

# Evaluation of microalbuminuria in type-2 diabetes mellitus under oral hypoglycemic agents: Association with age, sex, BMI, and renal clearance

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## ABSTRACT

**Background:** Diabetes mellitus (DM) is increasing drastically and affecting the individuals globally, especially in the low- and middle-income countries like India. The poor glycaemic control results in micro-vascular and macro-vascular complications, leading to dysfunction of multiple organs. This study aimed to evaluate the association between the risk factors and microalbuminuria levels among patients with type 2 DM on oral hypoglycaemic agents. **Materials and Methods:** Hundred type 2 DM patients fulfilling the inclusion and exclusion criteria were selected by convenient random sampling. Demographic details, biochemical markers, and anti-diabetic medication details were collected. The findings were analyzed statistically using Chi-square test and one-way analysis of variance (ANOVA) with SPSS software 21.0. **Results:** Among the different combination therapies, 59% were commonly using metformin and teneligliptin. There was a significant association noted between microalbuminuria and risk factors like age, duration of disease, body mass index (BMI) ( $25.5 \pm 2.9$ ), fasting blood sugar ( $151 \pm 53.2$  mg/dL), post prandial blood sugar ( $227.01 \pm 70.9$  mg/dL), blood urea ( $24.42 \pm 9.3$  mg/dL), and serum creatinine ( $1.5 \pm 0.2$  mg/dL) ( $P < 0.001$ ). One-way ANOVA showed statistical significance between microalbuminuria and the different treatment groups ( $P < 0.0001$ ). **Conclusion:** Microalbuminuria was associated with age, duration of diabetes, glycaemic control, and BMI. In contrast, there was no significant difference noted between the genders and microalbuminuria. Microalbuminuria is an early indication of nephropathy in diabetes patients. The early identification of the risk factors is important, and it is always recommended to screen for microalbuminuria in all the diabetic patients for early detection and prevention of diabetic nephropathy and their associated complications.

**Keywords:** Diabetes mellitus, diabetic nephropathy, microalbuminuria, oral hypoglycaemic agents

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## Introduction

Diabetes mellitus (DM) is a global health problem and one of four priority non-communicable and chronic metabolic diseases altering the anatomical and physiological needs of the body,

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resulting in diverse complications.<sup>[1]</sup> These problems affect the daily activity of the individuals and alter the quality of life. According to the global burden of DM, the estimated prevalence rate in 2019 was 463 million, followed by an estimated drastic upsurge in 2030 (578 million), and if the necessary steps are not taken to rectify the secondary complications, it will end up in 700 million by 2045. Additionally, a higher prevalence is noted in urban compared to rural areas and in the high-income than in the low-income countries.<sup>[2]</sup> In India, the prevalence of diabetes has been steadily increasing over the past few decades from 7.1% in 2009 to 8.9% in 2019. Currently, 25.2 million adults are estimated to have impaired glucose tolerance, which is expected to increase to 35.7 million by 2045.<sup>[3]</sup> The aetiological classification of type 1 and type 2 has been accepted globally; more than 85% are of type 2 diabetes with micro-vascular and macro-vascular complications.<sup>[4]</sup> These long-term vascular complications cause insults to vital organs like eyes, kidney, heart, and peripheral nerves, which increases the morbidity and mortality.<sup>[5]</sup> The American Diabetes Association (ADA) criteria for the diagnosis of DM include symptoms (polyuria, polydipsia, and unexplained weight loss) and a random blood glucose concentration of greater than 200 mg/dL (11.1 mM), a fasting blood glucose concentration of greater than 126 mg/dL (7 mM), or a blood glucose concentration of greater than 200 mg/dL (11 mM) 2 hours after the ingestion of an oral glucose load.<sup>[6]</sup> The primary goal of the researchers and clinicians is to reduce the blood glucose level, secondary complications, and treatment among the type 2 diabetes individuals.<sup>[7]</sup> Additionally, a multi-professional approach is required to reduce the secondary complications of DM through modifications of lifestyle with adequate diet and exercise and oral hypoglycaemic drugs. Lifestyle modifications must be combined with oral pharmacologic agents for optimal glycaemic control, particularly as type 2 DM progresses with continued loss of pancreatic beta-cell function and insulin production. Globally, over a period of 6 decades, metformin is considered as a first-line drug of choice to treat DM.<sup>[8]</sup> In recent years, combinations of novel drugs have been preferably used to alleviate and reduce the secondary complications in type 2 DM.<sup>[9]</sup> The micro-vascular and macro-vascular complications lead to dysfunction of multiple organs in chronic diabetes individuals with poor glycaemic control.<sup>[10]</sup> The macro-vascular complications are noted in the vital organs like heart and brain due to alteration in the blood flow, which affects the normal physiological actions. Additionally, the micro-vascular blood vessels affect the tissues and induce complications such as diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy.<sup>[11]</sup> Microalbuminuria (MAU) is an important risk factor for the progression of renal and cardiovascular diseases in DM patients. The identification of the acute renal complications at the earliest is necessary to prevent the chronic diabetes-induced renal failure and the complications.<sup>[12]</sup> Microalbuminuria is likely to be more in diabetes patients; hence, the American Diabetes Association had recommended annual screening of microalbuminuria to all type 2 diabetes patients irrespective of duration of DM.<sup>[13]</sup> Studies have documented the correlation of microalbuminuria with gender, body mass index (BMI), blood

pressure, and duration of disease.<sup>[14-16]</sup> There are only a few studies assessing the correlation between microalbuminuria and glycaemic control with oral hypoglycaemic agents. Therefore, this study was aimed to evaluate the microalbuminuria levels in type 2 diabetes patients treated with various oral hypoglycaemic drugs and to evaluate the association of microalbuminuria with the above-mentioned variables.

## Materials and Methods

A hospital-based cross-sectional study was conducted among the out-patients and in-patients of the diabetology department in a tertiary care teaching hospital in Puducherry over a period of 6 months between December 2017 and May 2018. The study was initiated after obtaining permission from the Institutional Ethics Committee (SVMCH/IEC/2017-oct/25). A total of 162 type 2 DM patients were screened for microalbuminuria. Hundred type 2 diabetes patients satisfying the selection criteria were selected via the convenient random sampling method. The sample size for the study was calculated using the formula

$$N = z^2 pq/e^2,$$

where  $z$  is 1.96 (table value for  $\alpha = 0.05$ ), prevalence  $p$  is 0.3,  $q = 1-p$  (0.7), and  $e$  = absolute precision (fixed as 10%). By applying the above values, the sample size was calculated to be 81 and then rounded to 100.

The study procedure and their roles were explained clearly to them. Additionally, written informed consent was obtained and the parameters and the values analysed were maintained confidentially. Type 2 diabetic patients of either gender and above 20 years of age treated with oral hypoglycaemic agents alone were included in the study. Patients with type 1 DM; those on insulin therapy; lactating mothers; patients with gestational DM, macroalbuminuria, or overt nephropathy; co-morbid conditions like hypertension, coronary artery disease, chronic kidney disease, liver disease, or thyroid disorders; patients on ACE inhibitors and chronic NSAID therapy; and those with history of heavy metal poisoning were excluded from this study. Demographic details, details of the oral anti-diabetic medication, and biochemical parameters including microalbumin levels were documented in a Microsoft Excel sheet.

Data collection: A specially designed case report form was used to record the following data.

1. Demographic and clinical parameters: Name of the patient, age, gender, BMI, blood pressure, age of onset of diabetes, duration of the disease, and oral hypoglycaemic agents (dose, duration, and frequency).
2. Biochemical parameters: Urine microalbumin, fasting blood sugar, post prandial blood sugar and HbA1c levels, blood urea, and serum creatinine.
3. Any adverse drug reaction during the study period was reported.

Parametric analysis:

Body weight (Kg), height and BMI,<sup>[17]</sup> and blood pressure.<sup>[18]</sup>

**Estimation of urinary microalbumin:** It was estimated by the immunoturbidimetry method using a Diatek Kit by means of an auto-analyser.<sup>[19]</sup> The diagnosis of microalbuminuria was done by calculating the albumin–creatinine ratio (ACR) of the spot urine sample. The urine microalbumin was estimated using the formula

$$\text{Urine Albumin Creatinine Ratio} = \frac{\text{Urine albumin (mg / dL)}}{(\text{UACR}) \text{ in mg / g Urine creatinine (g / dL)}}$$

Normoalbuminuria: UACR is less than 30 mg/g.

Microalbuminuria: UACR is  $\geq 30$  mg/g  $\leq 300$  mg/g.

Macroalbuminuria: UACR is more than 300 mg/g.<sup>[4]</sup>

**Estimation of blood sugar:** Blood samples were collected by venepuncture of antecubital vein with all aseptic precautions. The fasting blood sugar (FBS) and post prandial blood sugar (PPBS) were analysed using the glucose oxidase method.<sup>[20]</sup>

**Estimation of Fasting HbA1c:** The HbA1c levels were analysed using the immunoturbidimetric method in a semi-auto-analyser (Model-Chem-7).<sup>[21]</sup>

**Estimation of urea and creatinine:** They were analysed using the L-glutamate dehydrogenase (GLDH) method and Jaffe’s method, respectively, by means of an auto-analyser (Model-Diachem 300 plus).<sup>[22,23]</sup>

### Statistical analysis

The data collected were entered in the Microsoft Excel sheet, and it was analysed for descriptive statistics using SPSS Software 21.0. Chi-square test was used to find out the association between variables (in frequencies/percentages). *P* value < 0.05 was considered as statistically significant.

## Results

A total of 100 type 2 diabetes patients with microalbuminuria participated in this study with 44% of males and 56% females. The age of the participants ranged between 30 and 90 years, and the majority of them fall under the category of 51–60 years. The mean age of the analysed study population was  $56.1 \pm 11.7$  years. The mean duration of disease among them was  $7.0 \pm 6.0$  years, and 45% diabetic patients with microalbuminuria had their disease duration of 6–10 years, of which 58% were males and 42% were females. Additionally, table 1 depicts the BMI of study participants, with 8% obese (BMI above 30 kg/m<sup>2</sup>), 49% overweight ( $29.9 > \text{BMI} \geq 25$  kg/m<sup>2</sup>), and 43% were healthy ( $24.99 > \text{BMI} \geq 18.5$  kg/m<sup>2</sup>) [Table 1]. The mean and

SD of systolic and diastolic blood pressures were found to be  $126 \pm 14$  and  $76 \pm 8$  mmHg, respectively. The mean systolic and diastolic blood pressures were high in females,  $125 \pm 12$  and  $76 \pm 6$  mmHg, respectively, when compared to males. The mean and SD of FBS, PPBS, and glycated haemoglobin (HbA1c) were found to be  $151 \pm 53.2$  mg/dL,  $227.01 \pm 70.9$  mg/dL, and  $6.2 \pm 1.2\%$ , respectively. The mean FBS and PPBS were high in females when compared to males. Similarly, the mean and SD of urine microalbumin, serum creatinine, and urea were noted with  $151.4 \pm 95.7$  mg/dL,  $1.5 \pm 0.2$  mg/dL, and  $24.42 \pm 9.3$  mg/dL, respectively [Table 2]. Similar to that of fasting and post prandial blood sugar levels, the mean of urine microalbumin was also found higher in females with 229.86 mg/dL. 86% patients had more than 100 mg/dL of FBS, whereas 94% patients had PPBS >140 mg/dL. Glycated haemoglobin (HbA1c) more than 6.5% was found predominantly (40%) in the study

**Table 1: Demographic details of study participants**

Demographic data	Percentage of diabetic patients
Age (years)	
31-40	10
41-50	23
51-60	29
61-70	29
71-80	8
81-90	1
Gender	
Male	44
Female	56
Disease Duration (years)	
1-5	39
6-10	45
11-15	7
16-20	7
>20	2
Body Mass Index	
Underweight (<18.5)	0
Healthy weight (18.5–24.99)	43
Overweight (25–29.99)	49

**Table 2: Distribution of biochemical parameters and blood pressure**

Biochemical parameters	Mean±SD
FBS (mg/dL)	151.0±53.2
PPBS (mg/dL)	227.01±70.9
Obese (>30)	8
Values are expressed in Percentage	
Biochemical parameters	Mean±SD
FBS (mg/dL)	151.0±53.2
PPBS (mg/dL)	227.01±70.9
HbA1c (%)	6.2±1.2
Urine microalbumin (mg/dL)	151.4±95.7
Blood urea (mg/dL)	22.0±10.0
Serum creatinine (mg/dL)	1.0±0.3
Systolic blood pressure (mmHg)	125±14
Diastolic blood pressure (mmHg)	70±10

FBS - Fasting blood glucose (mg/dL), PPBS - Post prandial blood glucose (mg/dL), HbA1c - Glycosylated haemoglobin (%), Values are expressed in Mean±SD

participants [Table 3]. The commonly used OHAs were sulfonylureas, biguanides, DPP IV inhibitors, alpha glucosidase inhibitors, and so on; in the present study, a higher number of patients (59%) were treated with combination therapy of metformin and teneligliptin [Table 4]. The association of demographic variables with microalbuminuria was analysed using Chi-square test ( $X^2$ ) among the diabetic patients. This analysis found that there was statistical association with occurrence of microalbuminuria with BMI ( $P$  value < 0.05). Biochemical parameters like FBS and PPBS were also found to have significant association with occurrence of microalbuminuria with  $P$  value < 0.05. As these parameters increased, the chance of being microalbuminuric also increased [Table 5]. The different oral hypoglycaemic agents used by type 2 diabetic patients with microalbuminuria were metformin and tenelegliptin; metformin and glimepiride; metformin and voglibose; and metformin, glimepride, and voglibose combination ( $211.25 \pm 68.55$ ). These groups were compared with microalbuminuria using one-way analysis of variance (One-way ANOVA), which showed statistical significance ( $P$  value < 0.05) among them [Table 6].

### Discussion

Diabetes is a group of metabolic disorders, sharing the common underlying property of hyperglycaemia. Hyperglycaemia is associated with long-term vascular damage and dysfunction, which predisposes failure of various organs, especially the heart, brain, eyes, kidney, and nerves.<sup>[24]</sup> Renal complications in diabetic individuals are clinically denoted by increasing rates of urinary albumin excretion, ranging from normoalbuminuria to microalbuminuria and macroalbuminuria and finally leading to end stage renal disease. Various epidemiological and cross-sectional studies have reported that without specific interventions, 20–40% of T2DM patients with microalbuminuria progress to overt nephropathy.<sup>[25]</sup> Microalbuminuria also helps to identify the patients who need more rigorous cardiovascular risk management, especially more intensive blood pressure control and strict attention to glycaemic control and lipid levels. This study was conducted to evaluate microalbuminuria among diabetic patients and to examine the relationship between microalbuminuria and putative risk factors in patients treated with oral hypoglycaemic drugs. In this study, the age of the majority of the patients was between 51 and 60 years (29%), followed by 41 to 50 years (23%), and the findings were correlated with Ambayiram AV *et al.*, who reported that the maximum number of diabetic patients with microalbuminuria was in the age group of 51–60 (33.5%).<sup>[26]</sup> Among the 100 diabetic patients with microalbuminuria, 56% were females and 44% were males. Similarly, Abubakar *et al.* noted female preponderance for increased prevalence of microalbuminuria.<sup>[27]</sup> In contrast, Tauseef Ahmad *et al.* showed that microalbuminuria was slightly higher in males compared to females.<sup>[28]</sup> 45% of individuals were diabetic for 6–10 years and it was correlated with Ambayiram AV *et al.*, who showed that the majority of diabetic patients with microalbuminuria had their disease duration of 6–10 years.<sup>[26]</sup> Sana *et al.* showed that the prevalence of microalbuminuria

**Table 3: Frequency distribution of FBS, PPBS, and HbA1c**

Parameters	Percentage of diabetic patients
FBS	
70-110 mg/dl	21
111-200 mg/dl	65
>200 mg/dl	14
PPBS	
<140 mg/dl	6
141-300 mg/dl	76
>300 mg/dl	18
HbA1c	
4-5.6%	28
5.7-6.4%	32
≥6.5%	40

FBS – Fasting blood glucose (mg/dL), PPBS – Post prandial blood glucose (mg/dL), HbA1c – Glycosylated haemoglobin (%), Values are expressed in percentage

**Table 4: Distribution of oral hypoglycaemic agent usage among diabetic patients**

Drug combinations	Percentage of diabetic patients
Metformin + Teneligliptan	59
Metformin + Glimepiride	27
Metformin + Voglibose	10
Metformin + glimepiride + Voglibose	4

Values are expressed in percentage

**Table 5: Association of disease duration, BMI, FBS, PPBS, and HbA1c with microalbumin level in diabetic patients**

Parameters	P
Disease Duration	
<5 Years	0.33
>5 Years	0.23
BMI	
25-29.9	0.58
>30	0.026*
FBS	
70-110 mg/dl	0.207
>110 mg/dl	0.021*
PPBS	
<140 mg/dl	0.242
>140 mg/dl	0.032*
HbA1C	
4-5.6%	0.367
5.7-6.4%	0.242
≥6.5%	0.730

\* $P < 0.05$  is considered statistically significant

**Table 6: Distribution of urine microalbumin among diabetic patients who are on oral hypoglycemic agents**

Drug combinations	Mean±SD	P
Metformin + Teneligliptan	102.96±89.22	0.0001*
Metformin + Glimepiride	210.3±50.77	0.0001*
Metformin + Voglibose	252.7±43.44	0.0001*
Metformin + glimepiride + Voglibose	211.25±68.55	0.0001*

\* $P < 0.05$  is considered statistically significant

was increasing progressively with increased duration of diabetes (50% patients in 5–10 years, 90.9% in 10–15 years, and 100% in more than 15 years).<sup>[29]</sup> In this study, the majority of the individuals were diabetic in 6–10 years, followed by 1–5 years with microalbuminuria. This could be due to irregular intake oral hypoglycaemic agents and due to rapid development of diabetic complications. There is a strong association noted between albuminuria and increased BMI in diabetic individuals, which had been attributed to the glomerular deposition of lipids and the activation of the renin-angiotensin-aldosterone system (RAAS).<sup>[30]</sup> Similarly, Muthuvel *et al.* observed no significant changes in the incidence of microalbuminuria among the overweight patients and those with normal BMI, whereas it was significantly increased among the obese patients.<sup>[31]</sup>

The mean systolic and diastolic blood pressures were in the normal range in our study, although 61% of study patients had disease duration of more than 6 years, while minimal diabetic individuals showed elevated blood pressure and upsurge in the urinary microalbuminuria level. The target BP in patients with albuminuria is generally recommended to be less than 130/80 mmHg,<sup>[32]</sup> which has been maintained in patients in this study even without ACE inhibitors. A study done by Tanaka *et al.* has found that there was close association between blood pressure and urinary excretion of albumin, which is thought to be due to renal manifestation of generalised vascular endothelium dysfunction and strongly linked with increased cardiovascular disease risk.<sup>[33]</sup>

In this study, mean FBS ( $151 \pm 53.2$  mg/dl) and PPBS ( $227.01 \pm 70.9$  mg/dl) were elevated compared to the normal range. 86% patients showed elevation in their fasting blood glucose level more than 100 mg/dL and 94% with post prandial blood glucose showed elevation of more than 140 mg/dl. However, the mean HbA1c levels were within the normal range ( $6.2 \pm 1.2\%$ ), reflecting on the good glycaemic control. Nguyen *et al.* and Thakur *et al.* had shown similar findings in their studies which had significant relationship between FBS, PPBS, HbA1C, and microalbuminuria.<sup>[34,35]</sup>

Assessment of renal parameters is mandatory among the diabetic individuals to reduce the renal complications. In the present study, 62% of patients had blood urea  $>20$  mg/dL, whereas in 42% of diabetic individuals, serum creatinine was in normal limits ( $<1.2$  mg/dl) and the remaining 52% showed upsurge in the creatinine level. The upsurge in the urea and creatinine levels indicates that participants of the present study were affected with renal insult, especially diabetic nephropathy. The findings of the present study corroborate with Bamanikar, who showed the raised renal parameters in diabetic patients.<sup>[36]</sup>

Association of microalbuminuria in diabetic patients and other risk factors such as age, duration of disease, BMI, FBS, PPBS, and serum creatinine were found to have significant association with the occurrence of microalbuminuria ( $P$  value  $< 0.001$ ) and blood urea; significant association was seen at  $P$  value  $< 0.05$

level. This is in accordance with the fact that blood urea and serum creatinine are established markers of glomerular filtration rate (GFR). This study has some potential strengths, which involved only microalbuminuric diabetic patients, and to our knowledge, this is one among the very few studies done in South India.

## Limitations

The present hospital-based study was cross-sectional, and thus, longitudinal trends in the management of diabetes and potential risk factors could not be taken into account. Moreover, no long-term follow-up was done and hence, causal relationships cannot be ascertained. Prevalence of microalbuminuria among the diabetic patients attending our hospital was also not assessed in our study.

## Conclusion

Microalbuminuria is an early indication of nephropathy in diabetes patients. The risk factors associated with microalbuminuria were age, duration of diabetes, glycaemic control, and BMI. There was no effect of gender distribution on microalbumin levels. So, identification of the relevant risk factors is important and it is always recommended to screen for urine microalbumin levels for all the diabetic patients for early detection and prevention of diabetic nephropathy.

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## Conflicts of interest

There are no conflicts of interest.

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