The Effects of Vitamin D on the Renin-Angiotensin System

Sahar Ajabshir
Department of Dietetics and Nutrition, Florida International University, sajab001@fiu.edu

Arif Asif
Albany Medical College

Ali Nayer
University of Miami

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The effects of vitamin D on the renin-angiotensin system

Sahar Ajabshir¹, Arif Asif², Ali Nayer³*

¹Department of Dietetics and Nutrition, Florida International University, Miami, USA
²Division of Nephrology and Hypertension, Albany Medical College, Albany, USA
³Division of Nephrology and Hypertension, University of Miami, Miami, USA

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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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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 D₂(ergocalciferol) and D₃(cholecalciferol) are converted into 25-hydroxyvitamin D₂(25[OH]D₂) and 25-hydroxyvitamin D₃(25(OH)D₃), respectively (1). In the kidney, 25(OH)D is converted to its biologically active form 1,25-dihydroxyvitamin D (1,25(OH)₂D₃) 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)₂D 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

*Corresponding author: Ali Nayer, Division of Nephrology and Hypertension, University of Miami, Clinical Research Building, suite 825, 1120 NW 14th St., Miami, FL 33136, USA. Tel: 305.243.3583, fax: 305.243.3506, E-mail: anayer@med.miami.edu
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 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)₂D₃ and parathyroid hormone in 51 individuals with essential hypertension (7). An inverse relation of the serum 1,25(OH)₂D₃ 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. 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 (8). Zhou et 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.

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All authors wrote the paper equally.

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