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COMMENTARY

Effects of uric-acid-lowering therapy on renal outcomes: the future looks promising

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Hyperuricemia is common in patients with arterial hypertension, metabolic syndrome or kidney disease. Its role, however, as risk factor for both renal and cardiovascular (CV) outcomes and in the context of the well-established interrelationship between CV and chronic kidney disease (CKD) is largely disputed. For decades high-serum uric-acid levels were mainly considered as a result of renal dysfunction and not as true mediator of renal disease development and progression.[1,2] However, epidemiological studies suggest an independent association between asymptomatic hyperuricemia and increased risk of arterial hypertension, CKD, CV events and mortality.[3,4] Indeed, a recent systematic review and meta-analysis of observational cohort studies found that hyperuricemia is an independent predictor for incident CKD.[5] Further, data from experimental models of hyperuricemia have provided robust evidence in this direction. Hyperuricemia causes systemic and glomerular hypertension, elevated renal vascular resistance, proteinuria, renal dysfunction, and progressive renal and vascular disease in rats. The main pathophysiological mechanisms of these deleterious effects caused by uric acid are endothelial dysfunction, activation of the local renin–angiotensin system (RAS), increased oxidative stress, and a pro-inflammatory and proliferative action.[1,2]

The most appropriate method to evaluate the involvement of uric acid in the pathogenesis of CKD progression is to determine whether lowering uric acid slows the rate of renal disease progression. Unfortunately, only a few intervention studies support the beneficial influence of pharmaceutical reduction of serum uric acid on arterial hypertension, total CV risk, as well as on renal disease development and progression. In a recent systematic review and meta-analysis of eight randomized controlled trials (RCTs) with a total of 476 patients, the effects of uric-acid-lowering therapy (the xanthine oxidase inhibitor allopurinol) on kidney disease outcomes were investigated as compared with placebo or no treatment.[6] The authors analyzed change in kidney function (assessed by estimated glomerular filtration rate (eGFR), creatinine clearance, or serum creatinine concentration) from baseline to end of follow-up as the primary outcome. It was concluded that allopurinol treatment may slow the progression of CKD. However, due to small sample size, heterogeneity, and lack of power of the included studies, the authors acknowledged that there is inadequate evidence to recommend widespread use of allopurinol for the management of CKD.[6]

In this issue of *Hypertension Research*, Kohagura *et al.*[7] report on a retrospective observational study of 137 hypertensive Japanese patients with CKD stage 3 to 4 and asymptomatic hyperuricemia (serum uric acid $>7\ mg\ dl^{-1}$) who were newly started on xanthine oxidase inhibitors (allopurinol or febuxostat). There were no changes in other medications either before or after starting treatment with allopurinol or febuxostat. The majority of participants had achieved good blood pressure control with calcium channel blockers and/or RAS inhibitors. About 30% were diabetics. The doses of allopurinol (50–200 mg) and febuxostat (10–20 mg) were variable but rather small. Time interval either before or after treatment was ~1–3 months. eGFR decreased by $1.9\ ml\ min^{-1}$ per $1.73\ m^2$ before initiating xanthine oxidase inhibitors and reversely increased by $1.6\ ml\ min^{-1}$ per $1.73\ m^2$ after treatment without any significant changes in blood pressure. The increase in eGFR after treatment was greater, although not statistically significant, in those who achieved serum uric-acid levels below $6\ mg\ dl^{-1}$ than in those who did not. The increase in eGFR was smaller in those on RAS inhibitors, although again non-significant. Patients on febuxostat showed a more beneficial effect on eGFR than those on allopurinol, although this was not statistically significant. The urate-lowering effect was comparable between those on febuxostat and those on allopurinol. The multiple regression analysis revealed that the increase in eGFR after starting treatment with xanthine oxidase inhibitors was positively correlated with changes in systolic blood pressure and negatively with changes in serum uric acid and use of RAS inhibitors. The authors concluded that treatment with xanthine oxidase inhibitors for a few months may delay the progression of CKD without any significant effect on blood pressure in hypertensive adult patients with moderate to advanced CKD and hyperuricemia.[7]

As acknowledged and discussed by Kohagura *et al.*,[7] it is rather difficult to fully determine the direct association between urate-lowering therapy and the observed changes in renal function due to the limitations of the study design and the short duration of treatment. However, the reversal of eGFR decline after starting treatment with xanthine oxidase inhibitors provides some evidence in this direction. Furthermore, the neutral effect of treatment on blood pressure demonstrated in this

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study[5] might be influenced by the relatively advanced CKD stage and the high rate of comorbidities in the study participants.

Previous interventional studies suggested that treatment with allopurinol may have a renoprotective effect in CKD patients. Goicoechea *et al.*[8] recently reported *post hoc* follow-up data (median follow-up 7 years) of an earlier RCT[9] they conducted in which 113 patients with stable CKD and eGFRs $<60\ ml\ min^{-1}$ per $1.73\ m^2$ had been randomly assigned to standard treatment ($n=56$) or treatment with allopurinol ($100\ mg\ day^{-1}$) ($n=57$) for an average of 24 months. This RCT had shown that allopurinol conferred a benefit in terms of eGFR change and incident CV events. Observation was extended to a median of 84 months, and biochemical and clinical parameters, as well as changes in medical treatment, were recorded. In the *post hoc* analysis, main outcomes were a 'hard' renal end point (chronic kidney failure requiring renal replacement therapy and/or doubling of serum creatinine and/or a $\geqslant 50\%$ reduction in eGFR) and incident CV events. Even within the study limitations (*post hoc* design, single center and relatively small sample size), the findings of Goicoechea *et al.*[8] are impressive in terms of prevention of renal and CV events: 24 of 51 (47%) controls and 9 of 56 (16%) allopurinol-treated patients experienced a renal event (relative risk, 2.93), whereas 23 of 51 (45%) controls and 16 of 56 (29%) patients in the treatment group had a CV event (relative risk, 1.58). Thus, we are provided with some hard evidence to support using allopurinol to slow the progression of CKD and possibly to prevent CV events.

Another open question relates to the specific contribution of uric-acid lowering *per se vs.* the antioxidant effects of xanthine oxidase inhibition. The conversion of xanthine to uric acid generates reactive oxygen species, thus increasing oxidative stress. Therefore, whether xanthine oxidase inhibitors manifest their beneficial effects through uric-acid lowering or through their antioxidant properties is still not conclusive. To resolve this issue, a trial would need to compare different serum uric-acid targets (for example, $\leqslant 6.0$ *vs.* $\geqslant 7.0\ mg\ dl^{-1}$), no matter how attained, rather than compare allopurinol treatment to placebo. However, such a trial would prove problematic in patients with CKD because uricosuric drugs, the only viable alternative to xanthine oxidase inhibitors, generally are considered ineffective in this population of patients.

A stimulating finding of the study by Kohagura *et al.*[7] is that febuxostat, a non-purine, selective, xanthine oxidase inhibitor, produced a trend towards greater improvement in eGFR than allopurinol. Because the urate-lowering effects of febuxostat and allopurinol were comparable, this might indicate the important role of xanthine oxidase inhibition rather than the urate-lowering effect in improving eGFR. It would be interesting to ascertain in the future whether febuxostat, which seems to be a more selective and potent inhibitor of xanthine oxidase and which may have a better safety profile in patients with CKD, has similar or better renoprotective and CV effects as compared to allopurinol.

Our group has shown that febuxostat, administered over one-year period in reduced dosage according to residual renal function, appears to normalize serum uric-acid levels and preserve or even improve renal function in hyperuricemic subjects with moderate-to-severe CKD.[10] Furthermore, this therapy is safe and well-tolerated. Likewise, febuxostat, administered over a 6-month period in 70 patients with CKD stages 3b-5, was safe and efficacious.[11] Further, a greater reduction in serum uric acid with febuxostat was associated with an increase in eGFR and a tendency towards decreased proteinuria.[11] The above-mentioned findings[10,11] have been largely confirmed by a prospective randomized placebo-controlled study of 93 patients with CKD stages 3 and 4 who were treated with febuxostat ($40\ mg\ day^{-1}$) or placebo and followed up for 6 months.[12] At the end of the study the active group showed an improvement in mean eGFR of $3.2\ ml\ min^{-1}$ per $1.73\ m^2$, whereas the control group experienced a loss of $4.4\ ml\ min^{-1}$ per $1.73\ m^2$. The authors concluded that febuxostat controlled serum uric-acid levels and arrested the decline in eGFR for patients with moderate to advanced CKD.

A recent large population-based retrospective cohort study with 16 186 patients with hyperuricemia examined the association of urate-lowering therapy with kidney function decline.[13] The cohort was divided into three groups: patients receiving no urate-lowering therapy (11 192), patients with poor adherence (taking urate-lowering medications for $<80\%$ of therapy duration; 3902), and patients with good adherence (taking medications for $\geqslant 80\%$ of therapy duration; 1092). The study found that time on therapy and medication adherence were not associated with kidney function outcomes. However, hyperuricemia emerged as an independent risk factor for renal function decline. Indeed, in patients who reached target serum uric-acid levels of $<6\ mg\ dl^{-1}$, there was a 37% reduction in CKD progression (defined as $\geqslant 30\%$ decline in eGFR).

In conclusion, the study by Kohagura *et al.*,[7] even with the caveats intrinsic to its design, provides us with additional evidence to the growing body of studies suggesting that hyperuricemia is not a benign condition, uric acid emerges as a potentially modifiable risk factor for CKD, and therefore, urate-lowering therapy can mitigate kidney function decline. Moreover, it moves us a step forward on the long and winding road to find effective treatments for CKD. Given the favorable side-effect profile of urate-lowering therapy and the renal and CV benefits from normalizing serum uric-acid levels, a final consideration should not be if, but rather when, patients with asymptomatic hyperuricemia should be treated. Some guidance for that may be provided by Obermayer *et al.*,[14] demonstrating that a serum uric-acid level above $9\ mg\ dl^{-1}$ carries a threefold risk for new-onset kidney disease. Further studies are needed to determine which subgroups of CKD patients would potentially derive maximum benefit from treatment and the minimum decrease in serum uric-acid concentration required to experience benefits.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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