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The effects of vitamin D on the renin-angiotensin system

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The current literature indicates that maintaining adequate vitamin D levels may be an important consideration in the treatment of hypertension, especially in individuals with vitamin D insufficiency and deficiency.
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Editorial

In humans, 80-90% of required vitamin D is made in the skin upon sun exposure and the remaining 10-20% is ingested in fish, eggs and fortified dairy products. In the liver, vitamins D_2(ergocalciferol) and D_3(cholecalciferol) are converted into 25-hydroxyvitamin D_2 (25[OH]D_2) and 25-hydroxyvitamin D_3 (25(OH]D_3), respectively (1). In the kidney, 25(OH)D is converted to its biologically active form 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) by 1α-hydroxylase. The serum level of 25(OH)D is used to determine vitamin D status and normally ranges between 30-100 ng/mL (75–250 nmol/L). Vitamin D insufficiency and deficiency are defined as serum 25(OH)D levels of 20-30 mg/dL (50-75 nmol/L) and <20 ng/mL (50 nmol/L), respectively (2). The critical role of 1,25(OH)$_2$D in calcium and phosphorus homeostasis is well established (1,2). Accumulating evidence indicates that vitamin D also plays an important role in regulating the blood pressure.

A recent randomized, double-blind, placebo controlled study conducted by Nasri *et al.* demonstrated that oral supplementation of vitamin D led to a decrease in the blood pressure in individuals with diabetes mellitus (3). Sixty individuals were randomized to receive either vitamin D3 50,000 IU per week (n=30) or placebo (n=30) for 12 weeks. Five individuals (8.3%) had vitamin D deficiency and 27 others (45%) had vitamin D insufficiency. Vitamin D supplementation increased serum 25(OH)D levels from 84±52 nmol/L to 164±57 nmol/L (P= 0.001). Vitamin D supplementation led to a decrease in both systolic (121±13 to 110±9 mm Hg; P= 0.001) and diastolic blood pressure (81±8 to 76±7 mm Hg, P= 0.046). No statistically significant change in blood pressure was observed in the placebo group.

The pivotal role of the renin-angiotensin system in the regulation of the blood pressure is well established (Figure 1). Renin is secreted by the juxtaglomerular cells of the kidney in response

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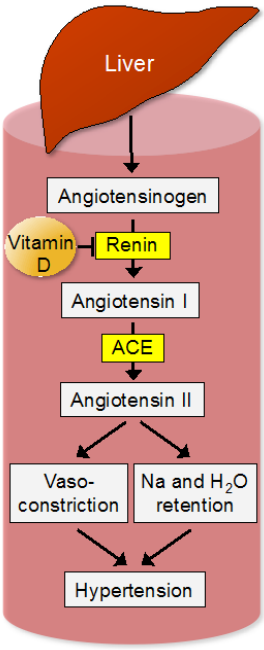

Figure 1. The effects of vitamin D on the renin-angiotensin system. 1,25-dihydroxyvitamin D suppresses renin gene expression, thereby inhibiting the renin-angiotensin system. ACE, angiotensin-converting enzyme; H_2O, water; Na, sodium.

to decreased renal blood flow. It converts plasma angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme. Angiotensin II leads to increased water and sodium reabsorption in the kidney and vasoconstriction. Mounting evidence indicates that vitamin D regulates the renin-angiotensin system. An inverse relationship between the blood pressure and serum 25(OH) D levels has been documented in a number of the epidemiological studies (4,5). In a cross-sectional study, Forman *et al.* explored the relation between 25(OH)D and the renin-angiotensin system in 184 individuals with normal blood pressure (6). Compared with vitamin D-sufficient individuals, those with vitamin D deficiency and insufficiency had greater plasma angiotensin II levels and a trend for higher plasma renin activity. In addition, the activity of the renin-angiotensin system in the kidney, as measured by the renal plasma flow in response to angiotensin II infusion, was greater in vitamin D-deficient than in vitamin D-sufficient individuals. These results suggested that decreased plasma 25(OH)D levels were associated with increased activity of the renin angiotensin system. Resnick *et al.* investigated the relation between the plasma renin activity and calcium-regulating hormones including calcitonin, $1,25(OH)_2D_3$ and parathyroid hormone in 51 individuals with essential hypertension (7). An inverse relation of the serum $1,25(OH)_2D_3$ level to the plasma renin activity ($r= -0.65$, $P< 0.001$) was observed. This study corroborated a link between calcium homeostasis, vitamin D metabolism and the renin-angiotensin system.

To unravel the molecular mechanisms involved in vitamin D-mediated regulation of the renin-angiotensin system, mice with loss-of-function mutations involving vitamin D receptor gene (VDR-null mice) were examined. The VDR-null mice develop hypocalcemia at 3 weeks of age, hyperparathyroidism, rickets and osteomalacia (8). Li *et al.* demonstrated that renin gene expression in the kidney and angiotensin II levels in the plasma were substantially increased in the VDR-null mice leading to hypertension and cardiac hypertrophy (9). In wild-type mice, pharmacological inhibition of $1,25(OH)_2D_3$ synthesis led to an increase in renin gene expression, whereas $1,25(OH)_2D_3$ treatment suppressed renin expression. Similarly, $1,25(OH)_2D_3$ markedly suppressed renin gene expression in cultured cells by a VDR-mediated mechanism. These investigators also demonstrated that the effect of vitamin D on renin gene expression was independent of calcium metabolism. The authors concluded that $1,25(OH)_2D_3$ is a negative regulator of the renin-angiotensin system. Subsequently, it was shown that $1,25(OH)_2D_3$ suppressed renin gene expression by binding to the transcription factor cAMP response element-binding protein (CREB), thereby suppressing the activity of the cAMP response element in the renin gene promoter (10).

To determine whether the inhibitory effects of $1,25(OH)_2D$ on the renin-angiotensin system is dependent on calcium or phosphorous, Zhou *el al.* examined the effects of dietary interventions

in 1α-hydroxylase knockout mice. Phenotypically resembling VDR-null mice, 1α-hydroxylase knockout mice demonstrate undetectable serum $1,25(OH)_2D$ levels and develop hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, growth retardation and skeletal abnormalities characteristic of rickets (11). Zhou *et al.* demonstrated that 1α-hydroxylase knockout mice developed hypertension and cardiac hypertrophy associated with the activation of the renin-angiotensin system in the kidney and heart (12). Despite the normalization of the serum calcium and phosphorus levels, a calcium- and phosphorus-fortified diet neither normalized the blood pressure nor suppressed the activity of the renin-angiotensin system in the 1α-hydroxylase knockout mice. However, $1,25(OH)_2D$ treatment led to the normalization of the activity of the renin-angiotensin system and blood pressure. In summary, the current literature indicates that maintaining adequate vitamin D levels may be an important consideration in the treatment of hypertension, especially in individuals with vitamin D insufficiency and deficiency.

Authors' contributions

All authors wrote the paper equally.

Conflict of interests

Authors declare no conflicts of interest.

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