Uric acid and decline in kidney function- partners in crime without any alibi

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Uric acid is a breakdown product of purine metabolism, regulated by the enzyme xanthine oxidase (XO). Pre-clinical studies suggest hyperuricaemia induces hypertension, renal microvascular disease and endothelial dysfunction and that it causes triglyceride accumulation in response to fructose ingestion [1]. XO may have further, uric acid independent, effects on the CV system. XO action generates superoxide, which has a role in renin-angiotensin system activation, in detrimental responses to fructose ingestion, and in ischaemia-reperfusion injury.

In this paper Kuwibara and colleagues [2] explored the relationship between serum uric acid level and change in estimated glomerular filtration rate (eGFR) over a 5-year period in a single centre retrospective cohort study. This was a well conducted analysis including over 13,000 Japanese patients. Higher baseline serum uric acid level was associated with greater odds of rapid eGFR decline (OR 1.27, 9%% CI 1.17-1.38 for each 1 mg/dl increment in serum uric acid. The authors were able to adjust for numerous potential confounders including age, body mass index, cardiovascular risk factors and diabetes status but were not able to account for difference in medication use or the presence or absence of proteinuria. The analyses were stratified by sex and sub-analyses stratified by baseline eGFR found similar results. This association has been shown before in Japanese patients and in patients with treated hypertension in the UK [3]. A novel finding from this study was that an increase in serum uric acid over a 5-year period was associated with a greater decline in eGFR (OR 3.77, 95% CI 3.35m to 4.26 for each 1mg/dl increase). Whilst, as the authors acknowledge, dissecting an independent effect of uric acid on decline in eGFR is challenging, independent of any influence of reducing kidney function on serum urate. Taken together, the epidemiological data are consistent, large in scale and suggest serum uric acid is associated with development of cardiovascular, renal and metabolic disease. However, these data cannot however prove causality. Experimental data support causality. Induction of hyperuricaemia causes a decline in renal function, glomerular hypertension and a small vessel renal arteriopathy in

rodent models. This may be mediate reno-vascular disease via increased renin production, COX-2 expression and thromboxane production [1].

One method of trying to better assess causality in humans is via use of Mendelian Randomization studies. Here, the relationship between a genetic polymorphism known to affect the exposure of interest (in this case uric acid level) and outcome is explored. This association should not be susceptible to confounding or reverse causation as presence of the phenotype of interest will be randomly determined at conception. Previous Mendelian Randomization studies have failed to demonstrate a clear association between instrumental variables for serum uric acid and chronic kidney disease and in one study, the instrumental variable was associated with better renal function in men [4]. Mendelian Randomization studies in this setting have numerous challenges. Several genes are associated with serum uric acid levels with renal urate transports accounting for most of the variance. Renal transport of serum uric acid is complex and it may be that activity of the transporters is related to renal function, rather than serum uric acid level itself. The mechanism of hyperuricaemia and whether intracellular levels are raised may be important with regard to the risk conveyed and our understanding of how this affects reported epidemiological relationships, or how it is affected by genotype, is limited. It is worth noting that a number of genes associated with chronic kidney disease in genome wide association studies are also associated with serum uric acid level.

So epidemiological and experimental data suggest hyperuricaemia may contribute to renal function decline but findings from Mendelian Randomization studies leave this open to debate. The more important question for clinicians is whether uric acid reduction slows decline in renal function and whether this reduction is sufficient to translate into either a reduction in progression to end stage renal disease (ESRD), requiring dialysis or transplantation, or a reduction in the increased cardiovascular risk associated with chronic kidney disease (CKD). Studies have reported an effect of allopurinol, the most widely used uric acid lowering drug, on renal function since the 1970s. It is important to recognize that xanthine oxidase inhibitors have been observed to have clear pleotropic effects such as improving endothelial function. Allopurinol is metabolised to oxypurinol, a purine analogue, which is a competitive inhibitor of xanthine oxidase. It lowers serum uric acid in a dose dependent fashion but also reduces formation of reactive oxygen species. Serum uric acid level can also be lowered by uricosuric drugs, such as probenecid, which do not directly reduce oxidative stress. Thus, an observed effect of allopurinol cannot be assumed to be due to uric acid reduction.

Clinical trials do suggest that allopurinol improves renal function or halts decline in renal function. Although many of the early reports were from uncontrolled or open studies, data from randomised and blinded trials are emerging. However, these studies have typically been small. Meta-analysis of these small studies (8 trials, n=476) showed only a difference in change in serum creatinine and but not change in eGFR [5]. There is as yet no evidence that allopurinol use will reduce rates of

progression to ESRD. This has not been adequately studied, rather than adequately powered trials failing to demonstrate effect. There are also insufficient data to draw conclusion about the effect of probenecid in the setting of CKD, and whilst it may be an ineffective uricosuric in CKD, trials testing allopurinol compared to allopurinol in patients with heart failure showed that allopurinol 600 mg (n=30) and not probenecid (n=26) improved forearm endothelial function [6] despite similar degrees of uric acid reduction. The cardiovascular effects of allopurinol at least may not be mediated via uric acid reduction.

No large trials of cardiovascular outcomes exist in patients with CKD, although data support the need for these to be performed. In a randomized, double-blind, placebo-controlled, parallel-group study in patients with stage 3 CKD and left ventricular hypertrophy (LVH), allopurinol 300 mg daily reduced LVH and improved endothelial function over a 9-month treatment period [7]. LVH is an independent predictor of stroke and other cardiovascular events and LVH regression appears beneficial. This raises the possibility that allopurinol will improve CV outcomes in patients with CKD. This notion is being tested in double blind placebo controlled trial of allopurinol in hemodialysis patients, aiming to regress LVH (clinicaltrials.gov NCT01951404).

The paper by Kuwibara et al is an important step forward. It adds fuel to fire surrounding the importance of uric acid in cardiovascular and renal disease - a fire that has burned for over half a century. We need now to conduct thoughtful prospective interventional studies of uric acid reduction. Large-scale trials are needed to assess the affect of XO inhibition on meaningful clinical outcomes in patients with CKD, such as progression to ESRD or cardiovascular outcomes. XO inhibitors have the most data to support conduct of large scale trials but smaller trials, perhaps with change in eGFR as an endpoint, are also needed to compare the effects of XO inhibition and uricosuric drugs. This will establish whether effects in renal disease are uric acid mediated, or due to other pleotropic effects.

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