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Review

Treatment of asymptomatic hyperuricemia in chronic kidney disease: A new target in an old enemy – A review

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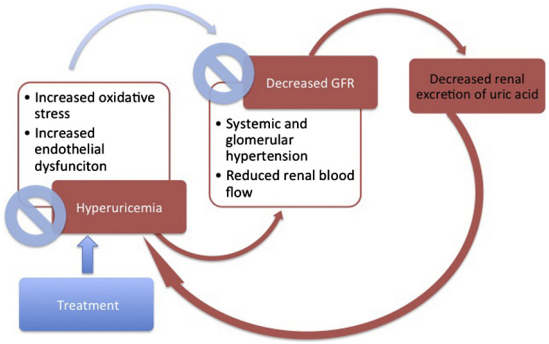
GRAPHICAL ABSTRACT



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ABSTRACT

Asymptomatic hyperuricemia is increasing in prevalence. There is a growing body of literature suggesting that uric acid has deleterious effects on vascular health and renal histological integrity. Several trials, reviewed herein, suggest that lowering the serum uric acid level is associated with a slowing in the rate of renal deterioration in those with chronic kidney disease. Given that there is little available in the general armamentarium to slow the rate of kidney deterioration, strong consideration could be given to the administration of agents or lifestyle changes that decrease uric acid production in hyperuricemic patients with deteriorating kidney function.

Introduction

The prevalence of asymptomatic hyperuricemia has been increasing over the past decades, and can be as high as 20–25% in adult males [1]. Multiple explanations, including changes in diet, an aging population as well as earlier screening [2,3] have been suggested as possible causes of this finding. However, the benefit of treating this common abnormality remains unclear.

Pathophysiology of uric acid metabolism

Uric acid is a weak acid that is a poorly soluble end product of endogenous and dietary purine metabolism. At a physiologic pH of 7.4, 98% of uric acid is in the urate anion form. Urate production is dependent on the balance between purine ingestion, *de novo* synthesis in cells, recycling and the degradation function of xanthine oxidase at the end of the purine pathway. Xanthine oxidase transforms xanthine to uric acid. In most animals, uric acid is further metabolized to highly water-soluble allantoin *via* the enzyme uricase. Humans and higher primates have inactivated the gene

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for uricase, thus the concentration of urate in humans is close to the limit of solubility [4].

Renal clearance of uric acid is greater in the presence of estrogenic compounds [5]. Studies have found that males younger than 65 years of age have a prevalence of hyperuricemia four times higher than that of females of the same age. After menopause, serum urate values increase in women to the same values as their male counterparts.

Urate levels have also been found to be increased in chronic kidney disease. The kidneys excrete two-thirds of uric acid produced daily and impaired excretion of uric acid is present in 90% of individuals with hyperuricemia [6]. The gut eliminates a third of the urate produced daily through colonic bacteria, which almost completely degrades the uric acid with very little left in the stool. This mechanism increases marginally in the presence of kidney failure.

Ninety percent of filtered uric acid is reabsorbed in the S1 segment of the proximal tubule [7]. Multiple urate transporters have been found, such as the urate transporter 1 (URAT1) which is expressed in the apical membrane of the proximal tubule cell and the urate transporter SLC2A9 (also known as glucose transporter 9), expressed on the basolateral side of the proximal tubule and on the apical membrane in the collecting duct [8].

Uric acid is secreted rather than reabsorbed in the S2 segment of the proximal tubule and post-secretory reabsorption occurs at a more distal site of the proximal tubule, with 10% of the filtered uric acid appearing in the urine [9].

Reviewing basic data on hyperuricemia and chronic kidney disease

In 1960, Talbott and Terplan found that nearly all subjects with gout had arteriosclerosis, glomerulosclerosis and interstitial fibrosis in their kidneys. As many of these subjects also had urate crystals in their tubules and interstitium, the disease was termed "gouty nephropathy" [10]. Unfortunately for this hypothesis, urate crystal deposition in the kidneys was also found in patients without renal disease. In addition, the diffuse renal scarring and the coexistent conditions of hypertension and vascular disease in many of the autopsy subjects led some to suggest that the renal injury in gout was secondary to these latter conditions rather than to hyperuricemia [11]. The common association of CKD and hyperuricemia was attributed to the uric acid retention due to impaired renal excretion for many decades until the seminal work of Kang et al. in 2002. In this study, hyperuricemia was induced in experimental rats and was associated with increased renal renin and COX-2 expression, especially in the preglomerular arterial vessels. The study concluded that hyperuricemia itself could mediate progression of renal disease through accelerated hypertension and vascular disease. This was the first experimental study to provide direct evidence that uric acid may be a key factor in renal disease and progression [12]. Thereafter, multiple studies showed that increasing the uric acid level could induce oxidative stress and endothelial dysfunction. Hyperuricemia was associated with the development of systemic and glomerular hypertension with increased vascular resistance and reduced renal blood flow [13,14]. In the tubular cells, uric acid was found to induce epithelial to mesenchymal transition, which had been widely accepted as a key contributor to the development of renal fibrosis in CKD [15].

Additional studies showed that lowering uric acid levels in diabetic mice led to a slowing in renal disease progression [16,17].

In another important preclinical study by Mazzali et al., hyperuricemic rats were found to develop hypertension as well as mild tubulointerstitial injury. Lowering uric acid levels was associated with prevention of the development of hypertension as well as a decrease in the incidence and the progression of renal injury. The mechanism also involved the renin-angiotensin system and down-regulation of nitric oxide expression in the macula densa [15].

Thus in laboratory studies, hyperuricemia has been found to induce renal injury, as well as to accelerate progression of renal disease. In addition, lowering the serum uric acid level was associated with amelioration of this effect.

Reviewing clinical data on hyperuricemia and CKD

One of the greatest advances in recent decades has been the advent of renal angiotensin aldosterone system (RAAS) blockade. With respect to uric acid metabolism, it is interesting to note is that not all RAAS blockade works in the same way. A review comparing the effect of angiotensin II receptor blockers (ARBs) on hyperuricemia showed that losartan was the only ARB that reduces serum uric acid levels [18]. A *post hoc* analysis of the trial on Reduction of Endpoints in Non-Insulin-Dependent Diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) showed that the uric acid-lowering effect of losartan was associated with long-term renal risk reduction [19].

Currently, small trials have been undertaken showing that treatment of hyperuricemia in CKD retarded progression of renal disease (see Table 1).

In a prospective randomized controlled trial by Siu et al. [20] allopurinol safely decreased uric acid levels in patients with CKD 3 and showed a trend to slower progression to end stage renal disease (ESRD). There was no improvement in hypertension in these subjects over the 12 months of the study. A recent review and meta-analysis by Kanji et al. in 2015 summarized the randomized controlled trials that were undertaken to assess the effect of treating hyperuricemia in CKD. There were 19 studies analyzed and although all the trials had small sample sizes, there was a statistically significant improvement in renal function in the patients treated with allopurinol. There was also improvement in blood pressure and proteinuria [21] though it should be emphasized that hypertension may or may not be affected by treatment of hyperuricemia as found in the studies by Goicoechea et al. [22], Kao et al. [23], and through the comprehensive review by Bose et al. in 2014 [24]. We would like to highlight some of these studies.

Goicoechea et al. conducted one of the largest trials in 2010 in Madrid. One hundred and thirteen patients were randomly assigned to receive control treatment or allopurinol. After approximately 24 months, the use of allopurinol was associated with slower renal disease progression, decreased number of hospitalizations and reduced cardiovascular risk [22]. Unfortunately while the study by Kao et al. [23] in 2011 showed that there was improvement in left ventricular mass in patients with CKD, the mechanism was not fully understood as there was no improvement in hypertension in this study and we may infer that improvement in hypertension is unlikely to be the mechanism to which control of hyperuricemia would minimize progression of renal disease.

Also, withdrawal of allopurinol therapy seemed to worsen renal disease progression [25]. A study by Talaat and elSheikh published in 2007 [25] followed 50 patients who had been using allopurinol for asymptomatic hyperuricemia. The patients were followed 12 months after allopurinol withdrawal and there was marked acceleration of renal disease progression.

Unfortunately, there has been no unified theory as to the mechanism of preventing renal disease progression through improvement of serum uric acid levels. A recent study by Jalal et al. showed that treatment of hyperuricemia in humans did not improve markers of oxidative stress or brachial-artery flow mediated dilation, a surrogate marker for endothelial dysfunction [26].