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COMMENT

Hyperuricemia: the third key player for nephrosclerosis with ischemia

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Nephrosclerosis is defined as kidney dysfunction and/or proteinuria associated with hypertension and aging without any other cause and is the second most common cause of end-stage renal disease [1]. However, the causes, pathophysiology, and pathological and clinical features of nephrosclerosis are heterogeneous, and the classification method is poorly established. The prevalence of nephrosclerosis with or without hypertension is reported to increase with aging [2]. Glomeruli in the aged kidney are divided into four basic types: normal, hypertrophic, with features of focal segmental glomerulosclerosis, and ischemic [3]. Additionally, implantation kidney biopsies of living kidney transplant donors without urinary abnormalities or kidney dysfunction revealed increased fibrous intimal thickening in the interlobular arteries with aging and hypertension [4].

A cross-sectional analysis previously found that hyperuricemia is, in addition to hypertension and aging, also associated with renal atherosclerosis in chronic kidney disease (CKD) patients [5]. In this issue of *Hypertension Research* [6], Kochi et al. clearly showed a stronger association between hypertension and proteinuria in participants with hyperuricemia compared with those without hyperuricemia. Additionally, they did not find any gender differences in these results [6]. Thus, it is assumed that hyperuricemia is, in addition to hypertension and aging, an important risk factor and modifier in the pathogenesis of nephrosclerosis. There have also been many reports of an association between CKD and uric acid levels. Japanese real-world data shows that 17.6% of CKD G3a patients and 30.3% of G3b patients have hyperuricemia [7]. Additionally, 2.3% of Japanese 9–10-year-old children were found to have hyperuricemia during pediatric health checkups. Thus, it is necessary to address hyperuricemia from a young age, including hereditary hyperuricemia [8].

Owing to its heterogeneity, nephrosclerosis can be characterized by either ischemia or glomerular hyperfiltration (Fig. 1). Nephrosclerosis with ischemia is pathologically characterized by atherosclerotic changes, mainly narrowed afferent arterioles with severe hyalinosis or medial thickening and collapsed glomeruli, and clinically by CKD without proteinuria [1, 3]. In nephrosclerosis with ischemia, glomerular hypoperfusion occurs because of arteriosclerosis of afferent or interlobular arteries. Conversely, nephrosclerosis with hyperfiltration is pathologically characterized by dilated afferent arterioles with mild hyalinosis and enlarged glomeruli and clinically by CKD with proteinuria [1, 3]. Nephrosclerosis with reduced nephron mass can begin in early life by so-called "developmental origins of health and disease" (DOHaD) [9]. The impact of DOHaD on nephron number at birth may predispose individuals to hypertension and CKD with proteinuria [10]. The presence of hyperfiltration is not only a factor in the development of proteinuria but also in the progression of kidney dysfunction. These two conditions frequently overlap, and many cases cannot be clearly distinguished.

However, in patients with nephrosclerosis, distinguishing between ischemia and hyperfiltration is important for determining the appropriate treatment strategy. It is assumed that patients with nephrosclerosis with ischemia are more likely to experience excessive initial drops in glomerular filtration rates (GFRs) when receiving renin-angiotensin system inhibitors such as angiotensin receptor blockers. This may be because when renin-angiotensin system inhibitors inhibit efferent arteriolar vasoconstriction, which reduces glomerular filtration pressure, the GFR falls

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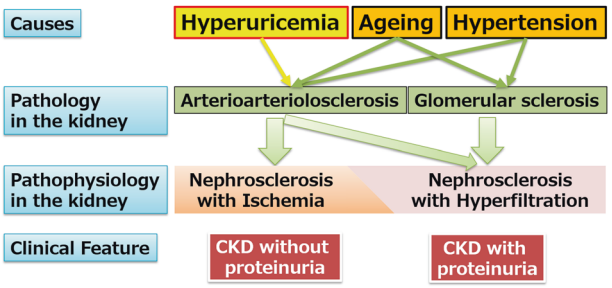

Fig. 1 The impact of hyperuricemia on the pathology and pathophysiology of nephrosclerosis. CKD chronic kidney disease

rapidly in patients with nephrosclerosis with ischemia because the decrease in glomerular filtration pressure has already occurred. Conversely, nephrosclerosis with hyperfiltration may be a good indication for angiotensin receptor blockers and sodium-glucose-transporter-2 inhibitors, which are effective in reducing glomerular hyperfiltration [11]. Another report evaluated the association between high-normal albuminuria and the glomerular sclerosis rate in living kidney transplant donors without kidney dysfunction [12]. In this report, living donors with hypertension and high-normal albuminuria already had glomerular sclerosis and reduced nephron mass, resulting in glomerular hyperfiltration. Further glomerular hyperfiltration after kidney donation did not occur in these donors. Thus, evaluating the pathophysiology underlying nephrosclerosis is an important clinical issue, including determining indications for drugs that inhibit glomerular hyperfiltration.

Albuminuria may be useful in determining the presence of hyperfiltration in patients with nephrosclerosis; however, albuminuria evaluation in non-diabetic hypertensive patients is not covered by insurance in Japan. Mild proteinuria is one indicator as a surrogate for albuminuria, and, furthermore, Kochi et al. have also shown a lower frequency of proteinuria in hyperuricemic patients without hypertension [6]. Aged normotensive patients with CKD and hyperuricemia have an increased risk of nephrosclerosis with ischemia; thus, attention should be paid to excessive drops in GFRs when using drugs that inhibit glomerular hyperfiltration.

Furthermore, a systematic review and meta-analysis conducted in 2018 revealed that uric acid-lowering therapy may delay the progression of CKD [13]. The post-hoc analysis of multicenter, randomized, double-blind, placebo-controlled, trial data for 395 patients with stage 3 CKD and asymptomatic hyperuricemia revealed that the mean estimated GFR slopes were significantly higher in the treatment group than in the placebo group in CKD patients without proteinuria [14]. Conversely, no beneficial association between initiating uric acid-lowering therapy and the incidence of CKD was observed in a cohort study [15]. These results, while still controversial, suggest that the preventive effect of uric acid-lowering therapy on the progression of atherosclerosis may be more useful in nephrosclerosis with ischemia.

In conclusion, hyperuricemia is an important contributing factor to both nephrosclerosis with ischemia and hyperfiltration. A treatment strategy for CKD should be recommended, assuming histopathological and pathophysiological assessment of intrarenal conditions.

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Compliance with ethical standards

Conflict of interest TS received personal fees for lectures from AstraZeneca and Mitsubishi Tanabe Pharma.

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