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Editorial

The grey zone of Hyperuricemia in chronic kidney disease

Uric acid (UA) is a derivative of the purine metabolism. About 70% of UA is eliminated by the kidney, and the remaining 30% by the gastrointestinal tract. Hyperuricemia (HUA) is caused by an imbalance between the production of UA and its excretion [1]. Predominantly (about 90%), HUA results from impaired renal excretion of UA. Reports link a decrease in glomerular filtration rate (GFR) with an increased prevalence of HUA [2]. The increased prevalence of HUA in patients with chronic kidney disease (CKD) is multifactorial. Decreased UA filtration due to reduced GFR, decreased tubular secretion of UA due to underlying tubulointerstitial disease and use of furosemide and cyclosporine (in glomerulonephritis and kidney transplantation), contribute to the increased prevalence of HUA in CKD patients [3].

To treat CKD patients with HUA, the nephrologist should know the answer to the following questions: (a) Is HUA a real cause of CKD or an epiphenomenon of reduced GFR? (b) Do the CKD patients with HUA require treatment and if so what is the drug of first choice? (c) What are the critical UA blood levels above which treatment should be administered? (d) What is the clinical significance of HUA in ESRD patients?

There are contradictory data regarding the relationship between HUA and CKD. Several studies have reported a link between HUA and incident CKD, progressive CKD and end stage renal disease (ESRD) [4–9]. Because of the reduced clearance of UA in CKD even at the earlier stages, HUA could be considered as an epiphenomenon of CKD and not a real cause per se, i.e. it may only reflect an advanced stage of CKD (severity of CKD). However, data from experimental animals suggest a causal role for HUA in CKD development and progression. Notably, in HUA animal models a kidney vascular disease develops which is characterized by arteriolopathy, cortical vasoconstriction and glomerular hypertension. The activation of the rennin-angiotensin system, increased oxidative stress and alterations in the levels of endothelin-1 and cyclooxygenase-2, have been proposed as reasons for the endothelial and vascular abnormalities reported in HUA animal models [10–13]. Nevertheless, because the findings from animal studies seem to be species-specific, they may not reflect accurately the underlying disease process in humans.

Interestingly, UA has been linked to diabetes and diabetic nephropathy, metabolic syndrome, oxidative stress, inflammation, hypertension and endothelial dysfunction, suggesting a causative role for HUA in the development and progression of CKD [3]. Data from animal studies suggest a causative role for UA in CKD pathogenesis; if this is also the case for HUA patients, then all should develop CKD, but in fact this does not happen.

Another important issue that must be addressed is whether HUA treatment ameliorates CKD. There is evidence that lowering of UA levels may have a beneficial effect on CKD progression suggesting a potential therapeutic target for CKD, and current therapeutic strategies to treat HUA in CKD patients are based on the use of the xanthine oxidase inhibitors allopurinol and febuxostat.

In this special thematic, issue Ramirez and Bargman [14] argue that HUA is associated with CKD and that treatment of asymptomatic HUA with xanthine oxidase inhibitors may improve renal function. On the other hand, Stefanidis [15] argue that HUA treatment does not improve CKD.

Data from two meta-analyses were not conclusive: According to the meta-analysis of Bose et al. [16] the use of allopurinol had no effect on the e-GFR in patients with or without CKD at baseline. However, according to a more recent meta-analysis including 992 patients with advanced CKD [17], the use of allopurinol was associated with a decrease in serum creatinine levels, proteinuria and regulation of blood pressure; the latter was postulated to have caused an improvement in the e-GFR of the patients. To note, both meta-analyses included studies that were single-center and characterized by a large heterogeneity of the trials, including differences in the case-mix, gender and ethnicity of the patients, follow-up data and end-points.

It is unclear whether allopurinol has a beneficial effect on renal function and, if so, whether it is mediated by the inhibition of reactive oxygen species or by lowering the UA levels per se. According to a recent single-center study by Jalal et al. [18], the use of allopurinol did not improve the markers of oxidative stress and the endothelial function in 80 patients with stage 3 CKD [18]. On the other hand, a single-center study by Goicoechea et al. [19] in 113 CKD patients showed that treatment with allopurinol slowed-down the progression of CKD and decreased the cardiovascular risk and the duration of hospitalization. However, the results of the Goicoechea et al. study could be explained by the concomitant use of statins, antiplatelet drugs, and drugs of the renin-angiotensin-aldosterone system. At present, there are no other studies to confirm a similar beneficial effect of allopurinol on cardiovascular risk in CKD patients.

Presently, some nephrologists hesitate to treat asymptomatic HUA in CKD patients, whereas others argue that if UA lowering therapy is safe and there is even a slight possibility that it improves renal function, it should be used in CKD patients. Of note, the side effects of allopurinol should be taken into consideration when deciding to treat HUA [15].

Febuxostat [20] and the newly introduced topiroxostat [21] were evaluated in CKD patients and were found to have a favorable effect. Interestingly, treatment with topiroxostat decreased albuminuria [21]. The main limitations in both studies were the small

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sample of the CKD patients, the short follow up and the single center design.

Notably, a favorable effect of the angiotensin II antagonist losartan on renal outcomes mediated by the decrease of UA levels has been reported [22].

The sodium glucose co-transporter 2 inhibitors (SGLT2) may be an alternative treatment approach: According to a recent randomized placebo controlled study, the SGLT2 inhibitor empagliflozin reduced both the progression of renal decline and serum UA levels in patients with diabetes mellitus [23]. The authors postulated that the beneficial effect of empagliflozin on kidney function was mediated by a decrease in UA levels [23]. However, this hypothesis remains to be tested by further studies.

The level at which HUA should be treated is still disputed [15]. This lack of consensus and the different numeric limits for HUA used in various studies precludes the reliability of the conclusions and impairs the understanding of UA lowering therapy on renal function.

The impact of UA in ESRD patients is also controversial. Several reports suggest that HUA predicts mortality in dialysis patients with advanced CKD, whereas others suggest that low levels of UA in dialysis patients is a mortality risk, an association that can be explained by reverse epidemiology [3]. In this regard, HUA may reflect a better nutritional status whereas low UA levels may reflect a form of protein energy wasting syndrome leading to increased mortality [3].

Even today, the real significance of UA remains obscure. It is also unclear whether HUA is causal, compensatory, coincidental or a consequence of CKD. In accordance, the impact of HUA on CKD mortality remains controversial [3]. Until all these questions are unanswered, the use of UA lowering therapy lies in the discretion of the nephrologists.

It is evident that more prospective randomized and well-designed trials with a larger number of CKD patients are needed to elucidate the role of HUA in CKD.

Conflict of Interest

The author declares no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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