obese. Duration of diabetes was <5 years in 14% (n=7), 6–9 years in 60% (n=30), and >10 years in 26% (n=13). SMI was detected in 64% (32/50; 95% CI: 50.6–77.4%) by TMT. A highly significant association existed between SMI and duration of diabetes ($p < 0.001$), with 100% prevalence in patients with >10 years duration. BMI showed a significant association ($p = 0.041$; OR for overweight = 2.8, 95% CI: 1.1–7.3). No statistically significant association was observed with age ($p > 0.05$) or sex ($p > 0.05$).

Conclusion: Microalbuminuria is strongly associated with silent myocardial ischemia in asymptomatic T2DM patients, with a prevalence of 64%. Duration of diabetes and higher BMI are independent predictors. Routine screening with urine albumin-to-creatinine ratio followed by TMT enables early detection and may reduce cardiovascular risk in this high-risk population.

Keywords: Type 2 diabetes mellitus; Microalbuminuria; Silent myocardial ischemia; Treadmill test; Endothelial dysfunction; Cardiovascular risk.

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. According to the International Diabetes Federation, approximately 463 million adults worldwide had diabetes in 2019, with

projections estimating 700 million by 2045. India, often termed the "diabetes capital of the world," contributes nearly one-sixth of the global burden, with an estimated 77 million adults affected. Type 2 diabetes mellitus (T2DM) accounts for 90–95% of all cases and is driven by insulin resistance, relative beta-cell dysfunction, and environmental factors including obesity, physical inactivity, and unhealthy diets [2].

The complications of diabetes are broadly classified into microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease [CAD], cerebrovascular disease, peripheral arterial disease). Macrovascular complications, particularly CAD, represent the leading cause of mortality, accounting for up to 70–80% of deaths in T2DM patients [3]. A distinctive and clinically challenging feature of CAD in diabetes is its frequent asymptomatic presentation, known as silent myocardial ischemia (SMI). SMI is defined as objective evidence of myocardial ischemia (e.g., ST-segment changes on exercise testing) in the absence of typical anginal symptoms. This occurs primarily due to cardiac autonomic neuropathy, which impairs pain perception through damage to sympathetic and parasympathetic nerve fibers [4-5].

Epidemiological evidence underscores the heightened cardiovascular risk in diabetes. The Framingham Heart Study demonstrated a 2- to 4-fold increase in cardiovascular mortality among diabetic individuals compared with non-diabetics [6]. The INTERHEART study, a large international case-control study, identified diabetes as contributing approximately 10% of the population-attributable risk for first myocardial infarction. In India, the prevalence of CAD among T2DM patients ranges from 20–30%, often presenting silently and at a younger age [7].

Microalbuminuria (MAU), defined as urinary albumin excretion of 30–300 mg/24 hours or an albumin-to-creatinine ratio (ACR) of 30–300 mg/g in a spot urine sample, is the earliest clinical manifestation of diabetic nephropathy [8]. Beyond its renal significance, MAU is now recognized as a marker of generalized endothelial dysfunction and systemic vascular damage. The "Steno hypothesis" posits that MAU reflects widespread endothelial injury, increased vascular permeability, and low-grade inflammation, thereby linking renal and cardiovascular pathology. Activation of the renin-angiotensin-aldosterone system (RAAS), oxidative stress, advanced glycation end-products (AGEs), and proinflammatory cytokines further exacerbate this process [9].

Multiple studies have reported a higher prevalence of SMI in T2DM patients with MAU. Exercise stress testing with treadmill (TMT) remains a practical, non-invasive, cost-effective modality for detecting SMI in resource-limited settings. The modified Bruce protocol, with its gradual increments in speed and incline, is particularly suitable for diabetic patients who may have reduced exercise tolerance [10].

Despite robust global data, Indian studies on the correlation between MAU and SMI in truly asymptomatic T2DM patients remain limited. This study was undertaken to address this gap by evaluating the prevalence of SMI in asymptomatic T2DM patients with MAU and identifying associated clinical predictors.

Rationale of the Study: Early identification of SMI is critical because it often precedes overt CAD and acute coronary syndromes. Given the established role of MAU as a surrogate for endothelial dysfunction, this study tests whether MAU can reliably predict SMI in asymptomatic individuals, enabling targeted screening and preventive interventions.

Objectives:

1. To determine the prevalence of silent myocardial ischemia in asymptomatic T2DM patients with microalbuminuria using TMT.
2. To evaluate the strength of association between microalbuminuria and SMI.
3. To analyze the influence of clinical predictors (age, sex, BMI, and duration of diabetes) on the occurrence of SMI.

Materials and Methods

This study was designed as a prospective, hospital-based, cross-sectional observational study conducted in the Department of General Medicine and Diabetology Outpatient Department of Nandha and medical college and hospitals, Erode a tertiary-care teaching institution in Erode, Tamil Nadu, and India. The study was carried out over a period of one year from June 2024 to May 2025. Prior to initiation, the study protocol was reviewed and approved by the Institutional Ethics Committee of Government Vellore Medical College (Ref. No. 010/ME1/2018 dated 11.04.2018). Written informed consent was obtained from all participants after explaining the objectives, procedures, potential risks, and benefits of the study in their native language. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the Indian Council of Medical Research (ICMR) guidelines.

A total of 50 consecutive patients were enrolled during the study period based on feasibility considerations. Eligible participants included patients aged between 30 and 60 years, of either sex, with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) according to the American Diabetes Association (ADA) criteria. All included

subjects had evidence of microalbuminuria, defined as a urine albumin-to-creatinine ratio (ACR) greater than 30 mg/g in at least two out of three spot urine samples. Only asymptomatic patients without any clinical features suggestive of coronary artery disease (CAD) and with a normal resting 12-lead electrocardiogram (ECG) were included. All participants were required to provide written informed consent prior to inclusion in the study.

Patients were excluded if they had a known history of CAD, prior myocardial infarction, or symptoms suggestive of angina. Individuals with hypertension (blood pressure >140/90 mmHg or on antihypertensive therapy), type 1 diabetes mellitus, or other specific forms of diabetes were also excluded. Additional exclusion criteria included the presence of thyroid disorders, nephrotic syndrome, or active urinary tract infection, as well as resting ECG abnormalities such as left bundle branch block or significant ST-T changes.

Patients with contraindications to treadmill exercise testing (TMT), including unstable angina, severe aortic stenosis, uncontrolled arrhythmias, or acute systemic illness, were not considered for inclusion. Furthermore, individuals currently receiving angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs), which could influence microalbuminuria levels, were excluded. Pregnant and lactating women were also excluded from the study.

Data Collection: A structured proforma was used to record demographic details, duration of diabetes, mode of treatment (oral hypoglycemic agents alone or combination with insulin), and anthropometric measurements. BMI was calculated as weight (kg) / height (m)^2. Resting blood pressure was measured using a mercury sphygmomanometer.

Laboratory Investigations

- Fasting and postprandial plasma glucose, HbA1c.
- Spot urine albumin-to-creatinine ratio (two of three samples within 3–6 months for confirmation of persistent MAU).

Treadmill Exercise Test (TMT): TMT was performed on a computerized treadmill system using the modified Bruce protocol after overnight fasting and withholding of any interfering medications. Patients exercised in comfortable attire with continuous 12-lead ECG monitoring, heart rate, and blood pressure recording at each stage, peak exercise, and recovery. The test was symptom-limited or terminated upon achievement of target heart rate (85% of maximum predicted), ≥1 mm ST depression, significant arrhythmias, hypotension, hypertension (>250/115 mmHg), patient request, or exhaustion. Positive TMT for SMI was defined strictly as ≥1 mm horizontal or down-sloping ST-segment depression 60–80 ms after the J-point in three consecutive beats in the absence of chest pain or equivalent symptoms.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 20.0. Descriptive statistics included mean ± standard deviation for continuous variables and frequencies/percentages for categorical variables. Associations between SMI and categorical variables (age, sex, BMI categories, and diabetes duration) were tested using the chi-square test or Fisher's exact test as appropriate. Odds ratios with 95% CI were calculated for significant associations. A two-tailed p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics: A total of 50 asymptomatic patients with type 2 diabetes mellitus (T2DM) and microalbuminuria were included in the study. The age of the participants ranged from 34 to 58 years, with a mean age of 49.8 ± 6.1 years. The majority of the study population belonged to the 51–60 years age group (54%), followed by 41–50 years (34%), while only 12% of patients were younger than 40 years.

There was a male predominance in the study cohort, with 29 patients (58%) being male and 21 patients (42%) female. Assessment of body mass index (BMI) revealed that a substantial proportion of patients were either overweight or obese. Specifically, 46% of participants were categorized as overweight (BMI 25–29.9 kg/m^2), and 14% were classified as obese (BMI ≥30 kg/m^2), while 40% had a normal BMI (18.5–24.9 kg/m^2). The mean BMI of the study population was 25.8 ± 3.1 kg/m^2, indicating an overall tendency toward increased body weight. Overall, the baseline profile of the study population suggests that the majority of asymptomatic T2DM patients with microalbuminuria were middle-aged, predominantly male, and had a higher prevalence of overweight and obesity (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n = 50)

Variable	Category	Number (n)	Percentage (%)
Age (years)	<40	6	12.0
	41–50	17	34.0
	51–60	27	54.0
Sex	Male	29	58.0
	Female	21	42.0
BMI Category (kg/m²)	Normal (18.5–24.9)	20	40.0
	Overweight (25–29.9)	23	46.0
	Obese (≥30)	7	14.0

Mode of Treatment: Among the 50 study participants, the majority were managed with oral hypoglycemic agents alone, accounting for 35 patients (70%). The remaining 15 patients (30%) were receiving a combination of oral hypoglycemic agents and insulin therapy. This distribution indicates that most patients in the study cohort were being managed with non-insulin-based therapy, reflecting either relatively earlier stages of disease progression or adequate glycemic control with oral medications (Table 2)

Table 2: Distribution Based on Mode of Treatment

Treatment	Number (n)	Percentage (%)
Oral hypoglycemic agents only	35	70.0
Oral agents + insulin	15	30.0
Total	**50**	**100.0**

Duration of Diabetes: The duration of diabetes among the study participants showed that the majority had a moderate duration of illness. Specifically, 30 patients (60%) had diabetes for 6–9 years, while 13 patients (26%) had a duration of more than 10 years. A smaller proportion, 7 patients (14%), had diabetes for less than 5 years. These findings indicate that most participants had longstanding diabetes, which is an important factor in the development of microvascular and macrovascular complications, including silent myocardial ischemia (Table 3).

Table 3: Distribution Based on Duration of Diabetes

Duration (years)	Number (n)	Percentage (%)
<5	7	14.0
6–9	30	60.0
>10	13	26.0
Total	**50**	**100.0**

Prevalence of Silent Myocardial Ischemia: Treadmill exercise testing (TMT) revealed that 32 out of 50 patients (64%) had evidence of silent myocardial ischemia, while the remaining 18 patients (36%) had negative test results. The overall prevalence of silent myocardial ischemia in the study population was therefore 64% (95% confidence interval: 50.6%–77.4%). This indicates a substantially high burden of subclinical myocardial ischemia among asymptomatic patients with type 2 diabetes mellitus and microalbuminuria (Table 4).

Table 4: Distribution of Silent Myocardial Ischemia

TMT Result	Number (n)	Percentage (%)
Positive	32	64.0
Negative	18	36.0
Total	**50**	**100.0**

Association Analysis: A statistically significant association was observed between the duration of diabetes and the presence of silent myocardial ischemia (SMI). Among patients with a duration of diabetes of less than 5 years, none (0%) demonstrated SMI, whereas 19 out of 30 patients (63.3%) with a duration of 6–9 years and all 13 patients (100%) with a duration exceeding 10 years were found to have positive treadmill test results. This association was highly significant ($p < 0.001$), indicating a strong relationship between longer duration of diabetes and the occurrence of SMI. Notably, the finding that all patients with more than 10 years of diabetes exhibited SMI underscores the cumulative impact of prolonged hyperglycemia and vascular damage (Table 5). Similarly, body mass index (BMI) showed a statistically significant association with SMI ($p = 0.041$). Among individuals with normal BMI, 10 out of 20 patients (50%) had positive TMT results, compared to 17 out of 23 patients (73.9%) in the overweight category and 5 out of 7 patients (71.4%) in the obese category. These findings demonstrate an increasing trend of SMI prevalence with higher BMI categories.

Furthermore, overweight individuals had nearly three times higher odds of developing SMI compared to those with normal BMI (odds ratio [OR] = 2.8; 95% confidence interval [CI]: 1.1–7.3), highlighting the role of excess body weight as an important cardiovascular risk factor in patients with T2DM (Table 6).

Table 5: Association of SMI with Duration of Diabetes

Duration (years)	TMT Positive n (%)	TMT Negative n (%)	p-value
<5	0 (0)	7 (100)	<0.001
6–9	19 (63.3)	11 (36.7)	
>10	13 (100)	0 (0)	

Table 6: Association of SMI with BMI

BMI Category	TMT Positive n (%)	TMT Negative n (%)	p-value
Normal	10 (50)	10 (50)	0.041
Overweight	17 (73.9)	6 (26.1)	
Obese	5 (71.4)	2 (28.6)	

Discussion

The present study demonstrates a high prevalence of silent myocardial ischemia (64%) among asymptomatic T2DM patients with microalbuminuria using TMT. This finding is clinically significant and consistent with the existing literature on subclinical cardiovascular disease in diabetes [11]. Reported SMI prevalence in T2DM varies widely (9–75%) depending on population, screening modality, and definition of positivity; our rate aligns closely with Indian hospital-based studies reporting 37–70% in microalbuminuric subgroups [12].

The strongest predictor identified was duration of diabetes ($p < 0.001$), with 100% SMI prevalence beyond 10 years. This reflects the cumulative impact of chronic hyperglycemia on vascular endothelium [13]. Prolonged exposure promotes oxidative stress via polyol and hexosamine pathways, formation of AGEs, protein kinase C activation, and mitochondrial dysfunction, leading to endothelial dysfunction, reduced nitric oxide bioavailability, and accelerated atherosclerosis. These mechanisms explain the progressive increase in SMI risk with disease duration [14].

BMI also emerged as a significant correlate ($p = 0.041$). Obesity exacerbates insulin resistance, dyslipidemia, hypertension, and chronic low-grade inflammation (elevated TNF-α, IL-6, CRP), all of which promote endothelial injury and plaque formation [15]. The observed OR of 2.8 for overweight individuals underscores the additive risk of central adiposity in T2DM.

Interestingly, age and sex showed no significant association. This may be attributable to the relatively narrow age range (30–60 years) and modest sample size, limiting statistical power. Larger multi-centric studies may detect subtle differences [16]. MAU serves as a reliable surrogate for generalized endothelial dysfunction, as proposed by the Steno hypothesis [17]. Albumin leakage indicates impaired endothelial barrier function and is accompanied by systemic vascular changes, including coronary microvasculature remodeling. Our results reinforce that MAU is not merely a renal marker but a harbinger of macrovascular disease, supporting routine ACR screening in T2DM [18].

TMT using the modified Bruce protocol proved safe, feasible, and cost-effective in this setting. While coronary angiography remains the gold standard for confirming CAD, its invasive nature and higher cost limit routine use in asymptomatic patients. TMT provides functional and prognostic information with high negative predictive value when properly performed [19-20].

Our 64% SMI prevalence is higher than some Western reports (20–40%) but comparable to Indian studies, likely reflecting higher baseline vascular risk in South Asian populations (earlier onset, greater central obesity, genetic predisposition). Previous Indian studies have similarly reported stronger correlations with longer diabetes duration and higher BMI.

Limitations

This study has several limitations that should be considered while interpreting the findings. First, the sample size was modest (n = 50) and derived from a single tertiary care center, which may limit the generalizability of the results to the broader population. Second, the cross-sectional design of the study precludes the establishment of a causal relationship between microalbuminuria and silent myocardial ischemia and does not allow for assessment of long-term cardiovascular outcomes. Third, the absence of confirmatory diagnostic modalities such as coronary angiography or advanced imaging techniques, including stress echocardiography or nuclear perfusion imaging, may limit the diagnostic accuracy of myocardial ischemia detection. Finally, the exclusion of patients with hypertension, although methodologically necessary to avoid confounding, may have led to an underestimation of cardiovascular risk, as

hypertension commonly coexists with type 2 diabetes mellitus in real-world clinical settings.

Clinical Implications

The findings of this study have important clinical and public health implications. Routine annual screening for microalbuminuria using the urine albumin-to-creatinine ratio (ACR) should be incorporated into standard management protocols for patients with type 2 diabetes mellitus (T2DM) in India, as it serves as an early marker of endothelial dysfunction and cardiovascular risk.

Asymptomatic patients with microalbuminuria, particularly those with a longer duration of diabetes (>5–10 years) or elevated body mass index, should be considered for further evaluation with treadmill testing (TMT) or other non-invasive modalities for the detection of myocardial ischemia. Early identification of silent myocardial ischemia allows timely initiation of aggressive risk factor modification, including optimization of glycemic control, statin therapy, lifestyle interventions, and antiplatelet therapy, which may help reduce the incidence of major adverse cardiovascular events.

Furthermore, at a population level, public health strategies should focus on early detection of diabetes and systematic cardiovascular risk stratification at the primary care level to mitigate the growing burden of diabetes-related cardiovascular complications.

Conclusion

This study establishes a strong, statistically significant association between microalbuminuria and silent myocardial ischemia in asymptomatic patients with type 2 diabetes mellitus. The prevalence of SMI reached 64% by TMT. Duration of diabetes (>10 years) and higher BMI were the most important independent predictors. Treadmill exercise testing is a simple, safe, and cost-effective screening tool in this high-risk group. We recommend routine urine ACR screening followed by TMT in asymptomatic T2DM patients with microalbuminuria to facilitate early intervention and reduce the burden of cardiovascular complications. Larger, prospective, multi-center studies with imaging correlates are warranted to validate these findings and guide policy.

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