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ORIGINAL RESEARCH

Correlation of random urine protein creatinine (P-C) ratio with 24-hour urine protein and P-C ratio, based on physical activity: a pilot study

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Abstract: Quantification of proteinuria is usually predicated upon 24-hour urine collection. Multiple factors influence urine collection and the rate of protein and creatinine excretion. Urine collection is often incomplete, and therefore creatinine and protein excretion rates are underestimated. A random urine protein-creatinine (P-C) ratio has been shown over the years to be a reliable alternative to the 24-hour collection for detection and follow up of proteinuria. However, urine protein excretion may be influenced by physical activity. We studied 48 patients with proteinuria and varying levels of physical activity to determine the correlation between the measures of urine protein excretion. The correlation coefficient (r) between 24-hour urine total protein and random urine P-C ratio was 0.75 ($P < 0.01$) in the overall study population, but varied according to the level of proteinuria and physical activity in a stratified analysis: r = 0.99 ($P < 0.001$) and r = 0.95 ($P < 0.01$) in bedridden patients; r = 0.44 (P = not significant [NS]) and r = 0.54 (P = NS) in semiactive patients; and r = 0.44 (P = NS) and r = 0.58 ($P < 0.05$) in active patients with nephrotic- (>3500 mg/day) and non-nephrotic (<3500 mg/day) range proteinuria, respectively. The correlation appeared to be stronger between random urine and 24-hour urine P-C ratio for the overall study population (r = 0.84; $P < 0.001$), and when stratified according to the level of proteinuria and physical activity: r = 0.99 ($P < 0.001$) and r = 0.92 ($P < 0.01$) in bedridden patients; r = 0.61 (P = NS) and r = 0.54 (P = NS) in semiactive patients; and r = 0.64 ($P < 0.02$) and r = 0.52 ($P < 0.05$) in active patients with nephrotic and non-nephrotic range proteinuria, respectively. We conclude that the random urine P-C ratio is a reliable and practical way of estimating and following proteinuria, but its precision and accuracy may be affected by the level of patient physical activity.

Keywords: random urine, 24-hour urine, proteinuria, protein-creatinine ratio, activity

Introduction

Proteinuria, a cardinal manifestation of kidney disease, usually requires timed urine collection for its quantification and evaluation. Twenty-four hour urine collection, the time-honored method of urinary protein quantitation, is cumbersome, and due to problems inherent in the collection of urine, is most often incomplete and unreliable, despite the fact that urine creatinine excretion is measured simultaneously to assure completeness of the collection. This is due to wide variations in creatinine excretion with changes in physical activity and dietary protein intake that make this assumption unreasonable and inaccurate. Over the years, attempts have been made to make use of the random urine protein-creatinine (P-C) ratio to simplify detection and follow up of proteinuria, and to avoid frequent urine collections.[1–5] However, urine protein excretion may also be influenced by level of physical activity, and it is unclear, based

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on current evidence, whether the correlation between the measures of urine protein excretion may be affected by level of physical activity. Herein, we report our pilot data collected in 48 patients with proteinuria who had varying levels of physical activity, to test our hypothesis that the strength of the correlation between random urine P-C ratio and 24-hour urine total protein would vary by level of patient physical activity. For academic interest, we also studied the correlation between random urine P-C ratio and 24-hour urine P-C ratio based on level of physical activity.

Methods

We conducted a prospective study of urine protein excretion in a clinically stable outpatient population of United States veterans at a single medical center. The Institutional Review Board at the medical center approved the study. All patients provided written informed consent for the study. Over an 8 month period, 56 sets of urine samples were collected for 50 patients. The reason that more than one urine sample was collected from some patients relates to the fact that some of the initial urine collections were incomplete, based on 24-hour urine creatinine excretion, and were therefore repeated. All patients were clinically stable, without acute illness, had proteinuria, and were seen in the outpatient setting (specifically, the medical clinic or chronic long-term nursing home care unit). All collections were made at a time when renal function was stable, as assessed by steadiness of serum creatinine levels. None of the patients had urinary tract infection or active glomerular disease. All patients submitted 24-hour urine collections and random spot urine specimens. The random spot urine specimens were submitted either immediately preceding or after completing the 24-hour urine collection. The majority of random urine samples were taken at times when patients would be normally ambulatory and active, usually between 9–12 AM, and occasionally, between 1–4 PM. Of the 56 urine studies, 2 of the 24-hour urine samples were discarded because of inadequacy of collection, and 2 because of the inability to measure urine protein excretion of <200 mg/L of urine, which is usually reported as negative. Therefore, 52 samples in 48 patients remained for statistical analysis.

Urine creatinine and protein measurements were conducted in the medical center's clinical laboratories. Urine protein excretion was quantified by the Esbach test.[6,7] Creatinine measurement was done using an autoanalyzer (Astra-8, Beckman Instruments, Brea, CA, USA).

The P-C ratio of an aliquot obtained from a patient's random spot urine specimen was compared to his or her total protein excretion over the 24-hour period. Based on previously published literature, these two measures of urinary protein excretion are known to be positively correlated in a linear manner.[3] To verify the assumption of linear regression and justify its use in our study population, we determined the residual differences between the observed and predicted values of proteinuria. We used the Shapiro-Wilk statistic to test for normality of the studentized residuals, and plotted the studentized residuals versus predicted values to test for linearity and homoscedasticity of the data. The strength of the linear correlation between the protein estimations of the spot and 24-hour urine collections was determined by calculating the Pearson correlation coefficient (r). The degree of deviation from the line of identity between the spot and 24-hour urine protein estimates was measured by the concordance correlation coefficient (p_c), and the simple linear regression method of least squares was used to obtain the best-fit regression line to the data. Completeness of the 24-hour urine collections was evaluated by comparing the total creatinine in the sample with the predicted creatinine, according to the gender and weight of the patient.[8,9] Analysis was conducted for the overall study population and also for a stratified subset, which we categorized according to the level of physical activity as follows: inactive (being bedridden), semiactive (using wheelchair or other assistive device for ambulation), and active (ambulating without any assistive device). All reported p values were two-sided, and we considered values <0.05 to be statistically significant.

Using the same methodology, the analysis was repeated to compare the patient's random urine P-C ratio to his or her 24-hour urine P-C ratio. All analyses were performed using STATA statistical software, version 8.0 (StataCorp, College Station, TX, USA).

Results

The baseline characteristics of our patient population are presented in Table 1. The majority of patients were male (98%) and physically active (52%). Of the remaining physically nonactive patients, 8 (17%) were bedridden, and 16 (31%)

Table 1 Baseline characteristics of 48 patients with proteinuria

	Inactive	Semi-active	Active
n	8	15	25
Male, n	7	15	25
Female, n	1	0	0
Mean age, years	69.8 ± 13.1	65.8 ± 5.7	61 ± 11.1
Creatinine excretion, mg/kg/day	11.6 ± 5.6	12.2 ± 3.8	14.7 ± 5.3
Creatinine clearance, mL/min	53.7 ± 40.3	45 ± 33.1	60.9 ± 35.2

were semiactive patients using wheelchairs. The mean age of the patients was 64.5 ± 12.1 years, ranging from 25 to 89 years.

Our study population reasonably met the assumptions of linear regression according to the analysis performed as described in the Methods section. The Shapiro-Wilk statistics between the studentized residuals and predicted measures of proteinuria were not statistically significant, indicating that our data was normally distributed (ie, we could not reject the null hypothesis of a normal distribution of our data). A plot of the studentized residuals versus predicted values of our data showed that, for the most part, the points were symmetrically distributed around the line of zero deviation in a relatively rectangular fashion as expected, indicating reasonable linearity and homoscedasticity of the data (Figures 1 and 2).

For the overall study population, the correlation coefficient between 24-hour urine total protein and random urine P-C ratio was r = 0.75 ($P < 0.01$). Twenty patients (23 urine samples) had daily total protein excretion equal or greater than 3.5 grams per 1.73 m^2 body surface area (BSA). In this group, the correlation coefficient of random urine P-C ratio (mg per liter/mg per liter) vs 24- hour urine total protein was r = 0.45 ($P < 0.02$). When activity of patients was considered, r was 0.99 ($P < 0.001$), 0.44 (P = NS), and 0.44 (P = NS) in the inactive, semiactive, and active patients, respectively (Table 2). Twenty-eight patients (29 urine collections) had non-nephrotic range proteinuria. In this group, the correlation coefficient for random urine P-C ratio vs 24-hour urine total protein was r = 0.63 ($P < 0.001$) and when the level of patient activity was taken into account, r was 0.95 ($P < 0.01$), 0.54 (P = NS), and 0.58 ($P < 0.05$) in the inactive, semiactive, and active patient groups, respectively (Table 2).

We also studied the correlation between random urine and 24-hour urine P-C ratio, which was stronger than the correlation between random urine P-C ratio and 24-hour total protein. This stronger correlation was observed for the overall study population (r = 0.84; $P < 0.001$) and when stratified according to the level of proteinuria and physical activity, r = 0.99 ($P < 0.001$) and r = 0.92 ($P < 0.01$) in bedridden patients; r = 0.61 (P = NS), and r = 0.54 (P = NS) in semiactive patients; and r = 0.64 ($P < 0.02$) and r = 0.52 ($P < 0.05$) in active patients with nephrotic and non-nephrotic range proteinuria, respectively (Table 3).

To evaluate the contribution of changes in the random urine P-C ratio to variations in the 24-hr urine protein, the coefficient of determination (R^2) was calculated. This showed that only 56% of the changes in 24-hour urine protein could be explained by the random urine P-C ratio variations. A scatter plot (Figure 3) of our data showed that despite significant correlation of random urine P-C ratio with 24-hour urine total protein excretion, the

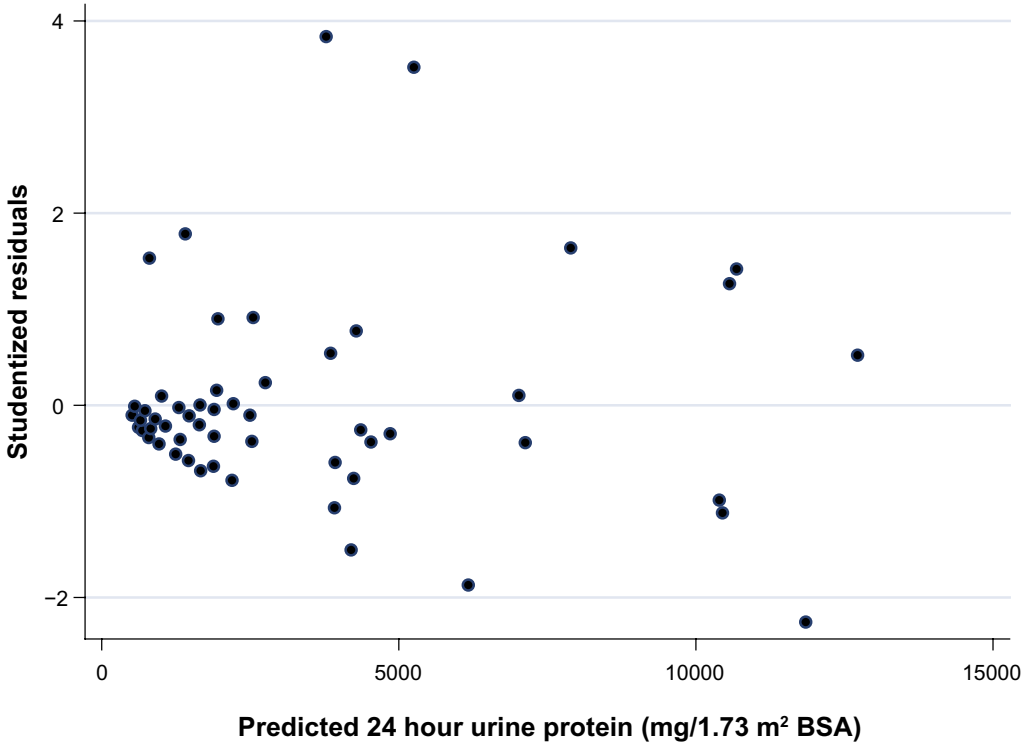

Figure 1 Scatter plot of studentized residuals vs predicted 24 hour urine total protein, showing reasonable adherence to the assumptions of linear regression.

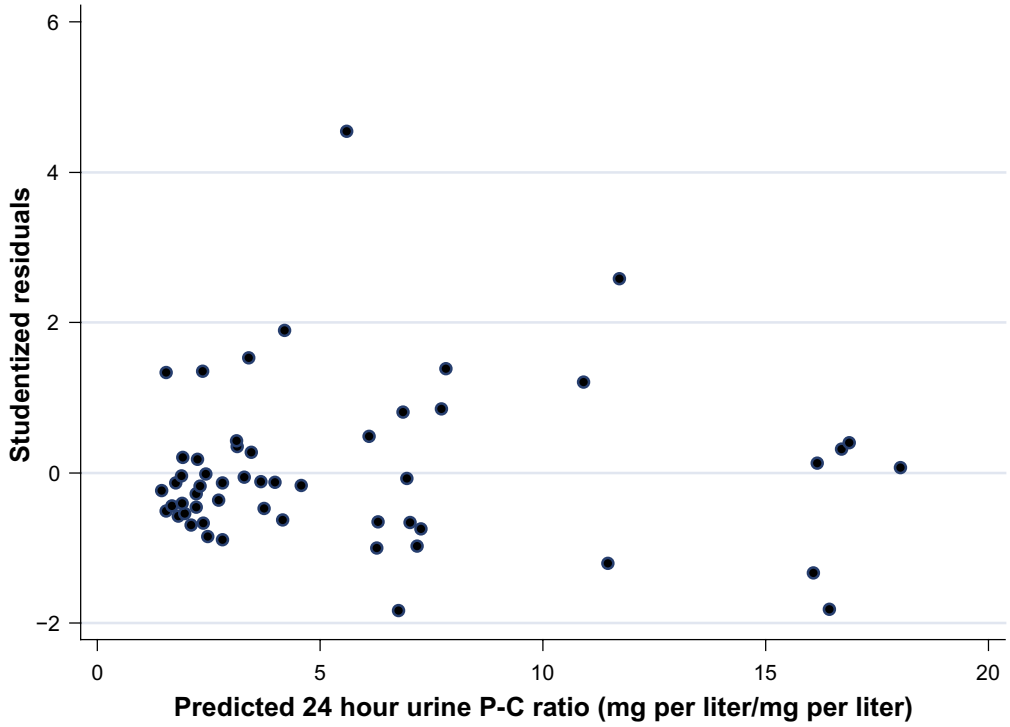

Figure 2 Scatter plot of studentized residuals vs predicted 24 hour urine P-C ratio, showing reasonable adherence to the assumptions of linear regression.

regression model was not a strong predictor of 24-hour urine protein. The correlation was significant for active and inactive patients, but not for semiactive patients. Regression analysis yielded a higher correlation (r = 0.84; $P < 0.001$) between random and 24-hour urine P-C ratios (Figure 4).

Discussion

Proteinuria, a cardinal manifestation of glomerular or tubular disease, requires timed (usually 24-hour) urine collection for its evaluation. Complete collection can be assured only if the patient has an indwelling Foley catheter or has an extreme awareness of the completeness of urine collection. Even in a closely supervised environment like a hospital, urine collection is often incomplete. Thoroughness of the collection can also be assured if daily creatinine excretion is within the expected range of 20 mg/kg for males, 15 mg/kg for females, and 8 to 10 mg/kg for bedridden patients. However, daily creatinine excretion can vary by as much 30 to 35%, dependent upon the intake of meat, menstruation, water intake, physical activity, stress, and fasting.[9–11] Therefore, and because of these difficulties and problems of day-to-day variation in protein and creatinine excretion, one has to obtain 2 to 3 urine collections. This becomes a problem, especially in elderly hospitalized patients who are often uncooperative, either because of debility or dementia, and who also carry a high risk of infection with Foley catheterization of the urinary bladder. Due to this, random urine P-C ratio is usually used for indirect quantification and follow-up of proteinuria. In the study of Shaw et al a P-C ratio (urine protein mg/L/creatinine mmol/L × 10) less than 125 excluded abnormal proteinuria, while a

Table 2 Correlation coefficient (r) of random urine P-C ratio vs 24 hour urine total protein according to the level of proteinuria and physical activity

	All specimens	Inactive	Semi-active	Active
24 hr urine protein mg/day/1.73 m^2 BSA				
>3500	0.45*	0.99***	0.44	0.44
<3500	0.63***	0.95**	0.54	0.58*

Notes: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Abbreviation: BSA, body surface area.

Table 3 Correlation coefficient (r) of random urine P-C ratio vs 24 hour urine P-C ratio according to the level of proteinuria and physical activity

	All specimens	Inactive	Semi-active	Active
24 hr urine protein mg/day/1.73 m^2 BSA				
>3500	0.59**	0.99***	0.61	0.64*
<3500	0.59***	0.92**	0.54	0.52*

Notes: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
Abbreviation: BSA, body surface area.

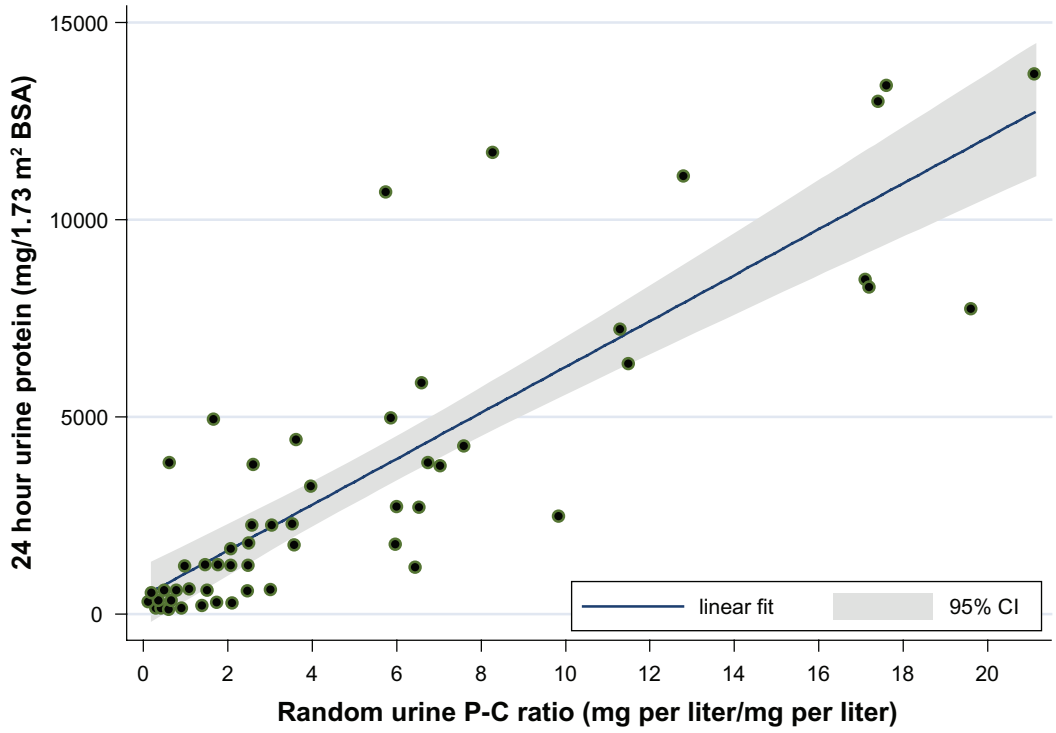

Figure 3 Scatter plot of correlation (r = 0.7540) of random urine P-C ratio and 24 hour urine total protein excretion. The best-fit line is shown, and the shaded area depicts the 95% confidence intervals.

ratio greater than 136 identified pathological proteinuria.[1] Sessoms et al also found a striking linear correlation between P-C ratios of random and 24-hour urine collections (r = 0.81; $P < 0.001$).[2] In the study of Ginsberg et al the correlation between 24-hour urine protein and random urine P-C ratios was excellent (r = 0.97).[3] They concluded that a random urine P-C ratio >3.5 represents nephrotic range proteinuria and a ratio <0.2 represents normal urine protein excretion.

However, subsequent studies have shown wide variation in the accuracy of random urine P-C ratio vs 24-hour urine protein excretion. Salesi et al found a correlation of 0.83 between random morning urine P-C ratio and 24-hour urine protein excretion in 74 patients with systemic lupus erythematosus.[12] In a systematic review of the literature, Price et al found sensitivity of 69% to 96%, specificity of 41% to 97%, positive predictive value of 46% to 95%, and negative predictive value of 45% to 98% for random urine P-C ratio to predict significant proteinuria, usually, but not universally, defined as protein excretion >300 mg in 24 hours.[13] Abitbol et al in a study of 76 children, reported a correlation ratio of 0.76 between random urine P-C ratio and 24-hour urine protein excretion, but the scattergram showed nonlinearity of correlation when proteinuria was in the nephrotic range.[14]

In our study, 20 of 48 patients had nephrotic range proteinuria by 24-hour urine collection. Of these 20 patients, 16 had a P-C ratio of >3.5 and 4 had a ratio below this. One patient in the latter group had a P-C ratio >3.5 on a repeated determination. The correlation of the random urine P-C ratio and 24-hour urine protein for all patients was high (r = 0.75) and statistically significant ($P < 0.01$). The correlation was even higher between random urine and 24-hour urine P-C ratios (r = 0.84; $P < 0.001$). Lower correlation between the observed random and 24-hour urine measurements in our patient population, compared to what is reported by others, could be due to older age and higher incidence of diabetes in our patients. The latter patients are known to have wide fluctuations in daily protein excretion. One major point in our study is the variation in correlation coefficient between 24-hour urine total protein and random urine P-C ratio based on physical activity. The correlation was 0.91 in bedridden patients while it varied widely in semiactive and active patients. The reason for the high correlation in bedridden patients could be the fact that all of them were catheterized, and therefore one can assume that the urine collection was complete. Alternatively, it could be an effect of the bedridden status of these patients, and lack of any physical activity. In an interesting study of 927 hospitalized pregnant women (over 20 weeks of gestation), Leanos-Miranda et al found a high correlation between random urine P-C ratio and 24-hour urine protein (r = 0.98; $P < 0.001$).[15]

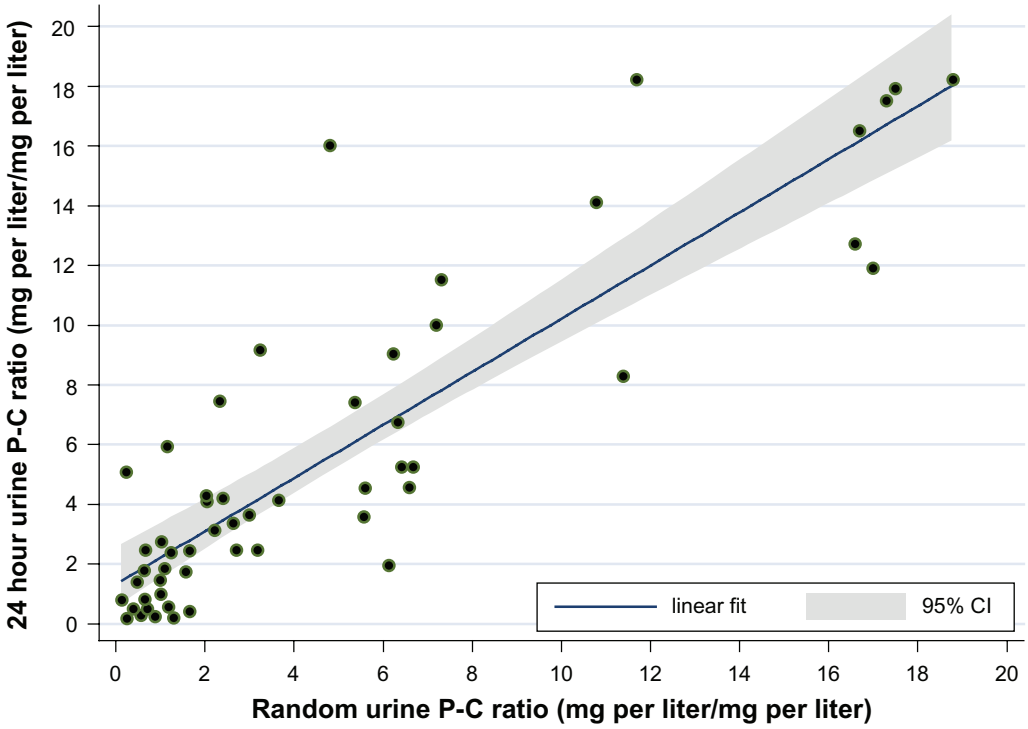

Figure 4 Scatter plot of correlation (r = 0.8429) of random urine P-C ratio and 24 hour urine P-C ratio. The best-fit line is shown, and the shaded area represents the 95% confidence intervals.

Our study has several strengths and limitations that should be acknowledged. Many studies performed to date on the usefulness of the random urine P-C ratio have yielded divergent results, as previously noted, reporting various degrees of correlation between random urine P-C ratio and 24-hour urine total protein. Admittedly, our sample population is small and may not be generalizable to the entire population, but it validates previously published findings that, indeed, the correlation between these measures of urine protein excretion is strong, supporting the use of random urine P-C ratio for estimation and follow-up of proteinuria. To the best of our knowledge, this is the first study to demonstrate the effect of physical activity on urine protein quantification. For medical care providers, this is a practical and clinically important consideration in the management of patients with kidney disease. Nevertheless, these findings need to be confirmed in a larger prospective cohort of patients.

In conclusion, the correlation between random urine P-C ratio and 24-hour urine protein excretion was highly significant in this pilot study of 48 United States veteran patients. The correlation was even stronger between random and 24-hour urine P-C ratios. In our study, similar to that reported by Ginsberg et al a random urine P-C ratio greater than 3.5 is highly suggestive of nephrotic-range proteinuria. It is a highly useful test in the outpatient clinic setting, but its precision and accuracy may be affected by the level of patient physical activity.

Disclosure

The authors report no conflicts of interest in this work.

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