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 (ACR) and total protein–creatinine ratio (TPCR) from 24-h urine collections. We acknowledged this limitation in our paper and explained why it was not crucial to the conclusions [1].

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 guidelines on unsupported assumptions. Once such studies are available, it will be possible to assess whether ACR performs sufficiently better to justify its greater cost.


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Reply

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 dysfuction [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-
lished) [5]. In their patients, Nasr et al. also noted a possible reversibility, upon treatment with allopurinol [1]. We thus propose that the rat DHA nephropathy model can be used to study the pathogenesis and pathophysiology of dihydroxyadeninuria as well as to examine putative interventions in human APRT deficiency. Hopefully, it can yield valuable knowledge, as it has for the complications of uraemia.

Conflict of interest statement. None declared.

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Reply

We thank Dr Ben-Dov and Dr Shuvy for their interest in our study. As they have noted, despite being well-recognized by researchers, 2,8-dihydroxyadenine (DHA) crystal nephropathy is an under-diagnosed disease in humans, especially in the United States. Because of their strong birefringence, DHA crystals are often mistaken by pathologists as oxalate crystals, leading to erroneous diagnosis of oxalosis. Three of the four patients with DHA crystal nephropathy that we have encountered at Mayo Clinic, Rochester were initially misdiagnosed as having oxalosis in two and chronic tubulointerstitial nephritis in one [1]. Not infrequently, the diagnosis of DHA crystal nephropathy is established retrospectively after the disease recurs in the transplant, especially in patients without history of stones. Early diagnosis of this disease is essential for the initiation of allopurinol treatment, which prevents recurrence of nephrolithiasis, provides preservation of renal function and prevents or stabilizes the disease recurrence in the renal allograft [1–3].

One intriguing and particularly troublesome aspect of DHA crystal nephropathy is its early recurrence post-transplant. Early recurrence is known to occur in primary hyperoxaluria, a more common autosomal recessive disease. In primary hyperoxaluria which is a systemic disease, the early disease recurrence is thought to be due to the release of systemic oxalate with rapid deposition in the allograft. In contrast, DHA disease is a renal-limited disease manifesting as stones or chronic kidney disease without known systemic manifestation, and therefore, the early recurrence is difficult to explain. It is noticeable that the recurrence occurs typically in recipients of deceased-donor kidneys [1,3], which suggests that ischemic acute tubular injury may be a predisposing factor.

The available animal models for DHA crystal nephropathy, namely, the knockout mouse model for adenine phosphoribosyltransferase deficiency [4], the dietary adenine enrichment mouse model [5] and the high adenine and phosphate diet rat model widely used to study chronic kidney disease, have accurately recreated the clinical and histologic aspects of human DHA crystalline nephropathy. Studying these animal models will help understand several aspects of this disease, including (i) the underlying molecular mechanisms and genotype–phenotype correlations, (ii) the pathogenic mechanisms by which DHA crystal deposition in the kidney leads to tubular atrophy and interstitial fibrosis, (iii) the predisposing factors for crystal deposition in the kidney which may lead to oliguria and ischemic acute tubular injury, (iv) the effects of osteopontin and other inhibitors of crystal formation and (v) the potential avenues for new treatments. Increasing clinicians’ awareness of DHA disease likely will result in more interest in investigating these animal models and human disease.

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