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COMMENTARY

Renal tubulointerstitial damage and salt-sensitive hypertension in chronic kidney disease: is the tubulointerstitium relevant beyond the glomerulus?

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Excessive salt intake is a classic and common risk factor that scritically impacts hypertension and cardiovascular disease (CVD) outcome. Recent work has made us aware of the significance of excessive salt intake at the level of global health care.[1] Salt dependency in hypertension is generally characterized by nocturnal hypertension. Nocturnal hypertension, which is also known as non-dipper type hypertension in ambulatory blood pressure monitoring, is associated with worse CVD outcomes among patients with chronic kidney disease (CKD).[2] Thus, it is crucially important to understand the underlying mechanisms of salt-sensitive hypertension so that medical treatment may be improved. Salt-associated blood pressure increases are driven primarily by alteration in the sodium balance, which is determined by sodium intake and excretion. The kidney has a pivotal role in sodium excretion, which is determined by the passive processes of sodium filtration in the glomeruli, pressure natriuresis in peritubular capillaries and active tubular reabsorption (Figure 1).

Previous studies suggest that tubulointerstitial inflammation may have a fundamental role in salt-sensitive hypertension progression.[3,4] First, many animal models of salt-sensitive hypertension are characterized by increases in infiltrating immune cells in tubulointerstitial kidney lesions.[4] Second, there is a dose–response relationship between the degree of infiltrating immune cells and blood pressure levels in those animal models.[3] Third, intervention to stop immune cell infiltration into the interstitium ameliorates hypertension development.[4]

As shown in various types of genetic hypertension, tubulointerstitial inflammation is associated with salt-sensitive hypertension in some animal models. These animal models show chronic kidney damage such as oxonic acid-induced hyperuricemia and protein-loading proteinuria.[3] Therefore, it is suggested that tubulointerstitial lesions may relate to the development of salt-sensitive hypertension, even in patients with pre-existing CKD. Definitive evidence of an association between tubulointerstitial inflammation and salt-sensitive hypertension in patients with CKD is not yet available. However, the cross-sectional associations between some forms of tubulointerstitial nephritis and hypertension have been documented.[5] Moreover, in this issue of *Hypertension Research*, Haruhara *et al.*[6] report that tubulointerstitial lesions, but not glomerular and vascular lesions, are associated with indices of salt-sensitive hypertension among patients with CKD who underwent renal biopsy.

This study is unique in terms of its systemic analysis of renal specimens, which focuses on components responsible for salt-sensitive hypertension among patients with CKD of various etiologies. Because tubulointerstitial lesions could lead to diminished glomerular filtration, associations between tubulointerstitial lesions and indices of salt-sensitive hypertension may merely depend on renal function. However, the association remained significant after adjustment for estimated glomerular filtration and global glomerulosclerosis. In addition, the researchers have shown that patients with more severe tubulointerstitial lesions exhibit higher indices of salt-sensitive hypertension even when those patients had preserved renal function. These findings suggest that tubulointerstitial lesions may be specifically associated with salt-sensitive hypertension among patients with CKD independent of renal function (Figure 1).

Previous studies indicate mechanisms involved in the association between interstitial inflammation and the development of salt-sensitive hypertension. Infiltrating immune cells express angiotensin II, which could be associated with salt-sensitive hypertension by three mechanisms: (1) decreased sodium filtration by vasoconstriction-mediated reduction of the glomerular filtration rate and augmentation of tubuloglomerular feedback; (2) stimulation of sodium reabsorption in proximal tubules; and (3) impaired pressure natriuresis.[3] Angiotensin II-induced inflammatory cytokines and reactive oxygen species (ROS) lead to nephron loss and peritubular capillary damage, both of which lead to impaired natriuresis.[3] Rarefaction of peritubular capillaries is associated with an impaired pressure natriuresis relationship.[5]

Interventions for interstitial inflammation using thymectomy or immunosuppressants successfully prevent hypertension development in association with reduced immune cell infiltration in an animal study.[3] However, in clinical practice, there is limited information regarding the efficacy of interventions targeting interstitial inflammation. It has been reported that immunosuppressants given to hypertensive patients with psoriasis or rheumatoid arthritis are significantly associated with blood pressure reduction.[7] Oxidative stress has a crucial role in pressure natriuresis impairment in the medulla and causes

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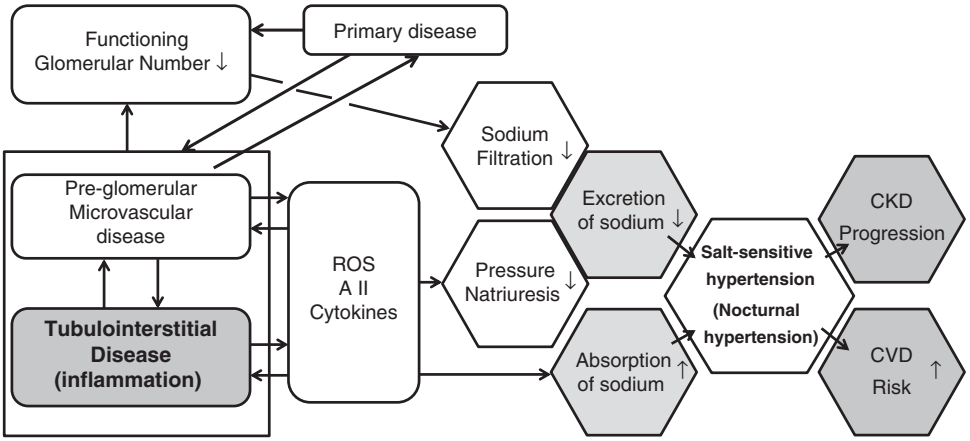

Figure 1 Hypothetical scheme of a link between tubulointerstitial disease and salt-sensitive hypertension among patients with chronic kidney disease. A II, angiotensin II; CKD, chronic kidney disease; CVD, cardiovascular disease; ROS, reactive oxygen species.

salt-sensitive hypertension.[8] Although antioxidant therapy shows promise in preventing salt-sensitive hypertension development, arterial remodeling and reducing interstitial inflammation in an animal study, it has failed to improve hypertension in humans.[4,9]

What factors contribute to the discrepancy in efficacy between animal and human models? Intervention timing may be important. We recently reported that tempol, a superoxide dismutase mimetic, failed to reduce blood pressure and actually exacerbated glomerulosclerosis and tubulointerstitial damages in advanced-stage, stroke-prone spontaneously hypertensive rats that were salt sensitive.[10] Because antioxidant therapy is associated with increase in proteinuria and larger glomeruli, particularly in juxtamedullary lesions, exacerbating glomerular hypertension was considered to be involved in the mechanism. These observations suggest that antioxidant therapy inadequately relieves vasoconstriction induced by oxidative stress and that systemic blood pressure is directly transmitted to glomeruli in cases of sustained hypertension and renal failure. Thus, we may need to consider the presence of irreversible renal damage and interactions with microvascular disease to determine clinically appropriate interventions for interstitial inflammation.

Subtle preglomerular vascular disease could facilitate the direct transmission of systemic blood pressure to glomeruli and post-glomerular microvasculature such as peritubular capillaries.[5] Pre-glomerular vascular disease could lead to ischemia and increased ROS production in tubulointerstitial areas because severe arteriolopathy with lumen narrowing lead to ischemia and eventually to salt-sensitive hypertension. In contrast, because interstitial inflammation may lead to renal arteriolopathy,[11] interaction between preglomerular vascular disease and tubulointerstitial inflammation may lead to a progressive cycle involving salt-sensitive hypertension.[5] The finding that glomerular hemodynamic alteration could modulate the progression of various types of CKD (for example, diabetic kidney disease and glomerulonephritis) independent of primary diseases[12,13] suggests an interaction between hemodynamic processes and immunological and metabolic processes. Thus, such interactions may critically impact CKD progression, as in the development of salt-sensitive hypertension (Figure 1).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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