# Albuminuria in Patients with Type 2 Diabetes Mellitus: a Single Center Cross-Sectional Study

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## ABSTRACT

### Introduction

Diabetes mellitus is one of the commonest non-communicable diseases in Nepal and is associated with long term microvascular and macro vascular complications. Detection of albumin in urine is the earliest recognizable feature in the development of proteinuric diabetic nephropathy. This study aims to study the prevalence as well the determinants of albuminuria in patient with Type 2 diabetes mellitus visiting the medical OPD of College of Medical Sciences-Teaching hospital.

### Methods

This was a cross-sectional study done from January to May 2022 among Type 2 diabetes patients presenting to medical OPD for the comprehensive diabetes management. Relevant epidemiological, clinical and laboratory data were obtained. Urine dipstick test was done to screen for albuminuria. The prevalence and determinants of albuminuria were studied.

### Results

Study among 360 patients with mean age of $58.5 \pm 10.9$ years and the mean duration since the diagnosis of diabetes of $6.8 \pm 5.5$ years, showed that the prevalence of albuminuria was 33.3%. Albuminuria in these patients was found to have significant association with age ($P<0.001$), duration since diagnosis of diabetes ($<0.001$) and HbA1c ($P<0.001$). No significant association of albuminuria was found with gender ($P=0.087$), hypertension ($P=0.063$) and previous use of Angiotensin-converting enzyme inhibitors/ Angiotensin II receptor blockers. ($P=0.217$)

### Conclusions

Albuminuria is highly prevalent among our cohort of diabetic patients. Increasing age, longer duration since diagnosis of diabetes and higher HbA1c are the factors significantly associated with it.

**Keywords:** diabetes mellitus; albuminuria; prevalence.

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## INTRODUCTION

Diabetes Mellitus is one of the commonest non communicable diseases in Nepal. The prevalence of diabetes in Nepal was reported by WHO to be 9.1% in the year 2016.[1] Diabetes is associated with long term macro vascular and microvascular complications which includes diabetic nephropathy as well.[2] The classical five stages of natural history of diabetic nephropathy starts with 'hyperfiltration', proceeding to a stage called 'silent nephropathy' where glomerular filtration rate normalizes, followed by 'incipient nephropathy, characterized by microalbuminuria. The fourth phase is called 'overt nephropathy' associated with macro albuminuria which then proceeds to the fifth stage of end stage renal disease (ESRD).[3] Hence, albuminuria in diabetes is the earliest recognizable feature in the development of proteinuric diabetic nephropathy with Kimmelstiel-Wilson lesions as the underlying pathology.[4]

Early diagnosis of albuminuria in diabetes provides an opportunity for therapeutic interventions that help prevent or delay the development of end stage renal disease.[5,6] In his study we aim to study the prevalence as well the determinants of albuminuria in patient with Type 2 diabetes mellitus visiting the medical OPD of College of Medical Sciences-Teaching hospital.

## METHODS

This is a cross-sectional study conducted at College of Medical Sciences-Teaching Hospital (COMS-TH) from January 2022 to May 2022 after ethical clearance from Institutional Review Committee of College of Medical Sciences-Teaching Hospital (Reference no. COMSTH-IRC/2021-155) All patients presenting to medical OPD who were diagnosed as having type 2 Diabetes Mellitus, based on American Diabetic Association criteria, were included in the study. Patient with known renal failure, glomerulonephritis, heart failure and acute febrile illness was excluded from the study. Urine microscopic examination was done to exclude diabetic patients with urinary tract infection and hematuria.

Convenient sampling method was used. Structured questionnaires were used to obtain a medical history including the duration of DM, presence of hypertension and others risk factors. Duration of diabetes was defined based on the patient reported time of the first diagnosis of diabetes. Hypertension was defined as either Systolic BP of more than 140 mmHg and/or a diastolic blood pressure of more than 90 mmHg or patients who were already on anti-hypertensive medications. All the patients were instructed to collect spot urine samples. Albuminuria was screened using dipstick tests manufactured by Acon Laboratories Inc. USA. The corresponding albumin concentration for dipstick results is as shown in Table 1. Patients with at least 1+ in dipstick results were considered having albuminuria.

**Table 1.** Corresponding albumin concentration for dipstick results.

| Dip Stick results | Albumin excretion mg/dL |
|---|---|
| Nil | 0 |
| Trace | 15 |
| 1+ | 30 |
| 2+ | 100 |
| 3+ | 300 |
| 4+ | 2000 |

The sample size was calculated using the formula, $N = Z^2 \times p \times q/e^2$

Where, N = minimum required sample size

p = prevalence from previous study, which was taken as 36%.[7]

Z = 1.96 at 95 % confidence Interval (CI)

q = 1-p

e = margin of error, 5%

We calculated the required sample size as 354 patients, however we took a sample size of 360 patients.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 18.0. Data are presented as mean (standard deviation) for continuous variables and as N (percent) for categorical variables. Demographic, anthropometric and health characteristics were compared using t-tests for normally distributed continuous variables, $\chi 2$ tests for categorical variables. A P value of <0.05 was considered significant.

## RESULTS

A total of 360 patients were included in the study. Mean age of the patients was $58.5 \pm 10.9$ years. Majority of them (60.0%) were female with a mean duration of $6.8 \pm 5.5$ years since the diagnosis of diabetes mellitus. Fewer than half of them (45.3 %) were hypertensive. ACE/ARBs were already prescribed to 28.9% of them. Of the 360 diabetics, 64 (17.8%) were under insulin therapy as well. The latest HbA1c available at the time of the OPD consultation had a mean value of $7.7 \pm 1.3$ %. The mean creatinine of the study population was $1.0 \pm 0.2$ mg/dl (Table 2).

Using dipstick test, 120 (33.3%) of the 360 patients were identified to have albuminuria in the spot urine sample. Of those 120 patients, 80 (66.7%) had 1+, 32(26.7%) had 2+ and 8(6.7%) had 3+ results on dipstick test for albumin (Table 2).

**Table 2.** Baseline characteristics of the study population.

| Variables | Values (N= 360) |
|---|---|
| Age in years (Mean $\pm$ SD) | 58.5 $\pm$ 10.9 |
| Gender<br>　　　Male<br>　　　Female | <br>144 (40.0%)<br>216 (60.0%) |
| Duration of diabetes in years (Mean $\pm$ SD) | 6.8 $\pm$ 5.5 |
| Hypertension | 163 (45.3 %) |
| Use of ACE/ARBs | 104 (28.9 %) |
| Use of Insulin | 64 (17.8%) |
| HbA1C in % (Mean $\pm$ SD) | 7.7 $\pm$ 1.3 |
| Creatinine in mg/dl (Mean $\pm$ SD) | 1.0 $\pm$ 0.2 |
| Albuminuria<br>　　　Dipstick 1+<br>　　　Dipstick 2+<br>　　　Dipstick 3+ | 120 (33.3%)<br>80 (66.7%)<br>32 (26.7%)<br>8 (6.7%) |

Analysing the different variables among albuminuric and non-albuminuric patients, albuminuria was found to be have a statistical significant association with age, duration of diabetes and glycemic control in term of HbA1c. The present study found no significant association of gender, hypertension and use of ACE/ARBs with the development of albuminuria in diabetic patients (Table 3).

Patients with albuminuria were found to be older as compared to non-albuminurics (62.8 $\pm$ 11.0 vs 56.3 $\pm$ 10.2, P<0.001). The prevalence of albuminuria was similar between both the gender. (P=0.087). The mean duration since the diagnosis of diabetes was significantly higher in those with albuminuria (9.8 $\pm$ 5.8 years) as compared to those without (5.2 $\pm$ 4.6 years) (P<0.001). The study found higher but statistically non-significant prevalence of hypertension among proterinurics (54.6%) as compared to non-albuminurics (43.3%) (P=0.063). The proportion of patients already on ACE/ARBs were similar in

both the groups (33.3% vs 26.7%, P=0.217). It was found that patients with albuminuria had higher HbA1c of 8.4 ± 1.35 % as compared to those without albuminuria who had a mean HbA1c of 7.3 ± 1.0 % (P<0.001) (Table 3).

group of 60-70 years and 71.4% in age group of 70 years and above (Figure 1).

Similarly, it was found that the among patients who were diagnosed diabetes in the last 5

**Table 3.** Comparison of different variables between patients with and without albuminuria.

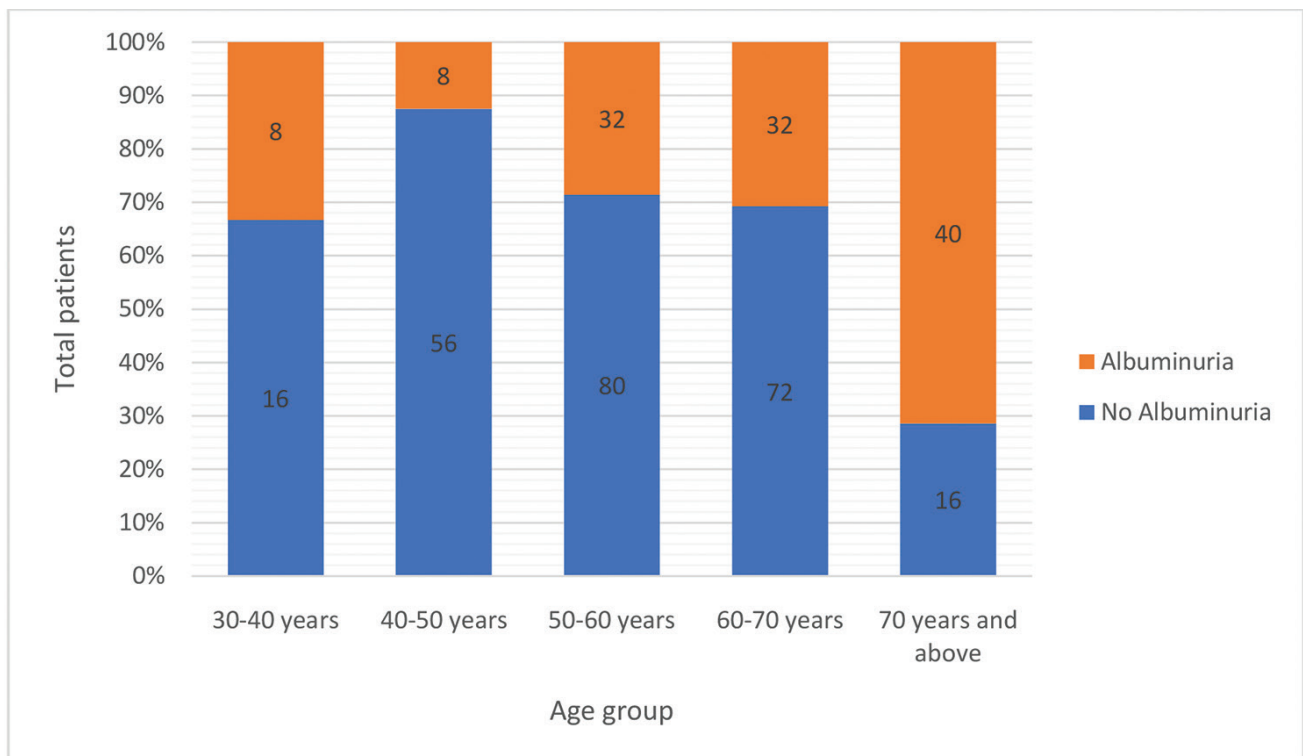| Parameters | Albuminuria (N= 120) | Non-albuminuria(N=240) | P value |
|---|---|---|---|
| Age (Mean ± SD) | 62.8 ± 11.0 | 56.3 ± 10.2 | <0.001 |
| Male : Female | 56 : 64 | 88 : 152 | 0.087 |
| Duration of diabetes (Mean ± SD) | 9.8 ± 5.8 | 5.2 ± 4.6 | <0.001 |
| Hypertension | 59 (54.6%) | 104 (43.3%) | 0.063 |
| Use of ACE/ARBs | 40 (33.3%) | 64 (26.7%) | 0.217 |
| HbA1c % (Mean ± SD) | 8.4 ± 1.4 | 7.3 ± 1.0 | <0.001 |



**Figure 1.** Distribution of patients with and without albuminuria as per age groups.

It was found that the frequency of albuminuria, except among those between 30-40 years of age, increases with increment in the age groups. The frequency was found to be 33.3% in age group of 30-40 years, 12.5% in age group of 40-50 years, 28.6% in age group of 50-60 years, 30.8% in age group of 60-70 years.

years, 22.7% had albuminuria. The percentage decreases to 20.0% when the duration of diabetes diagnosis is 5 to 10 years, again to increase to 61.5% as the duration of diabetes is more than 10 years (Figure 2).
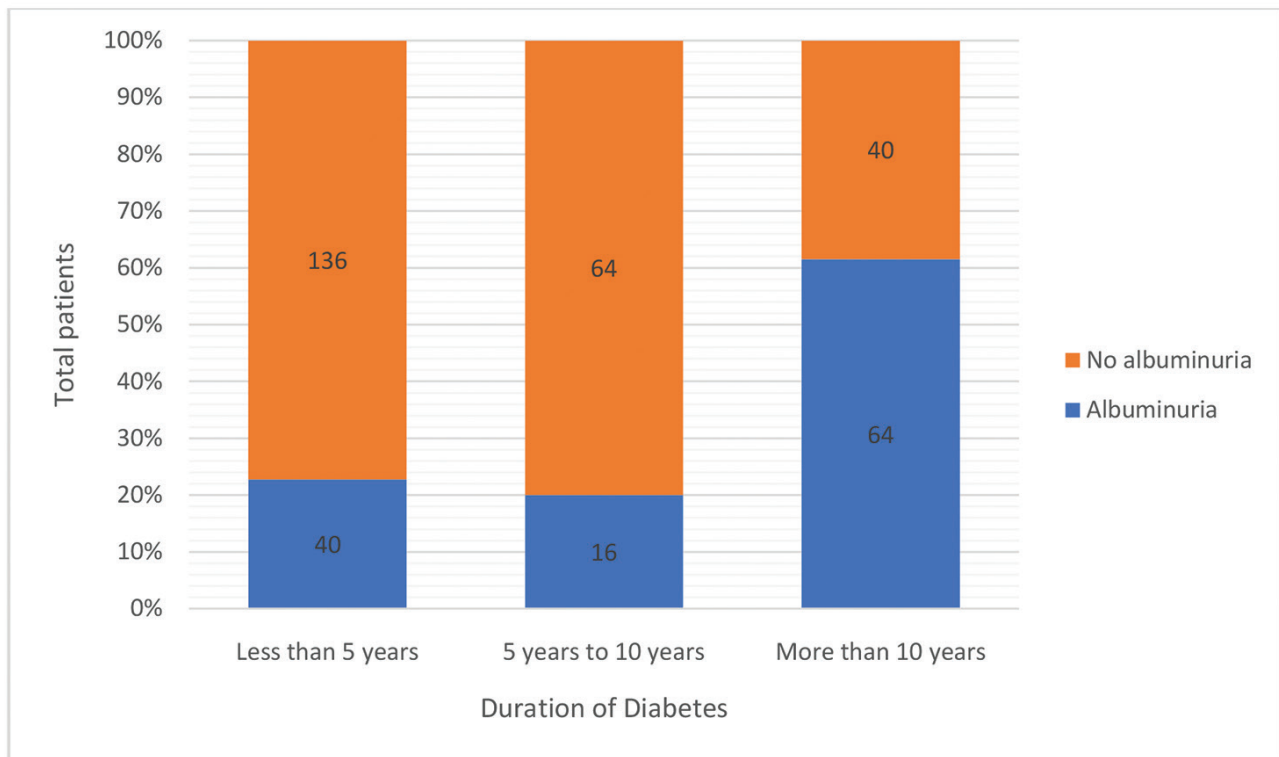
**Figure 2.** Distribution of patients with and without albuminuria as per duration of diabetes.

## DISCUSSION

This cross sectional study was done to determine the prevalence of albuminuria defined as 1+ or more in urine dipstick test, in unselected cohort of type 2 diabetes mellitus patients attending medical OPD of a tertiary care hospital. Although a population based quantitative study would be ideal for this study, there are financial and technical constrains especially in a country like ours.

We used the easily available semi qualitative dipstick test to determine albuminuria instead of quantitative test to determine the albumin creatinine ratio (ACR). A study done to compare the dipstick results to the actual measurement of albumin creatinine ratio found that 42 of 46 (91%) urine samples greater than or equal to 1+ for protein exceeded the albumin creatinine ratio of 30 mg/g. The positive predictive value of for a test result more than or equal to 1+ for protein was

91%.[8] Similarly, a large study including 919,383 adults compared same day measure of ACR with dipstick tests and found that urine dipstick categories of trace or greater for screening for ACR values greater than 30mg/g had a moderate sensitivity of 62% but a high specificity of 88%.[9] Because of the moderate sensitivity, the studies that used dipstick to estimate albuminuria might have underestimated the prevalence of albuminuria as compared to those studies that used quantitative method to measure ACR.

The present study showed that 33.3% of the patients had albuminuria. Similar study done at Palestine among a cohort of 550 patients found the prevalence of albuminuria to be 34.6%.[10] A study published in 2004 however had reported a high prevalence of albuminuria (58.6%) in Asians with Type 2 diabetes, of which 39.8% had microalbuminuria and 18.8% had macro albuminuria.[11] Another study from Yemen reported 64% prevalence of proteinuria of which

49% had microalbuminuria (ACR 30-300 mg/g) and 25.5% had macro albuminuria (ACR > 300 mg/g).[12] In contrast to all these afore mentioned studies, a study done in 1848 diabetic patients in southern India reported prevalence of diabetes related proteinuria of only 9.4%.[13]

There are variations in the prevalence of microalbuminuria in studies on Europeans (15-21%) and Americans (31%) as compared to Asians.[14,15] Subgroup analysis of the UKPDS study had also shown that Indian-Asian ethnicity was independently associated with development of albuminuria and renal impairment in diabetics with a hazard ratio 2.02 (95% CI: 1.59-2.60, P <0.0001).[16]

These variations could be attributed to many factors mainly the ethnic differences, variations in other cardiovascular risk factors, definition of proteinuria and the disease state. The other cause for the differences in prevalence could be because of the lack of adjustments for known risk factors. Our populations may also have higher incidence of proteinuria due to difference in other preventable factors like glycemic control, blood pressure control, diet, awareness and access to health care as well.

Age was shown to have statistical significant association with albuminuria in our study. Univariate analysis done during a previous study among resident of Minnesota found older age at diagnosis to be a factor significantly associated with persistence of proteinuria among patients with type 2 DM which was then confirmed as an independent risk factor in a multivariate proportional hazard analysis.[17] Another study done in India also found that the baseline age of diabetic patients was a risk factor for development of macro albuminuria with a hazard ratio of 1.05 (95% CI:1.02-1.08, P=0.001).[18]

Albuminuric patients were found to have longer duration since diagnosis of diabetes (Mean of 9.8 ± 5.8 years ) as compared to non-albuminuric patients (Mean of 5.2 ± 4.6 years) in the present study. The duration of diabetes has been shown to be a risk factor for diabetic nephropathy in plenty of studies.[19,20] In a cohort of Koreans with Type 2 Diabetes, it was found that duration of diabetes was an independent variable influencing the development of microalbuminuria (Risk ratio= 1.07, 95% CI 1.01-1.12, P <0.05). Patients with duration of diabetes of 0-5 years had incidence of microalbuminuria of 1/1000 person years as compared to the rate of 99.2/1000 person years when the duration of diabetes is >15 years.[21]

It has also been interestingly documented in a meta-analysis that prevalence of proteinuria increases with increasing duration of disease, at least up to 25 years, after which it may decline, probably due to decreased survivorship in those with proteinuria. Similarly, a maximum of 25-63% patients develop proteinuria as the disease progress, however the other 37-75% appear to be spared likely attributed to a combination of genetic and environment factors which includes parental history of high blood pressure, parental/ sibling history of kidney disease, smoking, race/ ethnicity, high protein intake, chronic analgesic use, decreased health care access, other socioeconomic factors, or exposure to intravenous dye or aminoglycosides.[22]

The present study showed that patients with albuminuria had higher HbA1c (8.4 ± 1.4%) as compared to patients with no albuminuria who had lower HbA1c (7.3 ± 1.0%). Similarly, a study done in India also found baseline HbA1c to be significantly associated with development of macro albuminuria with hazard ratio of 1.7 (CI:1.3-2.2, P<0.0001)(18) UKPDS and DCCT trials have shown the highest level of evidence of this causation by altering the risk factor of interest, which in this case, that strict glycemic control helps to prevent the development

of microalbuminuria and retinopathy.[19,23] Further, the specific link of hyperglycemia with nephropathy has been established by the fact that microvascular complications also occur in secondary causes of diabetes such as chronic pancreatitis, hemochromatosis and steroid-induced diabetes.[24,25] Similarly, common complications are seen in both Type 1 and Type 2 diabetes, despite each of them having a different pathophysiological mechanism.

Our study showed no significant relation between hypertension and albuminuria in diabetic patients. A population based study in Minnesota studied different risk factors for proteinuria in diabetics using a multivariate analysis but hypertension was found to be insignificant. (P=0.12).[17] There are however evidence that there is a correlation of diabetic nephropathy with hypertension.[26] Further, there are interventional studies that have clearly shown that treatment of hypertension in diabetics decreases the amount of protein excretion.[27] Thus, it is likely that effective treatment of hypertension after the diagnosis of diabetic in our patients might explain the relation between albuminuria and hypertension in this present study.

This study showed that the higher percentage of patients, who had been diagnosed as diabetics within last 5 years, were albuminuric as compared to those who have been diagnosed 5 to 10 years back. This may be because the cluster of patients with duration of diabetes diagnosis less than 5 years also includes most of those patients who presented late to medical consultations even though they had uncontrolled blood sugar since long which was undiagnosed. Further, few of those patients who must have developed overt diabetic nephropathy at the timeline of 5 to 10 years of diagnosis may be visiting a nephrologist instead of an internist.

**Limitations:** The limitations of our study is that this was a single center study that included patients following in a general medicine OPD. Few of those patients who already had an overt nephropathy might have been missed as they might be under the care of nephrologists. The other limitation is that we used a semi-quantitative method of dipstick for the screening of albuminuria instead of a quantitative estimation.

## CONCLUSIONS

In conclusion, albuminuria is highly prevalent among our diabetic patients. Increasing age, longer duration of diabetes and higher HbA1c are the factors significantly associated with it. This calls for the early screening of albuminuria and measures to target tight glycemic control along with other risk factors reduction.

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