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ORIGINAL RESEARCH ARTICLE

TOTAL PROTEIN TO CREATININE RATIO AS AN ALTERNATIVE TO ALBUMIN TO CREATININE RATIO TO PREDICT MICROALBUMINURIA IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Diabetic nephropathy is the most common complication of diabetes mellitus. Early detection of microalbumin in urine plays an important role in preventing the progression to late stages of chronic kidney disease. For a country like Nepal, the cost of assessment of microalbumin in urine is unaffordable by many patients for regular monitoring. Total protein to creatinine ratio (TPCR) might be a cheaper alternative for this. This study assessed the feasibility of using TPCR as an alternative method for predicting microalbuminuria in diabetic patients.

Methods: Type 2 Diabetic patients with age ranging 30-80 years were included in the study after ethical clearance. Urinary total protein was determined by pyrogallol red method and urinary creatinine by Jaffe's method. Urine for microalbumin was determined by nephelometry. Relationships between variables were examined by Pearson correlation or Spearman's correlation analysis as appropriate. Receiver operating characteristic (ROC) curve analysis was performed to obtain the cutoff value of TPCR for detection of albuminuria

Results: The mean age of the study population was 55.9 ± 11.8 years. There was significant positive correlation between TPCR and urine albumin ($\rho = 0.56$; $p < 0.01$) and between TPCR and ACR ($\rho = 0.47$; $p < 0.01$). The regression equation for TPCR and ACR was, ACR = 0.82 TPCR = 70.5, r2 = 0.88. ROC curve analysis showed that the urine TPCR had a sensitivity and specificity of 76% and 58% respectively, for the detection of albuminuria with a cutoff value of 95 mg/g(AUC=0.74, $p < 0.01$).

Conclusions: TPCR might be the cheaper alternative for the prediction of microalbuminuria in patients with type 2 diabetes mellitus.

INTRODUCTION

The prevalence of type 2 diabetes mellitus(T2DM) is increasing worldwide and is becoming a major public health problem.[1] Diabetic nephropathy (DN) is the most common complication of diabetes mellitus.[2] Early diagnosis is important in preventing the progression to late stages of kidney disease. A recent study by Molitch et al. had shown that the onset and progression of diabetic nephropathy can be decreased to a significant level with several intervention, if started earlier.[3] For this, early marker of diabetic nephropathy plays an important role.

The term 'microalbuminuria' is used when there is increased albumin excretion but not to the level of overt proteinuria. Microalbuminuria is the earliest clinical evidence of nephropathy with the appearance of low but abnormal level (30-300mg/day) of albumin in the urine. Without specific interventions, 20-40% of them will progress to overt nephropathy.[3] So, diagnosis at the point of microalbuminuria is of paramount importance in order to prevent overt nephropathy in diabetics. Not only with the nephropa-

thy, but microalbuminuria is also associated with the cardiovascular risk and it identifies patients who needs more aggressive cardiovascular risk management.[4] Hence, the identification and management of urine microalbumin excretion should be an important consideration in patients with diabetes.

Gold standard method for evaluation of proteinuria in nephropathy is the measurement of protein in 24-hour urine collection. However, collecting 24-hour urine is difficult and inconvenient for the patients. Studies have shown that total protein to creatinine ratio (TPCR) in spot urine sample can be an alternative method to predict urine protein excretion in 24-hour collection.[5-7] A study has shown that albumin to creatinine ratio(ACR)and TPCR are strongly associated with each other and routine measurement of TPCR may provide similar information as ACR in managing immediate complications of chronic kidney disease which may result from diabetes or any other cause.[8]

Microalbuminuria detection is an important screening tool in early diabetes because treatment can be started or intensified to at least slow down the progression of kidney disease.[9] ACR is a preferred marker over the TPCR, however, the cost of measuring albumin may limit its use in some countries.[10] For a country like Nepal, the cost of assessment of microalbumin in urine is high and is not affordable by many of the patients for regular monitoring. TPCR is a cheaper method, which can also give information about the renal involvement in diabetic patients.If TPCR is equally good marker for assessment of microalbuminuria then, it could replace ACR and could be a cheaper alternative for regular monitoring of diabetic patients which could also be done in the rural part of the country where sophisticated instrument for measuring microalbumin is not available.

The aim of this study is to correlate urine ACR with-TPCR in spot urine sample to find whether TPCR can predict the presence of microalbuminuria in diabetic patients.

METHODS

A cross-sectional study was carried out over a period of six months (from June 2018 to November 2018). The study group consisted of 106 Type 2 Diabetic patients with age range 30-80 years. The sample size was calculated using the formula $N = Z^2pq/E^2$, taking p as 6.3%[11] and allowable error 5%.Ethical clearance was obtained from institutional review board, Kathmandu Medical College and Teaching Hospital (KMCTH), Sinamangal and samples were collected only after informed consent. Diabetic patients visiting KMCTH were included in the study and patients with already diagnosed chronic kidney disease were excluded from the study. Random urine samples of all subjects were collected for analysis, and stored at -20^0 C until the test was performed.

The TPCR was calculated as spot urine total protein concentration divided by spot urine creatinine concentration. Urinary total protein was determined by pyrogallol red method and urinary creatinine by Jaffe's method. We used the cut off≥0.2 for TPCR.

The ACR was calculated as spot urinary microalbumin divided by spot urine creatinine concentration. Urine for microalbumin was determined by nephelometry. Patients were categorized into 3 different groups of albuminuria according to KDIGO Guideline 2017.HbA1C was determined by high performance liquid chromatography (HPLC).

Data analysis was done using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).Normally distributed variables were expressed as mean ± standard deviation and variables without normal distribution as medians (range). Relationships between variables are examined by Pearson correlation or Spearman's correlation analysis as appropriate. ROC curve analysis was performed to obtain the cutoff value of TPCR for detection of albuminuria. p-value < 0.05 was considered statistically significant.

RESULT

One hundred and six type 2 Diabetic patients were included in our study. The mean age of the study population was 55.9 ± 11.8 years. There were 45 (42.4%) female and 61 (57.6%) male participants. Table 1 show the demographic and biochemical characteristics of the study population.

Table 1: Characteristics of study population expressed as mean ± SD or median (range)

Variables	Mean ± SD or Median (range)
Age (Years)	55.9±11.8
Urine Creatinine (mg/dl)	60.6(3.7-286.5)
Urine Protein (mg/dl)	7.4(0.3-151.1)
Urine Albumin (mg/L)	17.85(1-1404)
Urine Albumin Creatinine ratio (mg/g)	29.86(4.16-6267.86)
Urine Protein Creatinine ratio (mg/g)	100(8.0-6700)

There was significant positive correlation between TPCR and urine albumin (ρ = 0.56; p <0.01) and between TPCR and ACR (ρ = 0.47; p < 0.01). The regression equation for TPCR and ACR was(ACR = 0.82 TPCR -70.5, r^2 = 0.88 (Figure 1))

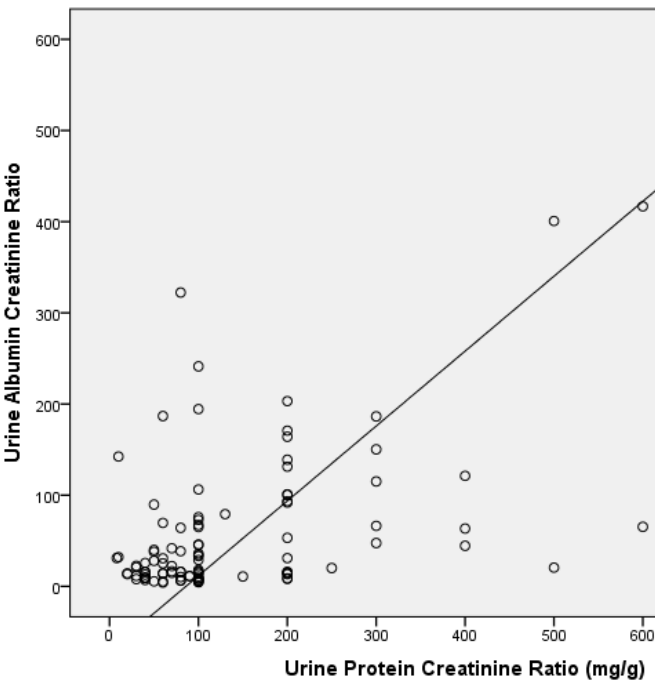

Figure 1: Correlation between Urine Protein Creatinine Ratio and Urine Albumin Creatinine Ratio.

Patients were grouped into normal albuminuria (n=53), microalbuminuria (n=46) and proteinuria (n=7) according to KDIGO 2017 guideline. Significant strong positive correlation was observed between TPCR and ACR in proteinuria range. However, there was only moderate positive correlation between TPCR and ACR in microalbuminuria range and no relationship was notice when ACR was in normal range (Table 2).

Table 2: Correlation between Urine Protein Creatinine Ratio and Urine Albumin Creatinine Ratio categorized.

ACR Category	Correlationcoefficient (Pearson, r/ Spearman's, ρ)	p-value
Normal (n = 53)	r = 0.09	0.5
Microalbuminurea (n = 46)	ρ = 0.3	0.02
Proteinurea (n = 7)	ρ = 0.8	0.01

Receiver operating characteristic curve (ROC) analysis showed that the urine TPCR had a sensitivity and specificity of 76% and 58% respectively, for the detection of albuminuria with a cutoff value of 95 mg/g (AUC=0.74, p < 0.01) (Figure 2)

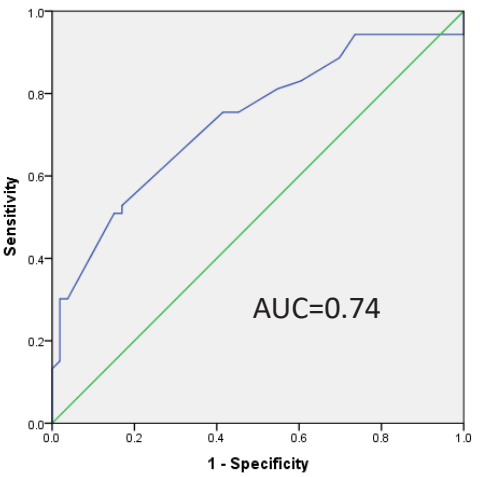

Figure 2: Receiver Operating Characteristic Curve analysis for Urine TPCR and Albuminuria(ACR)

When the study population was divided into different groups according to age, it was found that as the age increases, the mean value of both ACR and TPCR also increases accordingly (Figure 3 and Figure 4).

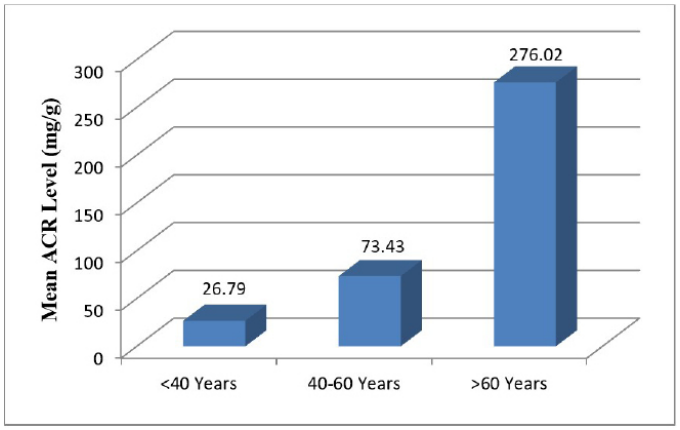

Figure 3: Mean ACR level in different age group.

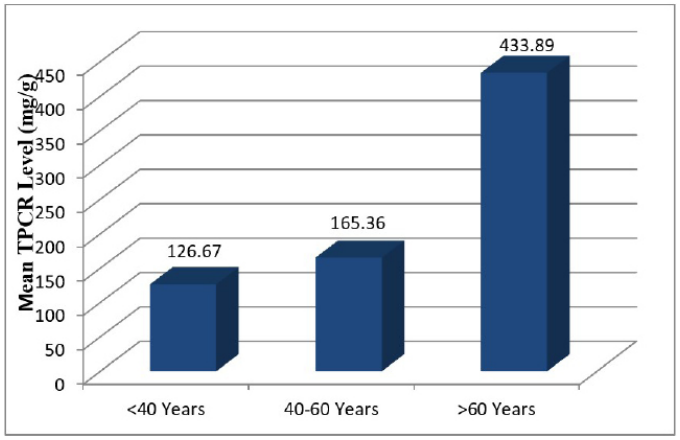

Figure 4: Mean TPCR level in different age group

DISCUSSION

As described earlier, the main problem associated with using the detection of albumin for assessing microalbuminuria in diabetic patients is its high cost and unavailability to general population. The measurement of total urinary protein is simple and inexpensive.

In this study, we found a significant positive correlation between TPCR and urine albumin ($\rho = 0.56$; $p < 0.01$) and between TPCR and ACR ($\rho = 0.47$; $p < 0.01$). The presence of microalbuminuria could be predicted by determining TPCR in diabetic patients. In similar studies in diabetic population,[12,13] similar findings with a significant correlation between the total protein to creatinine ratio and microalbumin in urine was seen. In another study by Yamamoto et al[14] done on patients visiting cardiovascular clinic, again a strong correlation between the TPCR and microalbumin was found.

In our study, 43% of study population had microalbuminuria and 7% had proteinuria which was similar to that in the study by Yamamoto et al.[14]The main objective of our study was to know whether TPCR could act as an alternative to ACR specifically in microalbuminuric group.

We found a significant strong positive correlation between TPCR and ACR in proteinuria range, however there was only moderate positive correlation between TPCR and ACR in microalbuminuria range. The reason for this finding could be that for mild proteinuria, proteins like Tamm Horsfall protein lead to tubular proteinuria and in severe proteinuria, albumin is the major protein component.[12] So, since albumin is the major component of proteinuria in severe proteinuria, there was stronger correlation between TPCR and ACR whereas only moderate correlation was seen in microalbuminuria range as proteins other than albumin is also excreted in this group.

The ROC curve analysis showed that that the urine TPCR had a sensitivity and specificity of 76% and 58% respectively, for the detection of albuminuria with a cutoff value of 95 mg/gm creatinine. In the study by Yamamoto et al[12] the ROC curve analysis showed that the TPCR had a sensitivity and specificity of 90.8% and 91.9% respectively for the detection of albuminuria with a cut-off value of 91mg/gm creatinine.

Methven et al[15] conducted a large scale study to investigate the optimal test to identify and quantify significant proteinuria. They assessed ACR, TPCR and 24 hour urine protein in 1696 patients attending kidney clinic and interestingly, TPCR highly correlated with 24 hour urine protein as compared to ACR. We already know that 24 hour urine protein is a gold standard technique to assess proteinuria, however having some limitations.[16] It was also found that TPCR could predict albuminuria in more than 90% of patients. While their study focused on the utility of TPCR to predict significant proteinuria, our study focuses on possibility of TPCR to predict microalbuminuria.

Proteinuria in diabetes is related to the duration of diabetes, and one of the limitations of the study is that we have not included the duration of diabetes, which could have some influence in the proteinuria in study population. In this study, we found that with

increasing age the mean value of ACR increases and similar finding was seen with TPCR as well, irrespective of duration of diabetes.

CONCLUSION

From our study, we can conclude that TPCR can replace ACR in severe proteinuria and also to some extent in microalbuminuria range.TPCR might be the cheaper alternative for the prediction of microalbuminuria in patients with type 2 diabetes mellitus.

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