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Editorial

Is VEGF a new therapeutic target for hypertension in chronic kidney disease?

The prevalence of end-stage renal disease (ESRD) is more than 1,000 per million population in Korea, and is increasing by about 5% every year. The most common cause of ESRD is diabetes, followed by hypertension and glomerulonephritis [1]. Hypertension, in particular, has been associated with 34% of all ESRDs in African-Americans [2]. Various mechanisms have been suggested to be involved in the development of hypertension, salt sensitivity being one of the important derangements related to hypertension. Total body sodium for homeostasis of the extracellular fluid volume is mainly regulated by the kidney [3]. Because extracellular fluid volume is controlled dynamically, excessive interstitial sodium is readily moved into the intravascular fluid for sodium excretion via the kidney.

Along with the influence of hypertension, vascular remodeling is closely related to the development and progression of chronic kidney disease (CKD). In CKD, large arteries remodel and become increasingly stiff. The greater pulse pressure reaching the glomerulus as a result of the increased arterial stiffness could induce renal damage, suggesting that the stiffening and remodeling of large arteries could affect the progression of CKD [4]. The maladaptive remodeling of the carotid artery and increased pulse pressure are independently associated with a faster decline of renal function and a faster progression to ESRD. In CKD, along with the changes in the aorta and large arteries, the microcirculation, consisting of small arteries and arterioles, capillaries, and venules [5], is changed significantly. In long-standing CKD, blood vessels are characterized by calcifications in both the intimal and medial layers, leading to vascular stiffening and a loss of compliance. As a result, both the pulsatile component of the blood pressure, as indicated by an augmented pulse pressure, and peripheral resistance, expressed as mean arterial pressure, are increased [6]. In the microcirculation, these changes may affect vasodilatory capacity, leading to a loss of capillary architecture and rarefaction [7]. Indeed, in patients with advanced CKD, it has been reported that the functional and structural number of capillaries is decreased [8].

In addition to CKD, aging is also associated with endothelial dysfunction, resulting in a decreased vasodilatory response of the microcirculation to a variety of stimuli [9]. Accelerated vascular aging, associated with Klotho deficiency, is also a characteristic of patients with CKD [10]. Even in childhood, ESRD is associated with structural abnormalities in arterial wall properties, comparable with adult levels [11].

Vascular endothelial growth factor (VEGF) was discovered as a factor capable of inducing endothelial cell permeability [12] and angiogenesis [13]. So far, seven members of the VEGF family have been identified: A, B, C, D, E, and placental growth factor 1 and 2. VEGF mediates its effects through VEGF receptors (VEGFR-1, VEGFR-2, and VEGFR-3), with VEGFR-2 as its primary cognate receptor expressed on endothelial cells. As VEGF-targeted therapies were introduced into clinical use for treatment of malignant disease, it was noted that hypertension and proteinuria were major toxicities of VEGF-targeted therapies. Hypertension occurs in up to 80% of patients receiving VEGF, and most of the patients taking these drugs reveal an elevation of blood pressure. Previous studies evaluating bevacizumab showed a dose-dependent development of hypertension [14]. Tyrosine kinase inhibitors such as sorafenib and sunitinib are also associated with hypertension and a pre-eclampsia-like syndrome [15].

At least two possible pathways for hypertension by VEGF-targeted therapy have been suggested. First, nitric oxide has a direct effect on the regulation of pressure natriuresis and tubuloglomerular feedback. VEGF inhibition may cause a disruption of normal endothelial nitric oxide synthase function, and cause sodium retention. Thus, extracellular fluid volume increases by changing the set point for sodium excretion [16].

In another pathway, a novel mechanism for VEGF-mediated control of extracellular fluid volume has been suggested. In response to high salt loading, the production of VEGF-C by macrophages increases, binding to VEGFR-3, and thus stimulating lymphatic vessel growth. This lymphatic capillary network is suggested to form a compartment that buffers the extracellular fluid volume in response to the increased sodium intake, blunting the rise in blood pressure. Inhibition of VEGF-C or macrophage depletion causes a decrease in lymphatic vessel density, and increased blood pressure in response to a high-salt diet [17].

VEGF-C is tightly associated with dyslipidemia, a potent risk factor as well as a therapeutic target in cardiovascular disease. In addition, it has been demonstrated that serum levels and expression levels of VEGF-C, but not VEGF-A, in atheromatous plaques were significantly increased in high-fat diet-fed apoE-deficient mice with advanced atherosclerosis, suggesting that VEGF-C was more closely related than VEGF-A to atherosclerosis with dyslipidemia [18]. Therefore, VEGF-C might have more impact on atherosclerosis and future cardiovascular events than VEGF-A in

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humans. It is also reported that a high-salt diet leads to activation of TonEBP in mononuclear phagocyte cells in the skin [17,19]. It was suggested that TonEBP increases VEGF-C production and increases lymphangiogenesis [20,21]. Therefore, VEGF-C can be a regulated by a sodium-excessive state and activation of high TonEBP in salt diet-induced hypertension.

In this issue of *Kidney Research and Clinical Practice*, Kim et al. have evaluated the serum and urinary concentration of VEGF-C in patients in various stages of CKD, including patients on maintenance hemodialysis [22]. They hypothesized that the change in serum VEGF-C would be associated with increasing blood pressure. Compared with healthy controls, serum VEGF-C levels were significantly decreased in patients with CKD, while the urinary excretion of VEGF-C was augmented in CKD patients. In patients on hemodialysis, VEGF-C was also decreased, but blood pressure did not directly reflect the changes in VEGF-C concentration. Kim et al. assumed that serum levels of VEGF-C might increase in hypertensive CKD patients because VEGF-C is involved in salt-sensitive hypertension, and hypertension in CKD patients may be linked to volume expansion. However, they demonstrated that serum levels of VEGF-C in CKD Stage 3–4 and Stage 5 hemodialysis patients were significantly lower than in controls. Therefore, they concluded that extrarenal fluid homeostasis occurring via the VEGF-C system was less likely to be involved in CKD patients with hypertension.

Although their findings are contradictory to the hypothesis, which is based on the previous reports, the work done by Kim et al. suggests a very interesting point, and may provide a new concept of hypertension in CKD patients that has therapeutic potential. First, if the serum level of VEGF-C is shown to be consistently low in subsequent reports, the notion that the premature vascular aging develops in CKD patients [22] is plausible, and the association between premature vascular aging and function of VEGF should be further investigated. The other issue is the therapeutic potential of VEGF in blood pressure control as well as the prevention of CKD progression. Augmentation of the effect of VEGF *in vivo* may modulate salt metabolism, leading to blood pressure control. If this hypothesis is consistently proven, we might have another maneuver to control blood pressure. As a start, we should have data that the individual antihypertensive agents or classes affect, or at least correlate with, the *in vivo* activity of various VEGFs. Renin–angiotensin system blockers and calcium channel blockers are the main agents for evaluation here.

More importantly, if the modulation of VEGF is positively associated with vascular remodeling in the ischemic tissue (especially in the glomerulus or interstitium), this may provide a new approach for preventing the progression of CKD. Augmentation of the biologic effect of VEGFs in the damaged tissue may show a new potential for tissue recovery or regeneration. Further investigation should be exploited in the near future.

Conflict of Interest

Author does not have any conflict of interest.

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