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Screening for proteinuria in a rheumatology clinic: comparison of dipstick testing, 24 hour urine quantitative protein, and protein/creatinine ratio in random urine samples

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SUMMARY Measurements of protein/creatinine ratio in 'spot' urine samples were compared with measurements of 24 hour quantitative proteinuria and side room 'dipstick' testing in 104 samples from 90 patients presenting consecutively to a rheumatology unit. Linear regression analysis showed a highly significant correlation between the random urinary protein/creatinine ratio and total protein excretion in 24 hour urine samples ($r=0{\cdot}92$, $p<0{\cdot}001$, $y=6{\cdot}55x+0{\cdot}04$). Although an approximation of 24 hour urinary protein excretion could have been made from the regression line: 24 hour urine protein=6·55×protein/creatinine ratio+0·04 (g/l), there was a wide scatter of values, particularly in patients with >1 g/24 h urinary protein excretion. Nevertheless, significant proteinuria (>300 mg/24 h) could have been confirmed or excluded with a sensitivity and specificity of 97% by adopting random protein/creatinine values of <0·04 as 'normal'. Specificity and sensitivity could have been increased to 100%, however, by excluding patients with values lying between 0·01 and 0·10 as all the false negatives (n=3) and false positives (n=3) lay within this range. In comparison, dipstick testing, although 100% sensitive, had a poor specificity due to the high false positive rate (40/83 (48%)) in patients with 1+ to 3+ readings. Assessment of random urinary protein/creatinine ratio may obviate the need for 24 hour urine collections in the initial assessment of suspected proteinuria. A wider application of this technique seems indicated in view of the obvious advantages in terms of cost, time, and patient convenience.

Screening for proteinuria is a common requirement in rheumatological practice, particularly in patients who are receiving second line agents such as gold and penicillamine. In current clinical practice it is usual to screen for proteinuria by dipstick testing, and when a positive result is obtained to confirm or refute the presence of proteinuria by a 24 hour collection.[1] As 24 hour urine collections are laborious, costly, and inconvenient the present study was designed to see if the 24 hour urinary protein excretion could be assessed accurately from the protein/creatinine ratio in random urine samples—a method which has previously been shown to correlate well with measured 24 hour urinary protein excretion in various other clinical circumstances.[2–6]

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Patients and methods

One hundred and four samples from 90 patients who presented consecutively to the centre for rheumatic diseases over a six month period were studied. In all cases a 24 hour urine specimen had been requested as part of the patients' routine clinical management because of a positive screening test for protein on dipstick examination. Forty seven (45%) of the urine collections had been performed on inpatients and the remainder on outpatients.

The procedure for urine testing was as follows: a random urine sample was obtained from all patients for dipstick testing (Multi-stix; Ames and Co), which was performed by the on duty nursing staff.

Patients with positive results (i.e., trace to ++++) were asked to provide a 24 hour urine sample in the usual way. In addition, these patients were asked to collect a random urine sample (20 ml in a plain universal container) either before or after completion of the 24 hour sample, but were specifically instructed *not* merely to take an aliquot from the 24 hour sample. Random urine samples from two patients failed to reach the laboratory, giving a total of 102 samples in which full data were available. Venous blood samples were taken from all patients at the end of the 24 hour urine collection.

Serum albumin and creatinine were measured with an SMAC II autoanalyser (Technicon Co Ltd, Tarrytown, USA), by the BCG and alkaline picrate methods respectively. Urine creatinine was measured on a Hitachi 704 discrete autoanalyser (Boehringer Mannheim GmbH) by the alkaline picrate method (kit reagents from Boehringer Mannheim GmbH). Urinary protein was measured by the ponceau-S TCA method.[7] This method has a detection limit of 50 mg protein/l in our hands.

Statistical tests used in analysis of the data were Spearman's rank correlation coefficient and linear regression analysis by the sum of least squares method.

Results

Diagnostic categories of the patients studied were as follows: rheumatoid arthritis 72 patients (80%), seronegative spondarthritis seven (8%) connective tissue disease four (4%), miscellaneous seven (8%). Most of the patients were receiving non-steroidal anti-inflammatory drugs or analgesics, or both. Forty four (61%) of the patients with rheumatoid arthritis were also receiving gold or penicillamine treatment. Four patients had, or were subsequently discovered to have, amyloid disease (three rheumatoid arthritis, one ankylosing spondylitis). The median age of the study group was 58 years (range 15–78). Median serum creatinine was 75 μmol/l (range 35–600), median serum albumin was 35 g/l (range 21–47). Median creatinine clearance was 84 ml/min (range 5–246).

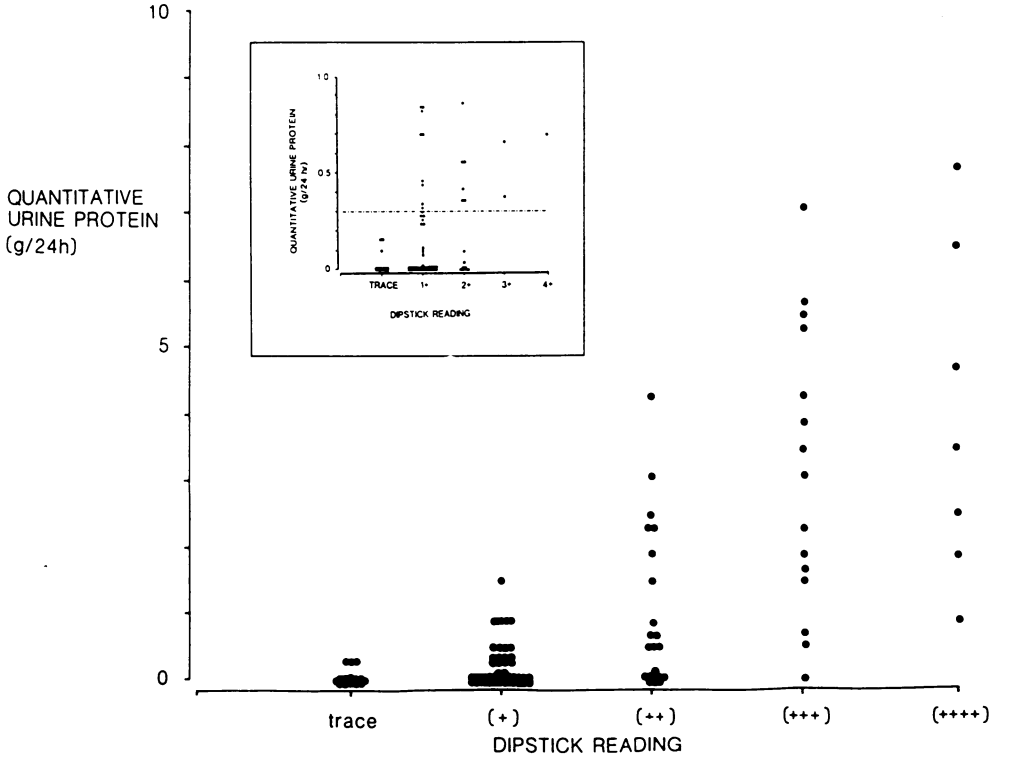

Fig. 1 *Comparison of dipstick testing and 24 hour quantitative protein excretion in 104 patient samples. Inset shows expanded view of data in patients with <1000 mg/24 h urine protein excretion. The number of data points in patients with 24 hour protein values of 0 were trace=12, 1+=25, 2+=6, 3+=1.*

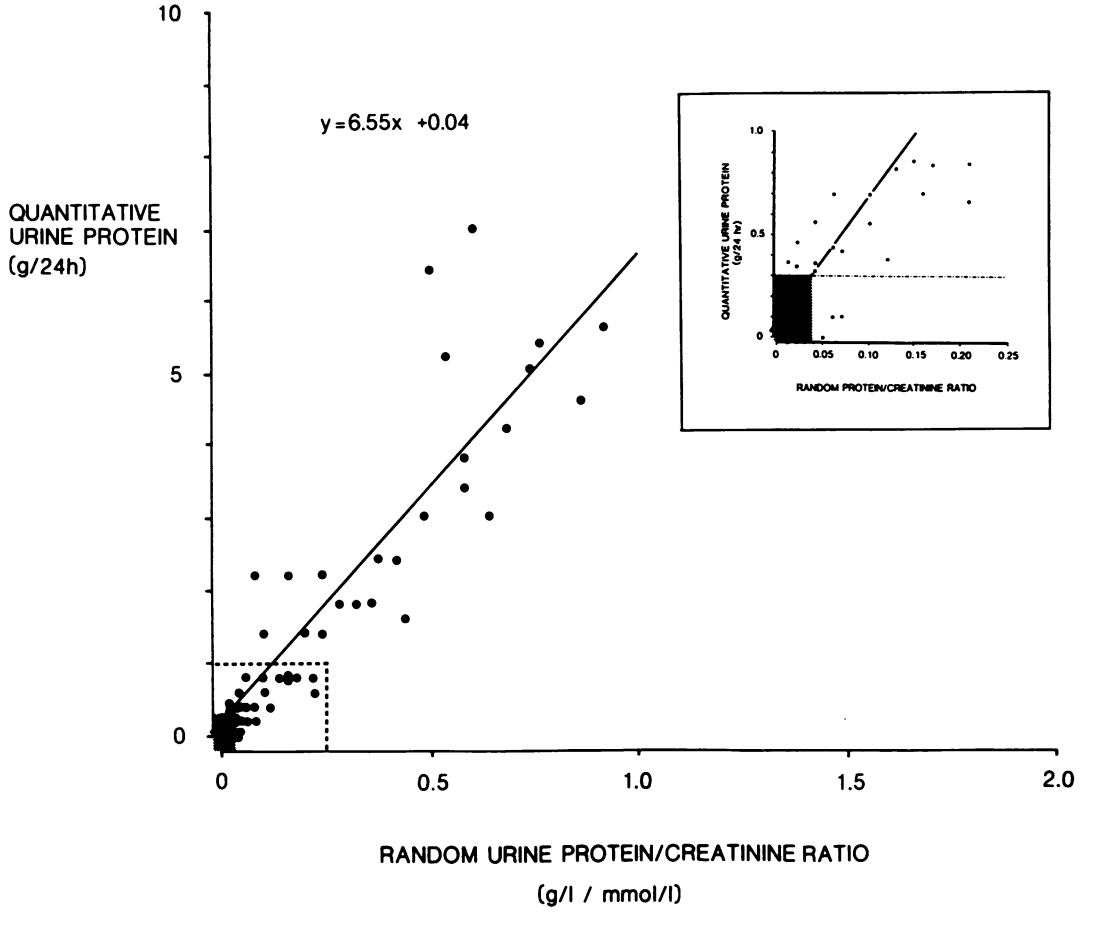

Fig. 2 *Comparison of random protein/creatinine ratio and 24 hour quantitative urine protein excretion in 102 patient samples. Note that no protein was detected in either sample in 42 cases (points omitted for clarity). Inset (note change of scale in axes) shows expanded view of data in patients with 24 hour urine protein excretion of less than 1000 mg and protein/creatinine less than 0·25 (the area enclosed by interrupted line in the main panel). The shaded area indicates the normal range for protein/creatinine ratio, as calculated from the regression line, for 24 hour urine protein excretion of <300 mg.*

Fig. 1 shows the results of dipstick testing in relation to the total urinary protein excretion over 24 hours. The inset shows details of these data in patients whose 24 hour urine protein excretion was less than 1000 mg. Twenty four hour urinary protein was less than 300 mg in all 15 of the patients with a trace of proteinuria on dipstick testing. The false positive rate, as defined above, was 76% in those with 1+ on dipstick (n=46), 8/21 (38%) in those with 2+, 1/15 (7%) in those with 3+, and none (0%) in those with 4+.

Preliminary analysis showed a significant correlation between absolute protein concentrations (g/l) in the random urine sample and 24 hour total protein excretion (Spearman's test: r=0·88, p<0·001; linear regression: r=0·70, p<0·001, y=0·30x+0·64). The closest correlation was obtained, however, when the protein excretion in the random sample was expressed as a function of the urinary creatinine concentration. The random urine protein/creatinine ratio was therefore used in subsequent analysis.

Fig. 2 shows the relation between the protein/creatinine ratio in random urine samples and the 24 hour urinary protein concentrations. The inset shows detail from the patient samples where the total excretion of protein was less than 1000 mg in 24

hours. In 42 subjects no protein was detected in either sample. These points are omitted from the figures for reasons of clarity.

There was a highly significant correlation between the random protein/creatinine ratio and 24 hour urinary protein excretion, using Spearman's rank correlation coefficient ($r=0{\cdot}91$, $p<0{\cdot}001$). Linear regression analysis yielded a similarly significant correlation ($r=0{\cdot}92$, $p<0{\cdot}001$), with a regression line of $y=6{\cdot}55x+0{\cdot}04$. When the 24 hour quantitative urine protein is plotted on the x axis (not shown) the regression line is $y=0{\cdot}13x+0{\cdot}01$.

From the regression line in Fig. 2 an estimate of the 24 hour urinary protein excretion (g/l) could be made by multiplying the urine protein/creatinine ratio (g/l/mmol/l) by 6·55 and adding 0·04. Unfortunately, the skewed distribution of the data renders calculation of confidence intervals unhelpful as the variation around the regression line was much wider at higher values of protein excretion than at lower values. Nevertheless, by using the regression equation we could have assigned patients into groups of significant proteinuria or insignificant proteinuria (i.e., >300 mg/24 h or ≤300 mg/24 h), with a sensitivity and specificity of 97%, by considering protein/creatinine values of <0·04 as normal and those of 0·04 or above as abnormal. Both sensitivity and specificity could have been increased to 100%, however, by excluding patients with protein/creatinine values of 0·01–0·10 as all the false positives and false negatives lay within this range.

Discussion

In recent years various workers have found a close correlation between 24 hour urinary protein measurements and random urinary protein/creatinine ratio in normal subjects,[2–5] patients with primary renal pathology,[2–5] and patients with systemic lupus erythematosus.[6] In this series of 104 patient samples—the largest reported study of patients with suspected proteinuria—we found a similarly close correlation between the protein/creatinine ratio and 24 hour urine protein excretion. We were also interested, however, to assess whether the protein/creatinine ratio would be sufficiently accurate to replace 24 hour urine collections in clinical practice; although urinary protein excretion is generally recognised to be less than 150 mg/24 h in normal subjects,[8] few clinicians would consider urinary protein levels of <200 mg/24 h to be worthy of investigation. Indeed, in rheumatological practice, a value of 300 mg/24 h has been considered to be the level at which one would consider stopping treatment with gold or penicillamine owing to nephrotoxicity.[9] If 300 mg of protein per 24 hours is taken as an arbitrary cut off point the presence or absence of significant proteinuria could have been predicted from the random urinary protein/creatinine ratio with a sensitivity and specificity of 97%. Moreover, both sensitivity and specificity could have been increased by excluding patients with protein/creatinine values lying between 0·01 and 0·10 as all the false positives and false negatives lay within this range.

This is a substantial improvement on dipstick testing as, in agreement with previous reports, neither the presence nor severity of proteinuria could have been confidently predicted by dipstick testing alone.[3 10 11] Thus where dipstick readings ranged from 1+ to 3+, there was a high incidence (40/83 (48%)) of false positives, though it should be emphasised that dipstick readings of 4+ correctly predicted the presence of significant proteinuria in all cases, whereas none of the patients with trace readings had significant proteinuria.

In many cases precise assessment of the degree of proteinuria is unnecessary. Rather, the clinician is more interested in classifying patients into broad categories by the degree of proteinuria, in order to decide which patients require further investigation, or in the case of gold and penicillamine treatment, to decide which patients can safely continue therapy. In this study we found that the correlation between the random protein/creatinine ratio and 24 hour quantitative protein measurements was sufficiently close to be of practical value in all the above respects. A wider application of this technique seems indicated in view of its advantages in terms of time, increased patient convenience, and reduced cost.

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