How to interpret the protein/creatinine ratio in patients with low GFR

Sir,

We read with interest the article introducing the strip test measuring protein-to-creatinine ratio (PCR) in random urine, reported by Guy and his colleagues [1]. PCR has good correlations with the total amount of protein excreted by urine in 1 day (P/day) and has a good diagnostic accuracy of estimating proteinuria [1,2]. By standardizing the changes in protein concentrations of random urine with the creatinine concentration, the trouble of collecting urine for 24 h was eliminated. Also, when the 24 h urine volume was insufficiently collected, P/day would falsely decrease, but still gave credible PCR results.

Despite all of these advantages, we investigated whether there were any problems with using PCR in the actual setting. In order to exclude cases in which an inappropriate amount of urine was collected, we selected 142 patients who showed differences of within ±20 ml/min/1.73 m² between creatinine clearance (Ccr) and the estimated GFR (eGFR) calculated using serum creatinine. The patients comprised 68 males (56.2 ± 14.5) and 74 females (57.8 ± 14.4). There was a good correlation between P/day (1325 ± 2536 mg/day/1.73 m²) and PCR (1781 ± 3525 mg/g) with r = 0.887 (P < 0.001). Patients were divided into two groups: 56 patients with Ccr of <50 ml/min/1.73 m² (low Ccr group) and 86 patients with Ccr of >50 ml/min/1.73 m² (high Ccr group), and the correlation coefficient between P/day and PCR in each group showed good results with r = 0.873, r = 0.987, respectively.

However, with the modified Bland–Altman’s difference plot [3], we plotted the differences between P/day and PCR according to Ccr, and the differences were generally small in most of the patients while there were some distinct differences in a few number of patients. Most of the values of distinct differences were positive in the high Ccr group and negative in the low Ccr group (Figure 1). In difference plot with 118 patients who showed P/day of <2000 mg/day/1.73 m², only 2 of 82 (2.4%) patients in the high Ccr group showed negative differences that were >100, while 21 of 36 (58.3%) patients in a low Ccr group showed negative differences that were >100 (Figure 2).

Even though the PCR showed good correlations with P/day, the PCR became greater than P/day in patients having highly reduced GFR. The correlation coefficient between Ccr (70.1 ± 44.5 ml/min/1.73 m²) and the total amount of creatinine in 24-h urine (14.3 ± 4.25 mg/kg/day) was r = 0.702 (P < 0.001). Thus, in patients with low GFR, regardless of the degree of dilution of urine, the decreased amount of creatinine in urine could falsely increase the PCR result.

In conclusion, unlike in early nephrotic syndrome patients or pregnant women [4,5], a PCR should be interpreted with caution in patients with renal diseases which accompany the decrease in GFR.

Conflict of interest statement. None declared.

Fig. 1. Agreement of the urine/creatinine ratio and 24-h urine protein against creatinine clearance in the whole study group (N = 142).

Fig. 2. Agreement of the urine/creatinine ratio and 24-h urine protein against creatinine clearance in the patients with 24-h urine protein <2000 mg/day/1.73 m² (N = 118).

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Reply

Sir,
We thank Professors Park and Kim for their interest in our paper [1] and would agree that there can be pitfalls in the use of creatinine ratios. It would be expected that, as GFR declines, urine creatinine excretion would also diminish, thus potentially causing an overestimate of the protein-to-creatinine ratio (PCR). In our group of patients with chronic kidney disease (CKD), 24-h creatinine excretion was indeed lower (95% range, 3–14 mmol/24 h) than might be expected in a normal population, and eGFR correlates with both 24-h creatinine excretion ($P = 0.03$) and random urine creatinine ($P = 0.01$). This would tend to support the data of Park and Kim. However, from their data, the fact that a number of samples from patients with low creatinine clearance (CCr) showed a large negative difference when PCR was subtracted from 24-h protein output is slightly fortuitous and relates to the choice of units for PCR. If PCR is expressed in mg/mmol rather than mg/24 h then the derived values are all positive. More important is that some patients had much lower differences than others and this appears more prevalent at lower CCr. Their observations also assume that there is a fixed relationship between PCR and 24-h protein loss. The examination of quantitative laboratory measurements from our patients suggest that this may not be the case and only at 24-h protein losses $>1$ g is PCR linearly related to 24-h protein loss (cumsum linearity test, $P > 0.01$). At protein loss $<1$ g/24 h, the relationship is not strictly linear (cumsum linearity test, $P < 0.01$). We have, however, reviewed our data and compared them to those of Park and Kim. In addition to testing with the PCR strip test, all random urine samples from our patient cohort had protein and creatinine quantitatively measured by a standard laboratory method (Roche Integra 800). We have calculated the difference between 24-h protein (mg/day) and PCR (mg/g) and examined the agreement with CCr. Only patients with 24-h protein $<2000$ mg and a difference between CCr and eGFR of $\pm 20$ ml/min were included (Figure 1). Although the pattern of results may be similar, it is clearly much less marked with fewer samples from our patients having a large difference at low CCr. It is possible that the choice of patients may have contributed to this. For example, all patients in our cohort had CKD, they were fewer in number, and few had CCr $>60$ ml/min. Second and third voided urine samples gave similar results to early morning urines (EMU).

There are several other instances where creatinine ratios should be interpreted with caution. Creatinine in very dilute urine samples, for example $<2$ mmol/l, may tend to undercompensate for urine dilution. (The scenario would be a urine protein of 100 mg and creatinine of 2 mmol/l, giving a significantly elevated PCR of 50 mg/mmol.) Other causes of a lower than expected creatinine excretion might include low skeletal muscle mass, reduced tubular secretion of creatinine induced by certain drugs and gender-related differences. In all these cases, caution should be exercised when interpreting PCR in random urine samples. If PCR is to be used for patients with CKD, one would hope that the nephrologist would have a greater awareness of the limitations of the test. In the primary care setting, any false positive results, albeit low in frequency, should be highlighted by a clinical review or confirmatory laboratory tests. Despite this, we believe that for the majority of patients, random urine PCR adequately predicts 24-h protein loss [2] and, for routine clinical use, offers a convenient alternative to 24-h urine collections.

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