ORIGINAL RESEARCH

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The Correlation Between Total Protein Level in 24-hour Urine Sample and Spot Urine Protein-to-creatinine Ratio in the Old Aged

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Abstract

Objective: This study aimed to determine the correlation between the total protein level in the 24-hour urine sample and the protein-to-creatinine ratio in spot urine to measure protein excretion in elderly patients and determine the reliability of protein-to-creatinine ratio in spot urine threshold for proteinuria.

Materials and Methods: A total of 50 patients, aged ≥65 years, wıth a spot urıne protein value of ≥15 mg/dL using urine dipstick and without the risk factors for transient proteinuria were included in the study. Daily protein excretion was determined by two different methods-protein-to-creatinine ratio in spot urine and total protein level in the 24-hour urine sample. The correlation between these two methods was evaluated.

Results: A strong positive correlation was found between the total protein level in 24-hour urine samples and the protein-to-creatinine ratio in spot urine ($r=0.879$, $p<0.005$). The sensitivity and specificity of the protein-to-creatinine ratio in spot urine increase as the proteinuria level increases to ≥3.5 g/day.

Conclusion: The protein-to-creatinine ratio in spot urine is a highly sensitive and specific test with a high agreement using the gold-standard method for proteinuria diagnosis and follow-up in elderly patients with chronic diseases. This will help clinicians to decide for elderly patients, especially when they are frail, with restricted mobility, incontinence, or difficulty in transferring due to medical, social, or economic reasons.

Keywords: 24-hour urine, clinical geriatrics, protein/creatinine ratio, proteinuria, spot urine

Introduction

Proteinuria is an independent risk factor for cardiovascular and renal diseases and is an indicator of target organ damage. It is the most common clinical finding of underlying renal disease. In addition to being an early sign of renal disease, it is also a guide for differential diagnosis, determining prognosis and following treatment (1). The gold-standard method used to determine daily protein excretion in urine is the total protein level in 24-hour urine sample (24-HUP) (2,3). The collection of 24-HUP is a time-consuming method highly dependent on patient cooperation, frequently interfering with the health quality of the patient.

Besides, geriatric syndromes, including cognitive disorders, restricted mobility, incontinence and increased frequency of chronic diseases, both interfere with convenience, sensitivity and specificity of 24-HUP results and make sample collection more cumbersome for the old aged. Furthermore, it may also increase hospital admission rates since the patient has to come at least once more to the clinics for leaving samples.

Protein-to-creatinine ratio in spot urine (PCR-SU) from an untimed specimen is the alternative method for proteinuria measurement (4). Since cheaper, more convenient and less time-consuming, PCR-SU is frequently used for the quantitative evaluation of proteinuria in practice (3,5,6).

Although there are studies that demonstrate a moderate-to-high correlation between 24-HUP and PCR-SU, this association is less evaluated in the old aged (7-9). This study aimed to determine whether there is a correlation between 24-HUP and PCR-SU for

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measuring protein excretion in old aged patients and determining the reliable PCR-SU threshold value for proteinuria.

Materials and Methods

All patients hospitalized between August 2015 and April 2016 in the Geriatrics Clinic of Ankara University Hospital were examined for inclusion into this study. All included patients were ≥65 years of age. Patients with urine pH >8, gross hematuria, presence of semen/leukocyte in the urine and history of iodinated contrast agent exposure in the last 24 hours were excluded since these may result in a false-positivity of proteinuria in the urine dipstick examination. Patients with urinary incontinence were also excluded since they would be unable to make a proper unine collection. Seventy-three in-patients were enrolled, of whom 23 were excluded [17 due to inadequate collection (missing some urine, pouring out, the wrong container), six due to over-collection]. Totally, 50 patients (27 males and 23 females) with proteinuria were included in the study. Daily urinary protein excretion was determined by two different methods: PCR-SU and 24-HUP. 24-HUPs were collected, excluding the first urine of the day and including the first-morning urine sample of the next day. Spot urine samples were taken as the first urine in the morning. The samples were collected during two consecutive days.

Total protein concentration levels were measured by a turbidometric assay using benzethonium chloride and creatinine level by Jaffe test in the Ankara University biochemistry laboratory. Serum creatinine levels were measured spectrophotometrically. The patients were categorized into three groups according to the glomerular filtration rate (GFR) levels: GFR <30 mL/min/1.73 m^2, GFR between 30-60 mL/min/1.73 m^2 and GFR >60 mL/min/1.73 m^2 per the National Institute for Health and Care guidelines. The modification of diet in renal disease Formula was used for GFR calculations.

Excellence

All tests for this study were performed in the Ankara University Biochemical Laboratory, a standardized laboratory inspected regularly by the ministry of health of Turkey.

Ethic

The protocol of this study was approved by the Ankara University Faculty of Medicine Medical Research Ethics Committee as dated 28.4.2014 and numbered 07-292-16. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki. All of the patients signed the informed consent forms.

Statistics

All analyses were performed in Windows XP using SPSS version 22.0 (IBM Co., New York, USA). The Pearson correlation test was used to determine the relationship between the PCR-SU and the protein levels in 24-hour urine sample. P<0.05 was considered statistically significant. Differential thresholds, sensitivity and specificity of protein-to-creatinine ratio levels in spot urine were calculated using the receiver operator curves (ROC) curve for thresholds of ≥0.3, ≥0.5, ≥1 and ≥3.5 g/day proteinuria in 24-HUP, corresponding to the upper and lower limits of 1+ ,2+, 3+ proteinuria in dipstick analysis and nephrotic range proteinuria, respectively. The limits of agreement between the two parameters were analysed by the Bland-Altman Plot, using the Med Calc statistical software version 7.6.0. This method depicts the mean difference and 95% confidence interval of the difference and limits agreement as mean difference ±1.96 standard deviation.

Results

The mean age of the study group was 74.9 (±6.795) (minimum 65, maximum 91) years. Hypertension (HT) was detected in 92% (n=46), chronic kidney disease (CKD) in 70% (n=35), diabetes mellitus (DM) in 58% (n=29) and coronary arterial disease (CAD) in 46% (n=23) of the patients. The mean serum creatinine level was 1.31 g/dL (0.60-5.18), and the GFR was 42.50 mL/min/1.73 m^2 (minimum 8, maximum 103) (Table 1).

A strong and positive correlation was found between 24-HUP and PCR-SU (r=0.879, p<0.005) (Figure 1). Although, there was a significant correlation between the two methods in all three groups, GFR <30 mL/min/1.73 m^2 had the strongest correlation (r=0.937, p<0.005). Correlation values decreased as GFR increased (GFR between 30-60 mL/min/1.73 m^2: r=0.801, p<0.005 and GFR >60 mL/min/1.73 m^2: r=0.635, p<0.005). The ROC analyses, detected PCR-US discriminant values of 0.545, 0.465, 0.812, 3.683 mg/mg as indicators of ≥0.3, ≥0.5, ≥1.0 and

Table 1. Clinical and laboratory findings of the study population

Variable	
Male/female, percentage (number)	54/46% (27/23)
Age, years (mean ± standard deviation)	74.9±6.7
Hypertension, percentage (number)	92% (46)
Diabetes mellitus, percentage (number)	58% (29)
Coronary arterial disease, percentage (number)	46% (23)
Chronic renal disease, percentage (number)	70% (35)
Serum creatinine (gr/dL) (mean, min-max)	1.31 (0.60-5.18)
Glomerulary filtration rate (MDRD) (mL/min/1.73 m^2) (mean, min-max)	42.50 (8-103)
24-hour urine protein mg/day (mean, min-max)	388 (50-6.655)
Spot urine protein/creatinine ratio (mean, min-max)	0.545 (0.77-10.080)

MDRD: Modification of diet in renal disease

≥3.5 g/day of proteinuria in 24-HUP, respectively (Table 2). When the proteinuria level increased to ≥3.5 g/day, the sensitivity, specificity and discriminant values of PCR-SU also increased.

Discussion

This study detected a strong correlation between PCR-SU and 24-HUP in old aged patients with underlying HT, DM, CKD and CAD.

The world population is ageing. According to the World Health Organisation, first time in history, most people are expected to live over their sixties. Therefore, any medical laboratory test should be evaluated for coherence to use in the old aged. HT and DM are the most common chronic diseases in elderlies, and the main complication of these two diseases are kidney damage (10,11). Furthermore, CKD and CAD incidence is increasing in this age group (12). So, it is evident that any test should be quick, cheap and reliable. In this regard, proteinuria detection in a urine sample is essential since both elderlies and disease burden with renal complications also increase. In our study, we demonstrated that proteinuria detection in spot urine is a reliable, sensitive and specific method. We found 80-85% sensitivity levels and 81-100% specificity levels of proteinuria detection with PCR-SU in elderlies. Our results are compatible with studies conducted on younger-aged populations (3,6). Studies analysing the correlation between 24-HUP and PCR SU are frequently disease-specific and have younger populations (3,4,13).

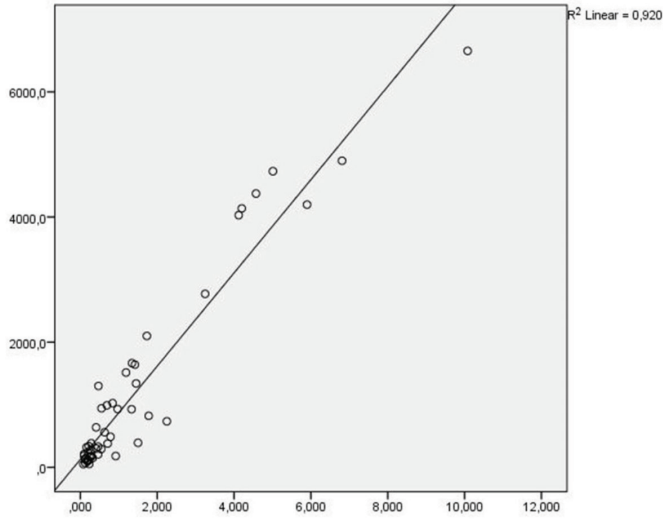

Figure 1. Correlation between spot urine protein-to-creatinine ratio and total protein level in 24-hour urine sample of the elderlies

According to our results, PCR-US is a convenient method for screening, diagnosis and follow-up of proteinuria in the elderlies. This correlation seems to be true for specific diseases and most common chronic conditions with renal complications in this age group.

The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative Guidelines support the use of PCR-SU (preferably in the first morning urine or in the spot urine sample at any hour if there is no first morning urine sample) to detect and monitor proteinuria (14). In our study, we collected our specimens as the first urine in the morning. Since our patients were hospitalised, we could also observe the patients' specimen collection appropriateness. This may be among the reasons of our higher specificity and sensitivity levels. Other studies are conducted mostly on outpatients (3,6,15,16).

Various studies reported that 10-20% of the patients who collect 24-hour urine cannot follow the procedures of urine collection (16,17). Due to cognitive losses, physical barriers and social problems in elderlies, it is more challenging to perform the examination correctly. Improper sample collection rates are, therefore, estimated to be much higher in the old aged. Not surprisingly, in our study, we detected that 31% of the patients collected their urine samples inappropriately. Although our rates are slightly higher than reported in the literature, this may be because our patients were older, had geriatric syndromes impeding proper collection, and all were in-patients with acute problems. We also excluded patients with urinary incontinence, which has up to 30% prevalence and is among the main problems in collecting 24-hour urine

Table 2. Disriminant protein- to-creatinine levels that predict threshold levels for proteinuria at 0.3, 0.5, 1.0 and 3.5 g/day

24-h urine total protein Threshold (g/day)	Discriminant values of spot urine PCR (mg/mg)	Sensitivity (95% CI)	Specificity (95% CI)	Area under the ROC curve (95% CI)
≥0.3	0.545	80.0 (62.69-90.49)	95.0 (76.39-99.11)	0.927 (0.856-0.998)
≥0.5	0.465	95.6 (79.01-99.23)	81.4 (63.30-91.82)	0.948 (0.892-1.0)
≥1.0	0.812	93.3 (70.18-98.81)	82.8 (67.32-91.90)	0.937 (0.873-1.0)
≥3.5	3.683	87.5 (52.91-97.76)	100.0 (91.80-100.00)	1.0 (1.0-1.0)

CI: Confidence interval, PCR: Polymerase chain reaction, ROC: Receiver operator curves

in this age group. Therefore, we estimate that inappropriate specimen collection might be more frequent among the geriatric age group. From this point of view, we believe that proteinuria detection by PCR-SU in the old aged has more significant importance when compared with younger groups as 24-hour urine collection has higher rates of inappropriateness in the old aged.

Price et al. (18) in their review of 16 articles comparing 24-HUP and PCR-SU for detection of proteinuria recorded that PCR-SU has a 69-96 % sensitivity and a 41-98% specificity for the detection of proteinuria of ≥300 mg/day. In this review, it was stated that evaluating proteinuria by the PCR-SU method may rule out the presence of significant proteinuria (18). In our study, by using the ROC curve and taking 24-HUP as the gold- standard method for proteinuria detection, we calculated the discriminant values of PCR-SU as 0.545 mg/mg, 0.465 mg/mg, 0.812 mg/mg and 3.683 mg/mg for ≥0.3, ≥0.5, ≥1.0, and ≥3.5 g/day proteinuria in 24-HUP with 80%, 95%, 93% and 87% sensitivity, and 95%, 81%, 82% and 100% specificity levels, all respectively. According to our results, we can say that PCR-SU has a high correlation and agreement with 24-HUP in old aged patients with different chronical diseases. Besides, when the patients were grouped according to GFR levels, there was a significant correlation between both methods in all groups, but GFR levels of <30 mL/min/m^2 was detected to have the highest correlation. In clinical practice, this will help clinicians since follow-up frequency increases as CKD progresses and more specific results are essential for clinical decision making of patients with advanced clinical diseases.

In summary, the main aim of geriatrics is comprehensive assessment of patients in a single centre with a multidisciplinary approach (19). Diminishing application rates to the hospital is among the aims of geriatric approach, especially for patients with transfer and mobilization difficulties. This study detected that PCR-SU is a highly sensitive and specific method with a high agreement with the gold-standard method. Since HT prevalence is up to 50-75%, and DM prevalence is up to 30% in the elderlies, at least three out of four patients admitting to geriatrics clinics will be analysed for proteinuria, which is among complications of these and many other chronic diseases (10,20,21). Using PCR-SU instead of 24-HUP will decrease caregiver burden, patient burden as well as healthcare utilisation and health personnel burden. This is essential in the old-aged group, especially in those with limited mobility and transfer options, both economically, medically and socially. According to our results, we consider that PCR-SU can be used for proteinuria detection in old aged patients with chronic diseases affecting renal function, both for diagnosis and follow-up reliably. Malnutrition is a common geriatric syndrome, and proteinuria may alert clinicians for the planning of nutrition (22).

Study Limitations

This study has some limitations and strengths. First, our sample size was limited. Thus, specific analyses for patients with different chronic diseases could not be performed. On the other side, to our knowledge this is the only study conducted in the old aged. Second, since our study population were in-patients, we can not generalise our findings for all patients. However, we were able to monitor the in-patients for appropriateness of sample collections. Futhermore, the same physician followed up the specimens collection process.

Conclusion

PCR-SU is a highly sensitive and specific test with a high agreement with the gold-standard method for proteinuria diagnosis and follow-up in old aged patients with chronical diseases. This will help clinicians for clinical decision making in old aged patients, especially when they are frail, have restricted mobility or have difficulty in transfer secondary to medical, social or economic reasons.

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Ethics

Ethics Committee Approval: The protocol of this study was approved by the Ankara University Faculty of Medicine Medical Research Ethics Committee as dated 28.4.2014 and numbered 07-292-16. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki.

Informed Consent: All of the patients signed the informed consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K.C., V.A., Concept: Ö.K.C., V.A., Design: Ö.K.C., V.A., Data Collection or Processing: Ö.K.C., V.A., Analysis or Interpretation: Ö.K.C., V.A., Literature Search: Ö.K.C., V.A., Writing: Ö.K.C., V.A.

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