Section: Biochemistry

Original Research Article

CORRELATION AND PRACTICALITY OF SPOT URINE PROTEIN-TO-CREATININE AND ALBUMIN-TO-CREATININE RATIOS COMPARED TO 24-HOUR URINE PROTEIN MEASUREMENT IN TYPE 2 DIABETES MELLITUS

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Abstract

Background: Proteinuria is a critical marker of renal function and an indicator of diabetic nephropathy in Type 2 Diabetes Mellitus (T2DM) patients. The 24-hour urine protein excretion test is accurate but impractical for routine use. This study aimed to evaluate the correlation between the protein-to-creatinine ratio (PCR), albumin-to-creatinine ratio (ACR) and 24-hour urine protein excretion and also assess the reliability of PCR and ACR as practical alternatives. **Materials and Methods:** The cross-sectional observational study included 334 T2DM patients. PCR, ACR, and 24-hour urine protein excretion were done for the patients. Correlation analyses, regression models, and Bland-Altman plots evaluated the relationships between PCR, ACR, and 24-hour urine protein excretion, as well as their associations with estimated glomerular filtration rate (eGFR). **Result:** Correlation analysis showed a weak but significant positive correlation between ACR and 24-hour urine protein excretion ($r = 0.156$, $p = 0.005$), and between PCR and 24-hour urine protein ($r = 0.169$, $p = 0.002$). ACR and PCR were perfectly correlated. Regression analyses confirmed that ACR ($\beta = 1.093$, $p = 0.005$, $R^2 = 0.024$) and PCR ($\beta = 1.068$, $p = 0.002$, $R^2 = 0.028$) significantly predict 24-hour urine protein. PCR significantly predicted eGFR, but ACR did not. Bland-Altman analysis highlighted significant disagreement between PCR/ACR and 24-hour urine protein, suggesting proportional bias. **Conclusion:** PCR and ACR are practical, cost-effective alternatives to 24-hour urine protein measurements for assessing proteinuria in T2DM patients. A multifaceted approach incorporating multiple markers is recommended for accurately diagnosing and managing kidney involvement early in diabetic patients. Future research should refine these markers and identify additional parameters to enhance diabetic nephropathy assessment.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder characterized by chronic hyperglycemia due to insulin resistance and/or deficiency.[1] The rising global incidence of T2DM is accompanied by increased complications, notably diabetic nephropathy. Approximately 20% of diabetic nephropathy patients progress to end-stage renal disease (ESRD), significantly impacting both morbidity and mortality.[2]

Proteinuria is a crucial marker for diabetic nephropathy and a key predictor of renal disease progression.[3] Monitoring proteinuria is essential for early detection and management of kidney involvement in T2DM. Guidelines recommend screening for proteinuria 5 years after diagnosis in Type 1 Diabetes Mellitus and at diagnosis in Type 2 Diabetes Mellitus patients without proteinuria, with annual monitoring until 75 years of age.[4]

Traditionally, 24-hour urine collection has been the gold standard for measuring protein excretion. However, this method is often impractical due to its time-consuming nature and potential for collection errors.[5] Alternative methods, such as the protein-to-creatinine ratio (PCR) and albumin-to-creatinine ratio (ACR) in spot urine samples, have been developed. These methods normalize protein excretion to creatinine concentration, accounting for variations in urine concentration.[6] The ACR is specifically endorsed by KDIGO (kidney disease: Improving Global Outcomes) guidelines as a valuable prognostic marker for patients with T2DM and chronic kidney disease (CKD).[7]

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While ACR is widely used due to its sensitivity in detecting early renal damage, PCR offers a cost-effective alternative with comparable predictive value for renal disease progression.[8] However, the accuracy and reliability of PCR and ACR compared to 24-hour urine protein measurement, especially in T2DM patients, remain debated, with results varying based on proteinuria levels, additional renal conditions, and patient demographics.[9]

Aim

To evaluate the correlation between the protein-to-creatinine ratio (PCR), albumin-to-creatinine ratio (ACR), and 24-hour urine protein excretion in patients with Type 2 Diabetes Mellitus (T2DM). This study aims to assess the practicality and cost-effectiveness of PCR and ACR as alternatives to 24-hour urine protein measurement for evaluating proteinuria and kidney function.

Objectives

1. Comparison of Ratios: Measure and compare PCR and ACR in spot urine samples with 24-hour urine protein excretion in T2DM patients.
2. Correlation Analysis of ACR and PCR: Assess the correlation between ACR/PCR and 24-hour urine protein excretion.
3. Diagnostic Accuracy: Determine the diagnostic accuracy of PCR and ACR in detecting significant proteinuria compared to 24-hour urine protein measurements.
4. Limitations and Reliability: Identify potential limitations or factors affecting the reliability of PCR and ACR as surrogate markers for 24-hour urine protein in diabetic nephropathy management.
5. Clinical Recommendations: Provide recommendations for incorporating PCR and ACR into routine clinical practice for early detection and monitoring of kidney involvement in T2DM patients.

MATERIALS AND METHODS

Study Design: This cross-sectional, observational study evaluated the correlation between PCR, ACR, and 24-hour urine protein excretion in T2DM patients.

Study Period: The study was conducted from January 2022 to December 2023.

Study Area: The study was conducted at a Government Tertiary Care Hospital in Tamil Nadu, India.

Study Population: The study included 338 adult patients (aged 18 years and above) diagnosed with T2DM who attended the outpatient diabetes clinic at the Government Tertiary Care Hospital.

Inclusion Criteria

1. Confirmed diagnosis of T2DM.
2. Informed consent provided by the patient.
3. Ability to collect a 24-hour urine sample.

Exclusion Criteria

1. Chronic renal failure due to glomerulonephritis, systemic conditions, or hypertension.
2. Pregnant women.
3. Patients with significant muscle wasting.
4. Patients on medications known to affect kidney function or proteinuria (e.g., ACE inhibitors, ARBs).
5. Refusal to participate.

A total of 338 subjects were included in the study. Data collection, Serum and urine samples were collected and analysis done.

1. Demographic and Clinical Data: Information on age, gender, duration of diabetes, glycemic control (HbA_1c), and medication history was collected.
2. Urine Sample Collection:
   - 24-Hour Urine Collection: Participants were instructed to collect urine over a 24-hour period. The total volume was measured, and an aliquot was used for protein quantification.
   - Spot Urine Sample: A morning spot urine sample was collected for PCR and ACR measurements.
3. Laboratory Measurements:
   - 24-Hour Urine Protein: Quantified using standard biochemical methods such as protein-dye binding method.
   - Creatinine (Serum and Urine): Measured using the Jaffe's kinetic method.
   - PCR: Calculated from spot urine samples using protein-dye binding or turbidimetric procedures.
   - ACR: Measured using immunoturbidimetry.
   - eGFR: Estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 2021.

Statistical Analysis: Sample size was determined using the formula for correlation studies:

$N=((Z_\alpha+Z_\beta)/C)2+3$

Z_α: The probability of type I error (significance level) is the probability of rejecting the true null hypothesis.

Z_β: The probability of type II error (1 – power of the test) is the probability of not rejecting the false null hypothesis.

Using a two-sided test, 5% significance level test ($\alpha=0.05$) with power 80% power ($\beta=0.2$), the required sample size is approximate 50 (n=50). The final sample included 338 subjects.

1. Descriptive Statistics: Reported means and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables.
2. Correlation Analysis: Pearson correlation coefficient (r) was used to assess the relationship between PCR, ACR, and 24-hour urine protein.
3. Regression Analysis: Linear regression was employed to evaluate the predictive value of PCR and ACR for 24-hour urine protein excretion.
4. Bland-Altman Analysis: Assessed agreement between PCR, ACR, and 24-hour urine protein measurements.
5. Subgroup Analysis: Analyzed based on degrees of proteinuria and other clinical factors.

Statistical significance was set at $p<0.05$. Analyses were conducted using SPSS software (version 21).

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RESULTS

The study included 334 patients with T2DM. Descriptive statistics for continuous data were expressed as mean and standard deviation, while non-normally distributed interval data and ordinal data were presented as medians and ranges [Table 1].

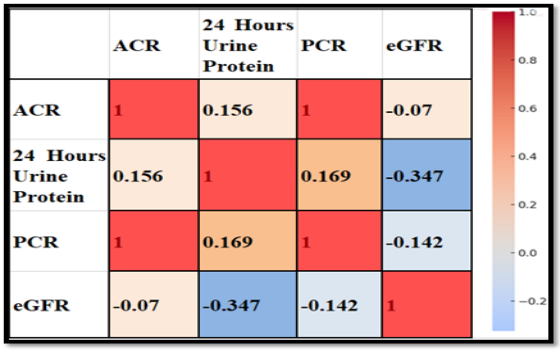
Table 1: Descriptive Statistics of Clinical Parameters.

	Mean/ Median	Standard Deviation/ Range
Age	55.04	10.887
HbA1c	6.8	4.7-17.8
Fasting Plasma Glucose (mg/dL)	127	64 – 451
Postprandial Plasma Glucose (mg/dL)	190	51 – 665
24-Hour Urine Protein (mg)	129	20 – 8640
PCR (mg/mmol)	18.3	0.3 – 970
ACR (mg/mmol)	23.6	4.3 – 975
Urea (mg/dL)	24	22 – 140
Creatinine (mg/dL)	0.8	0.3 - 8.75
eGFR (mL/min/1.73 m²)	96	6 – 168

Correlation Analysis showed the following results

- ACR and 24-Hour Urine Protein: A statistically significant positive correlation was observed ($r = 0.156$, $p = 0.005$).
- ACR and PCR: A perfect correlation ($r = 1.000$, $p < 0.001$).
- ACR and eGFR: No significant correlation was found ($r = -0.070$, $p = 0.210$).
- 24-Hour Urine Protein and PCR: A weak positive correlation was observed ($r = 0.169$, $p = 0.002$).
- 24-Hour Urine Protein and eGFR: A significant negative correlation was noted ($r = -0.290$, $p < 0.001$).

Correlation Heatmap Illustrating Relationships between Albumin-to-Creatinine Ratio (ACR), 24-Hour Urine Protein, Protein-to-Creatinine Ratio (PCR), and Estimated Glomerular Filtration Rate (eGFR) depicted as [Figure 1]



Note: A visual representation where values closer to 1 (dark red) indicate a strong positive correlation, values closer to -1 (dark blue) indicate a strong negative correlation, and values closer to 0 (white) indicate weak or no correlation.

Table 2: Regression Analysis Results for Predictors of 24-Hour Urine Protein and Estimated Glomerular Filtration Rate (eGFR)

Predictors	Outcome	β (Standardized Coefficient)	p-value	R^2	Interpretation
Albumin-to-Creatinine Ratio (ACR)	24-Hour Urine Protein	1.093	0.005	0.024	ACR significantly predicts 24-hour urine protein, explaining 2.4% of the variance.
Protein-to-Creatinine Ratio (PCR)	24-Hour Urine Protein	1.068	0.002	0.028	PCR significantly predicts 24-hour urine protein, explaining 2.8% of the variance.
Protein-to-Creatinine Ratio (PCR)	Estimated Glomerular Filtration Rate (eGFR)	-0.033	0.09	0.020	PCR significantly predicts eGFR, explaining 2.0% of the variance
Albumin-to-Creatinine Ratio (ACR)	Estimated Glomerular Filtration Rate (eGFR)	-0.017	0.210	-	ACR does not significantly predict eGFR.
Protein-to-Creatinine Ratio (PCR)	Albumin-to-Creatinine Ratio (ACR)	1.000	1.000	0.000	PCR is a significant predictor of ACR.

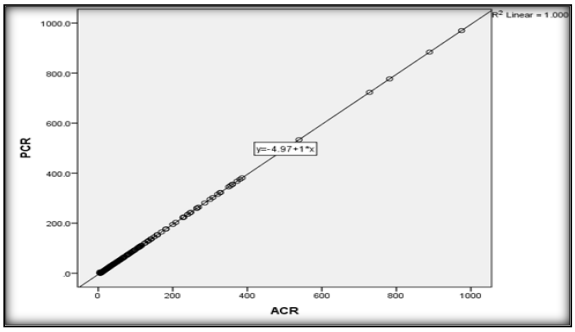


Figure 2: Scatter Plot with Regression Line Depicting the Relationship Spot Urine PCR and Spot Urine ACR in Patients with Type 2 Diabetes Mellitus

Regression Analysis Results for Predictors of 24-Hour Urine Protein and Estimated Glomerular Filtration Rate (eGFR) shown in [Table 2] and [Figure 2].

The ANOVA and subsequent post hoc Tukey analyses reveal distinct patterns of variation among clinical parameters across the three different PCR groups which were

Group I: Protein Creatinine Ratio < 15 mg/mmol
Group II: Protein Creatinine Ratio 15 -50 mg/mmol
Group III Protein Creatinine Ratio >50 mg/mmol

Significant differences in PCR and ACR across groups, particularly between Groups 1 and 3, and

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Groups 2 and 3, suggest notable variations in proteinuria and kidney function indicators.

Significant differences in eGFR between Groups 2 and 3 emphasize the impact of varying levels of kidney function on overall eGFR measurements.

The lack of significant differences in HbA_1C across the groups suggests that glycemic control may not differ substantially among the groups in this study.

The significant differences in Fasting Plasma Glucose between Groups 1 and 3 highlight the variability in albuminuria, which may be indicative of differing stages of kidney disease or damage. This finding supports the importance of monitoring albumin/creatinine ratios in assessing kidney function.

The observed variations in PCR, ACR, and eGFR across different groups suggest significant differences in proteinuria and kidney function that warrant further investigation. These findings highlight the importance of a multifaceted approach to evaluating renal health and suggest that comprehensive assessment strategies utilizing multiple markers (e.g., PCR, ACR, eGFR) are crucial for accurate diagnosis and management of kidney-related conditions.

The Bland-Altman analysis reveals significant disagreement between PCR and 24-hour urine protein excretion, particularly at higher levels of proteinuria, due to proportional bias. These findings highlight the need for cautious interpretation of PCR values in clinical practice and suggest the utility of using additional or alternative methods for assessing proteinuria in patients with diabetes mellitus shown in [Figure 3].

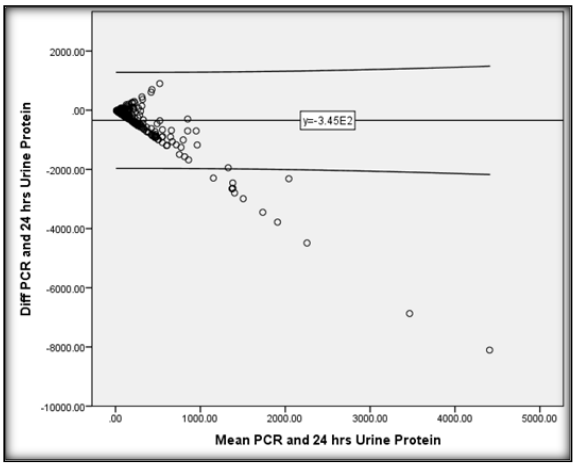

Figure 3: Bland-Altman Plot Showing Agreement Between Spot Urine PCR and 24-Hour Urine Protein Measurement in Patients with Type 2 Diabetes Mellitus

DISCUSSION

ACR and 24-Hour Urine Protein showed positive correlation with a weak association. This finding is consistent with previous studies, which report similar correlations in patients with diabetic nephropathy.[10] But ACR and PCR showed a perfect correlation indicating these measures are nearly identical.[11] Though no significant correlation was found between ACR and eGFR, which contrasts with other studies showing a moderate negative correlation.[12] 24-Hour Urine Protein and PCR showed weak positive correlation reflecting variability in protein excretion.[13] But a significant negative correlation between 24-Hour Urine Protein and eGFR aligning with findings from other research indicating that increased proteinuria is associated with decreased renal function.[14] The ANOVA and subsequent post hoc Tukey analyses reveal distinct patterns of variation among clinical parameters across the three different PCR groups. Significant differences in PCR and ACR across groups, particularly between Groups 1 and 3, and Groups 2 and 3, suggest notable variations in proteinuria and kidney function indicators. These findings align with existing research indicating that proteinuria markers can vary significantly with different levels of kidney dysfunction and disease severity. [15,16] Significant differences in eGFR between Groups 2 and 3 emphasize the impact of varying levels of kidney function on overall eGFR measurements. This is consistent with previous studies showing that eGFR can vary substantially among different patient populations.[17] The lack of significant differences in HbA1C across the groups suggests that glycemic control may not differ substantially among the groups in this study. This finding is consistent with research indicating that while proteinuria and kidney function can be affected by glycemic control, they do not always show direct correlations.[18]

The significant differences in Fasting Plasma Glucose between Groups 1 and 3 highlight the variability in albuminuria, which may be indicative of differing stages of kidney disease or damage. This finding supports the importance of monitoring albumin/creatinine ratios in assessing kidney function. The observed variations in PCR, ACR, and eGFR across different groups suggest significant differences in proteinuria and kidney function that warrant further investigation. These findings highlight the importance of a multifaceted approach to evaluating renal health and suggest that comprehensive assessment strategies utilizing multiple markers (e.g., PCR, ACR, eGFR) are crucial for accurate diagnosis and management of kidney-related conditions.

CONCLUSION

This study offers valuable insights into the relationships and predictive capabilities of Albumin-to-Creatinine Ratio (ACR) and Protein-to-Creatinine Ratio (PCR) in assessing proteinuria and kidney function in patients with Type 2 Diabetes Mellitus (T2DM). PCR and ACR are practical, cost-effective alternatives to 24-hour urine protein measurements for assessing proteinuria in T2DM patients. Regular monitoring of proteinuria using multiple markers can

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assist in managing diabetic nephropathy. Personalized treatment strategies should consider the limitations of PCR and ACR, especially in patients with high levels of proteinuria. The observed variations in biomarkers across different groups underscore the need for personalized patient care. Tailoring treatment based on a combination of biomarkers can enhance the management of renal health in T2DM patients.

In summary, while ACR and PCR are valuable tools in the assessment of proteinuria, a multifaceted approach incorporating multiple markers is recommended for accurately diagnosing and managing kidney involvement in diabetic patients.

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