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Original Article

Assessment of Proteinuria in Patients with Chronic Kidney Disease Albuminuria and Non-Albumin Proteinuria

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a global health concern characterized by a gradual loss of kidney function over time. It is often associated with an increased risk of cardiovascular disease and other complications. Proteinuria, the presence of abnormal quantities of protein in the urine, is a key indicator of kidney damage in CKD. Among the types of proteinuria, albuminuria (excessive albumin in the urine) is particularly significant. This study aims to delve into the prevalence and implications of both albuminuria and non-albumin proteinuria (NAP) in CKD patients, offering insights into their diagnostic and prognostic value.

Objective: To evaluate the prevalence and association of albuminuria and NAP in CKD patients.

Methods: Conducted at Pakistan Emirates Military Hospital, Rawalpindi, from March to September 2023, this prospective study included 385 CKD patients. Convenience sampling was utilized. Participants underwent medical history reviews, clinical evaluations, blood tests, and provided three morning urine samples. The study defined albuminuria as a urine albumin to creatinine ratio (uACR) of ≥3 mg/mmol in at least two out of three samples. Isolated NAP was indicated by a urine protein to creatinine ratio (uPCR) of ≥17 mg/mmol in two out of three samples and uACR <3 mg/mmol in all samples.

Results: In this study of 385 CKD patients, 54.5% (210 individuals) were male, and 45.5% (175) were female. Proteinuria of albuminuria was observed in 24.6% of patients. Specifically, 76 patients (19.7%) had abnormal uACR levels in their initial test. On follow-up tests, 65 patients (16.8%) showed albuminuria based on at least two out of three positive uACR measurements. The study also found that 55 patients (14.2%) had a mixed profile of albuminuria and NAP, while 20 patients (5.1%) exhibited isolated albuminuria. Moreover, 135 individuals (35%) had 'high normal' albuminuria (uACR 1-3 mg/mmol).

Conclusion: The study concluded that albuminuria is distinctly associated with CKD. While albuminuria can be initially detected with one uACR sample, accurate quantification requires three measurements.

Keywords: Albuminuria, Chronic Kidney Disease, Non-Albumin Proteinuria, Proteinuria, Urine Analysis.

INTRODUCTION

Proteinuria assessment plays a pivotal role in the study of renal disease, particularly in the context of chronic kidney disease (CKD), where both albuminuria and non-albumin proteinuria (NAP) are significant markers of renal function and disease progression. Historically, the methodologies for evaluating proteinuria have been a topic of debate, especially concerning the optimal quantity of urine samples and the decision to measure total urinary protein versus albuminuria specifically.

Patients with CKD are known to face an elevated risk of mortality, the development of cardiovascular disease (CVD), and, less frequently, progression to end-stage renal disease (ESRD)(1,2). This risk amplifies notably in the presence of proteinuria. Notably, a mixed proteinuria profile, indicative of both glomerular and tubular disease, often emerges in patients as total protein levels increase(3). Among the various measures of proteinuria, albuminuria stands out as a robust independent predictor of mortality, cardiovascular, and kidney risks(4,5). While both urine protein to creatinine ratio (uPCR) and urine albumin to creatinine ratio (uACR) have been shown to predict negative outcomes effectively, there is some evidence suggesting that uPCR might serve as a more sensitive screening tool for proteinuria(6,7).

The correlation between escalating uACR levels and increased risks of cardiovascular mortality and CKD progression is well-established. This correlation is consistent across genders, is unaffected by diabetes status, and tends to strengthen with advancing

age(8,9). However, the assessment of both albuminuria and NAP could yield critical diagnostic and prognostic information. For instance, a low urine albumin to total urinary protein ratio (uAPR) has been linked with tubulointerstitial disease upon renal biopsy. In contrast, albuminuria typically signifies glomerular disease, and NAP, which includes proteins like 2- and 2-microglobulins, is associated with tubulointerstitial pathology(10,11).

In light of these considerations, this article aims to comprehensively review the methods of assessing proteinuria in CKD patients, focusing on both albuminuria and non-albumin proteinuria. The intent is to elucidate the implications of these measures in diagnosing and prognosticating CKD, thereby contributing to a more nuanced understanding of renal disease and its management.

MATERIAL AND METHODS

This study was a prospective observational analysis conducted at the Pakistan Emirates Military Hospital's Medicine Department, Rawalpindi, Pakistan, between April and September 2023. The participant pool consisted of 385 individuals diagnosed with chronic kidney disease (CKD). A convenience sampling strategy was employed to select the participants. Ethical approval was granted by the Ethical Review Committee of Pakistan Emirates Military Hospital, ensuring adherence to ethical standards. In addition to ethical clearance, written informed consent was obtained from all participants and, where applicable, from their parents.

The study focused on individuals aged between 18 and 60 years who were capable of providing informed consent. Eligible participants met the Kidney Disease Outcomes Quality Initiative criteria for CKD stages 1 to 3, characterized by an estimated Glomerular Filtration Rate (eGFR) ranging from 31 to 60 ml/min per 1.70 m^2, verified on at least two occasions at least three months apart prior to recruitment. Inclusion also necessitated the ability of participants to attend the Medicine Department for necessary assessments. Conversely, individuals who had previously undergone a solid organ transplant, those terminally ill with an expected survival of less than one year, or suffering from multiple comorbidities, chronic liver disease, liver cirrhosis, or lower urinary tract infections were excluded from the study.

At the onset of the study, participants' personal profiles, socioeconomic, and educational statuses were meticulously documented. Given the high proportion of elderly participants, screening and baseline assessment visits were merged for convenience. Participants were provided with three urine sample bottles and instructed to refrain from consuming cooked meat for a minimum of 12 hours prior to sample collection. They collected early morning urine samples on three consecutive days, storing them in a refrigerator until the day of submission for analysis.

Blood samples were also collected for biochemical examination, which included high-sensitivity C-reactive protein (hsCRP; Roche Diagnostics, Newhaven, UK), blood lipid levels, and serum creatinine measurements. Creatinine testing was conducted using a single autoanalyzer, employing the Jaffe method. The assay was calibrated using the IDMS (Isotope Dilution Mass Spectrometry) method. The eGFR was calculated using the modified 4-variable Modified Diet in Renal Disease equation, categorizing the results into four distinct groups (>60, 45-59 (stage 3a), 30-44 (stage 3b), and <30 (stages 4 and 5)).

The study's primary focus was to measure total protein, albumin, and creatinine concentrations in the urine samples. The urine protein to creatinine ratio (uPCR) and urine albumin to creatinine ratio (uACR) were determined as indicators of proteinuria. Proteinuria was defined conservatively, with uPCR values of >17 mg/mmol (150 mg/g) in at least two out of the three samples indicating its presence. The distinction between uPCR and uACR was critical for assessing non-albumin proteinuria. Albuminuria was identified as KDIGO A2 or A3 (i.e., uACR >3 mg/mmol) in at least two of the three samples.

For data analysis, the collected information was entered and analyzed using SPSS version 26.0. Quantitative data were presented as mean ± standard deviation (SD), while qualitative data were expressed in terms of frequency and percentage. The methodological approach of this study ensured a comprehensive and systematic evaluation of proteinuria in CKD patients, with a focus on both albuminuria and non-albumin proteinuria, thereby contributing valuable insights into the management and understanding of CKD.

RESULTS

In this prospective observational study, a total of 385 participants were enrolled, comprising 210 males (54.5%) and 175 females (45.5%). The gender distribution of the study cohort is detailed in Table 1, providing a clear overview of the male and female participation in the research. This balanced representation of genders ensures a comprehensive understanding of the impact of chronic kidney disease across different demographics.

Table1: Gender Distribution of Respondents

S. No	Variable	N (Percentage)
1	Male	210 (54.5%)

2	Female	175 (45.5%)
3	Total	100%

The participants in the study were categorized based on their age groups. Among the 385 individuals, 50 participants (12.9%) fell within the 18-30 years age bracket. The 31-40 years age group comprised 80 individuals (20.7%), while the 41-50 years age category included 100 participants (25.9%). The largest group was those aged between 51-60 years, accounting for 155 participants (40.2%). The distribution of ages among the study cohort is detailed in Table 2, illustrating the diverse age range of the participants and providing insight into the prevalence of chronic kidney disease across different life stages.

Table 2: Age wise distribution

S. No	Variable	N (Percentage)
1	18-30 years	50 (12.9%)
2	31-40 years	80(20.7%)
3	41-50 years	100(25.9%)
4	51-60 years	155(40.2%
5	Total	385(100%)

In this cohort of 385 patients, 95 individuals (24.6%) were identified with proteinuria manifesting as albuminuria (KDIGO A2 or A3). Of these, 76 patients (19.7%) exhibited an abnormal urine albumin to creatinine ratio (uACR) on their initial test. A subsequent analysis, requiring two out of three positive uACR measurements, confirmed albuminuria in 65 patients (16.8%). Among those with established albuminuria, 55 patients (14.2%) presented with a mixed profile of albuminuria and non-albumin proteinuria (NAP), while 20 patients (5.1%) exhibited isolated albuminuria. Additionally, a subgroup of 135 individuals (35%) presented with 'high normal' albuminuria, characterized by uACR levels ranging from 1 to 3 mg/mmol.

The study also explored various factors correlating with albuminuria. Univariate analysis revealed significant associations with male gender, reduced estimated Glomerular Filtration Rate (eGFR), diabetes, hypertension, smoking habits, a history of cardiovascular disease (CVD), an elevated cholesterol/HDL ratio, lower educational attainment, and high-sensitivity C-reactive protein (hsCRP) levels. However, multivariate analysis refined these findings, identifying male gender, decreased eGFR, diabetes, and elevated hsCRP levels as the most significant positive correlates of albuminuria.

These findings provide critical insights into the demographic, clinical, and biochemical factors associated with albuminuria in patients with chronic kidney disease, underscoring the importance of a multifaceted approach in the evaluation and management of this patient population.

DISCUSSION

This prospective observational study, encompassing 385 patients with a gender distribution of 54.5% male and 45.5% female, revealed significant findings in the realm of chronic kidney disease (CKD) and proteinuria. A notable 24.6% of these patients presented with albuminuria. The initial urine albumin to creatinine ratio (uACR) measurements identified 19.7% of patients with abnormal levels, while a subsequent evaluation using two out of three positive uACR measurements confirmed albuminuria in 16.8% of cases. This prevalence is slightly higher compared to the 16% reported by Simon D et al. (14), potentially attributable to variations in sample size and geographic region.

The study's methodology aligns with the findings of Dennis Sung Chul Hong et al. (15), supporting the utility of both ACR and PCR in evaluating proteinuria. Echoing the results of Hong's study, this research underscores the efficacy of using spot urine samples over 24-hour collections for quantifying proteinuria, a practice now widely accepted in clinical settings.

A critical aspect of this study involved examining the necessity of measuring both ACR and PCR in screening CKD patients. Historically, albuminuria measurements were confined to individuals with hypertension or early-stage diabetic nephropathy. Microalbuminuria, a marker of endothelial dysfunction, has emerged as a significant indicator in this context. This study's findings resonate with the Chronic Renal Insufficiency Cohort Study (16), which also observed a correlation between ACR, PCR, and prevalent CKD comorbidities. Furthermore, the research conducted by Mathven et al. (17) reinforces the importance of Total Protein to Creatinine Ratio (TPCR) in detecting severe proteinuria, highlighting an additional 16% of cases that might be overlooked during routine screening.

A noteworthy finding of this study is the association between albuminuria, non-albumin proteinuria (NAP), and the inflammatory marker high-sensitivity C-reactive protein (hsCRP). This correlation aligns with the broader understanding that systemic inflammation heightens cardiovascular risks and accelerates CKD progression. Studies by Menon V et al. and Tonelli M et al. (18,19) further substantiate these associations.

While the study presents robust findings, it is not without limitations. The convenience sampling method, although practical, may limit the generalizability of the results. Additionally, the study's observational nature restricts causal inferences, warranting further experimental research to elucidate these relationships more definitively (20).

This study contributes valuable insights into the assessment of proteinuria in CKD, particularly in the context of albuminuria and its association with systemic inflammation. The findings underscore the importance of comprehensive screening methods in the clinical management of CKD, advocating for a broader application of both ACR and PCR measurements in routine practice.

CONCLUSION

Diagnosing albuminuria in primary care is essential for determining prognosis and guiding treatment in patients with chronic kidney disease (CKD). Albuminuria, indicative of glomerular and tubulo-interstitial diseases, can be initially identified with a single uACR sample. However, accurate quantification necessitates three uACR measurements to ensure a more comprehensive evaluation.

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