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COMMENT

Effects of Uric Acid-Lowering Therapy on the Kidney (HTR-2023-0096.R2)

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Commentary Revised DRAFT (R1) - COMMENTARY to *KohaguraIkeda K, et al. Febuxostat and renal outcomes: post-hoc analysis of a randomized trial. Hypertension Research 2023, in press (HTR-2022-0674.R2)*

In recent years, hyperuricemia has been shown to be associated with a variety of diseases. The association between chronic kidney disease (CKD) and hyperuricemia is particularly important. Reduced kidney function decreases uric acid excretion, resulting in hyperuricemia. In addition, high serum uric acid levels were reported to be involved in the development and progression of CKD [1]. Kuwabara et al. reported that the cumulative incidence rates of CKD for five years were significantly higher in patients with uncomplicated asymptomatic hyperuricemia compared with normouricemia patients, both in males and females [2]. Uchida et al. also reported in a cohort study of patients with CKD stage 3-4 that the risk of end-stage kidney disease significantly increased with higher uric acid levels, with serum uric acid ≥ 6 mg/dL [3].

Several mechanisms have been proposed by which uric acid may induce kidney injury (Fig. 1). The first is an enhancement of the renin-angiotensin system (RAS). Uric acid promotes renin secretion and stimulates prorenin receptors which enhance intra-kidney RAS [4]. Suppression of endothelial nitric oxide synthase by uric acid also induces vasoconstriction, leading to systemic hypertension and decreased renal perfusion [5]. These, coupled with increased RAS, lead to glomerular hypertrophy and glomerulosclerosis [4, 5]. Uric acid in the urinary tubule also stimulates intracellular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [1]. Stimulation of NADPH oxidase cause oxidative stress, leading to inflammation, mitochondrial dysfunction, and proliferation of vascular smooth muscle cells; they induce glomerular damage and albuminuria. Uric acid itself may also promote leukocyte recruitment [4, 5]. Inflammation through chemokines produced by recruited immune cells and epithelial-to-mesenchymal transition leads to tubular damage [4, 5]. Thus, elevated uric acid levels lead to renal glomerular and tubular damage, and may contribute to the onset and progression of CKD (Fig. 1).

Given this background, uric acid lowering therapy (ULT) could theoretically be renoprotective. In the FEATHER trial in patients with CKD stage 3 compared febuxostat with placebo, the primary outcome, estimated glomerular filtration rate (eGFR) reduction, did not differ between the two groups. However, in the subgroup analysis with no proteinuria or mild renal dysfunction, febuxostat significantly preserved eGFR compared with placebo [6]. The FREED (Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy) is a randomized controlled trial (RCT) that examined the effect of febuxostat on the occurrence of cerebral, cardiovascular, and renal events in patients with one or more risk factors for cardiovascular disease [7]. This trial showed a 25% reduction in the rate of the cardio-renal composite outcome in the febuxostat group compared with the non-febuxostat group [7]. For individual events, prevention of macroalbuminuria was identified as the primary contributor to the reduction in the primary composite outcome [7].

The present study reported by Kohagura et al. is a post-hoc analysis of this FREED study [8]. In this paper, the primary composite renal endpoint was significantly lower in the febuxostat group compared with the non-febuxostat group [8]. In addition, for individual components of the renal endpoint, the developing or worsening macroalbuminuria was significantly lower in the febuxostat group than in the non-

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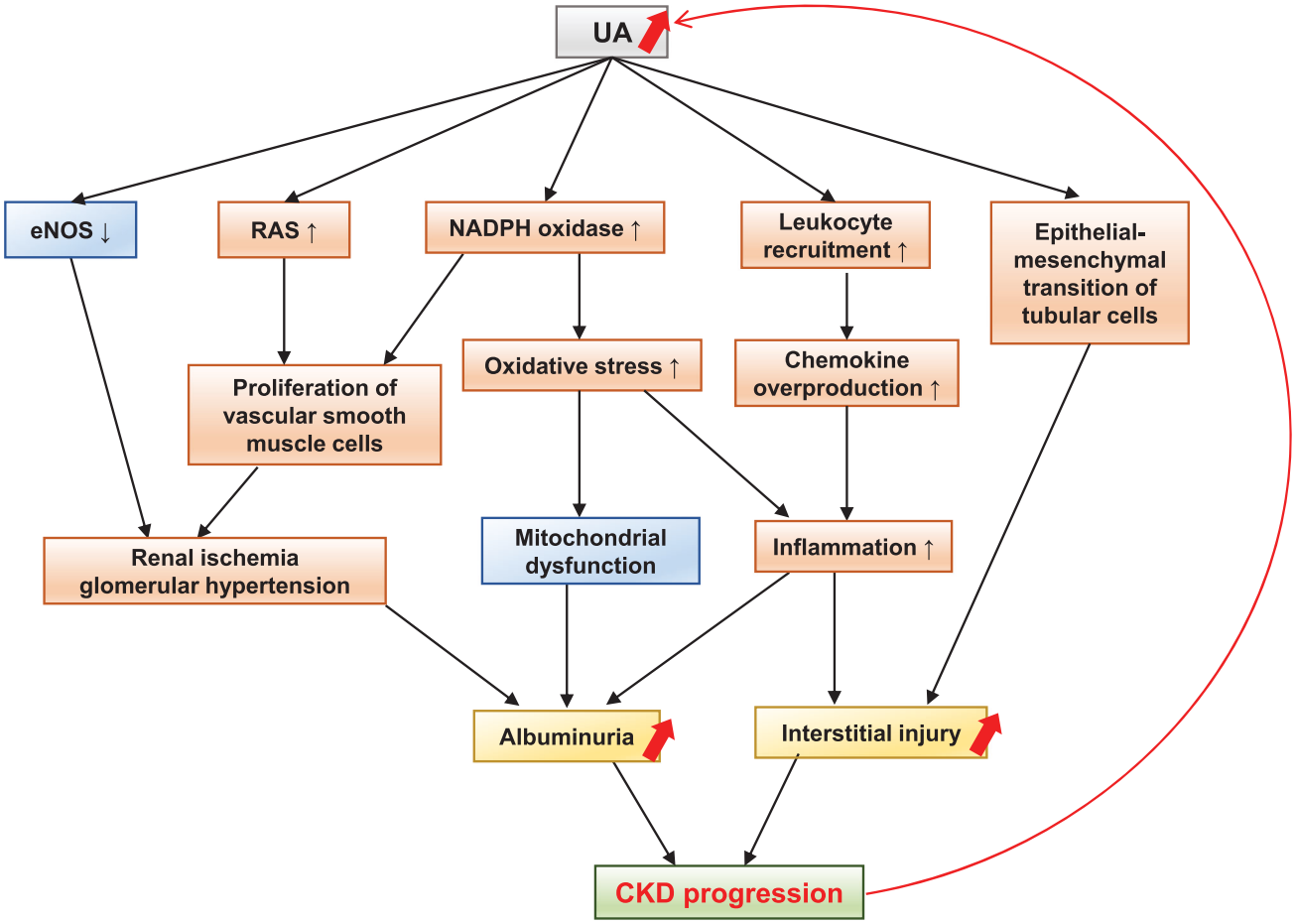

Fig. 1 Effects of uric acid on the kidney. UA uric acid, eNOS endothelial nitric oxide synthase, RAS renin-angiotensin system, NADPH nicotinamide adenine dinucleotide phosphate, CKD chronic kidney disease

febuxostat group [8]. These effects were similar among subgroups classified with baseline eGFR of 60 ml/min/1.73 m^2 and urinary albumin/creatinine ratio (UACR) of 30 mg/g Cr [8].

However, the renoprotective effect of ULT is not consistent; despite some positive data, whether ULT is renoprotective remains controversial. RCTs in CKD patients, such as the CKD-FIX study and the PERL Study, reported that allopurinol had no favorable effect on eGFR reduction and albuminuria [9, 10]. One possible answer to this issue may be the diversity of underlying diseases causing CKD. Watanabe et al. reported that the underlying disease of CKD, along with gender, may influence the prognosis for cardiac and renal outcomes associated with hyperuricemia and the efficacy of treatment with ULT [11]. These findings suggest that there may be a specific patient population for whom ULT provides renal protection. In addition, different uric acid-lowering medications may have different therapeutic effects. In our network meta-analysis of RCTs comparing the renoprotective effects of ULT in CKD patients, topiroxostat and febuxostat were renoprotective in CKD patients, while allopurinol showed no beneficial effect [12]. In other words, the combination of drug and patient background may influence whether ULT is renoprotective. The present study reported by Kohagura et al. may also provide a clue to these issues [8]. To date, however, there is not enough consensus on the renoprotective effects of ULT. Further studies are needed to determine in what populations ULT is renoprotective and which agents are more beneficial.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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