Prevalence because vasopressin–V2R–AQP2–cAMP pathway has the major role in water absorption in collecting duct principal cells. Cyclophosphamide–induced hyponatraemia may correspond to type D (nephrogenic syndrome of inappropriate antidiuresis) among the four subtypes of syndrome of inappropriate antidiuresis proposed by Robertson [3].

It is interesting that cyclophosphamide can suppress the production of interleukin-1 (IL-1) and tumour necrosis factor (TNF) from human monocytes through its metabolites. Nuclear factor kappa B (NF-κB) and pro-inflammatory cytokines may downregulate V2R and AQP2 in acute inflammatory conditions, and the authors proposed a hypothesis that cyclophosphamide-induced suppression of IL-1 and TNF-α may upregulate V2R and AQP2 in the kidney. According to Hasler et al., NF-κB is a negative regulator of AQP2 transcription at a post-V2R level [4]. However, it is not clear whether the expression of V2R may be altered by pro-inflammatory cytokines in other conditions than sepsis animal models. Studies are required to provide direct evidences showing that the vasopressin–V2R–AQP2–cAMP pathway in the renal collecting duct is affected by cyclophosphamide administration or cyclophosphamide metabolites and which level (V2R or post-receptor) is the major determinant.

Conflict of interest statement. None declared.

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Proteinuria or albuminuria?

Dear Editor,

Methven et al. [1] present some interesting data concerning the use of urinary albumin to creatinine (ACR) and protein to creatinine (PCR) ratios in the detection of significant proteinuria. Their observation that PCR and ACR thresholds may need to be modified in relation to age and gender is particularly important.

In 1696 individual 24-h urine collections, they observed a better relationship between PCR and 24-h urinary protein than between ACR and 24-h urinary protein and concluded that PCR is a more sensitive screening test than ACR to predict clinically relevant proteinuria. We feel that their conclusion needs to be examined a little more closely, given that both PCR and 24-h total protein loss were based on the same total protein measurement and that the reference measure itself—total protein loss—is flawed. Given the study design, it is perhaps more remarkable that the differences between ACR and PCR in terms of predicting total proteinuria were so marginal. The converse comparative analysis, ability of PCR and ACR to predict 24-h urinary albumin loss, was not undertaken.

Some of the limitations of this study acknowledged by the authors are of central importance. The PCR and ACR estimates were obtained from a 24-h collection and may not, therefore, reflect the situation in a random or early morning ‘spot’ urine sample in which ACR and PCR would more usually be estimated [2]. The population studied was that attending a general nephrology clinic and the results may not be generalizable to primary care populations.

The authors also demonstrate, as others have before [3], that there is a poor relationship between ACR and total protein loss at lower levels of proteinuria. This should not be interpreted as a criticism of ACR measurement, which is based on specific immunoassay detection of a single protein in urine. Rather, it reflects imprecision of total protein measurement against a variable background of clinically insignificant proteins (e.g. Tamm–Horsfall glycoprotein), compounded by the non-specificity and susceptibility to interferences of the chemical reactions used to estimate total protein concentration.

Recommendations, including those from NICE [4], that ACR should replace PCR as the test of choice for proteinuria detection were not based solely upon their relative abilities to estimate total protein loss, but on factors including that albumin measurement can be standardized and is more precise at lower levels of proteinuria, that it is the test of choice in people with diabetes and that it is the predominant protein in the vast majority of proteinuric kidney diseases [5]. It is noteworthy that ACR and PCR had equal diagnostic performance amongst the subset of patients of Methven et al. receiving renin–angiotensin system blockade, amongst whom the proportion of albumin to total protein was higher.

An overwhelming body of evidence is accumulating pointing to the significance of low-level protein loss in terms of morbidity and mortality: such data can only be gathered using urinary albumin assays. To persevere in assigning primacy to total protein loss misses the point.

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Edmund J. Lamb

Paul E. Stevens

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Dear Sir,

We thank Drs Lamb and Stevens for their interest. Clearly, we agree on the importance of urinary protein quantification in the assessment of chronic kidney disease. They criticized our methodology because we derived albumin–creatinine ratio versus albumin–creatinine ratio. Nephrol Dial Transplant 2010; 10.1093/ndt/gfq140.

We demonstrated the inferior performance of ACR to TPCR at clinically relevant levels of proteinuria. Drs Lamb and Stevens assume this is due to imprecision of total protein assays and the confounding effect of physiological urinary proteins. They also assume that high levels of non-albumin proteinuria are irrelevant to patient outcomes, but present no evidence. In a follow-up study of a similar cohort (submitted for publication), ACR fails to detect clinically relevant total proteinuria (>0.5 g/day) [2,3] in 17% of patients. We found this subgroup to have poor outcomes (all-cause mortality, commencement of renal replacement therapy [RRT]).

We also agree on the prognostic importance of low-level proteinuria. However, Drs Lamb and Stevens assume that only ACR can detect low-level proteinuria of clinical significance. They present no comparative outcome studies to support this belief (admittedly widely held). In a further study (in press), we unexpectedly found that TPCR performs as well as ACR as a predictor of all-cause mortality and commencement of RRT in the microalbuminuria range.

We agree that the albumin immunoassay has strengths, but albumin is a complex molecule, making standardization more challenging than for simpler analytes such as creatinine. Albumin does not exist in urine as a single species, and there has been much debate regarding the clinical significance of non-immunoreactive albumin [4].

We remain undecided as to whether ACR or TPCR is the optimal test to predict prognosis in chronic kidney disease. However, we think it better to test their relative merits in comparative outcome studies, rather than basing guide-


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Acquired DHA nephropathy in rats

Nasr and colleagues [1] described a small series of patients who lost their kidneys to 2,8-dihydroxyadeninuria, a consequence of adenine phosphoribosyltransferase (APRT) deficiency (OMIM: 102600). They pointed to the possible underdiagnosis and misdiagnosis, which stemmed from the lack of awareness and similarities to other crystal deposition diseases, respectively. In contrast to the general medical community, dihydroxyadenine (DHA) nephropathy is well recognized among researchers utilizing animal models to study chronic kidney disease (CKD). In fact, an acquired form of the disease is extensively used to model CKD in rats [2]. Dietary adenine enrichment was shown in the 1980s by Koeda et al. to convert to DHA which precipitates and forms tubular crystals in rat kidneys, accompanied by progressive tubular and glomerular dysfunction [3], the latter being apparent within days [2]. However, while initially considered irreversible beyond 4–6 weeks of exposure [4], we have recently shown that a considerable functional as well as some structural improvement is the rule even after a prolonged 7-week exposure to excess dietary adenine (a time point at which extensive damage and dysfunction were already estab-