



# VITAMIN D AND THE HEART

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## ABSTRACT

*Animal studies have revealed that the biologically active metabolite of vitamin D—1,25 dihydroxy-vitamin D (1,25[OH]<sub>2</sub>D)—can modulate various processes involved in the pathogenesis of cardiovascular disease (CVD) through its role in calcium homeostasis and through the participation of its receptor—a steroid hormone nuclear receptor—in the regulation of gene transcription. Its effects appear to support normal myocardial contractility, vasomotor activity, and nitric oxide production, while reducing the risk of cardiac hypertrophy and atherosclerosis. Thus, vitamin D may be beneficial in patients with heart failure, arrhythmias, ischemic heart disease, or hypertension. Additionally, its effects appear to be enhanced by common cardiac drugs such as beta blockers, thiazide diuretics, aspirin, etc., which suggests it may permit a reduction in drug dosages and, consequently, in the risk of adverse effects. Evidence of its potential benefits is very preliminary, and its therapeutic value in specific heart-related conditions is unknown. Current recommendations for achieving maximum cardiac benefit from vitamin D are to monitor vitamin D status—especially in elderly patients, who may present with symptoms that could be related to CVD or to vitamin D insufficiency—and to encourage optimal intake. Food sources are limited; therefore a nutritional supplement should be prescribed. Patients should also be encouraged to increase their sun exposure, because vitamin D<sub>3</sub>—the form produced in the skin on exposure to ultraviolet light—has demonstrated particular efficacy in conditions that contribute specifically to heart disease. Naturally, this recommendation should be accompanied by instructions to follow current guidelines for increasing sun exposure without increasing the risk of skin cancer.*

## INTRODUCTION

The role and function of Vitamin D are detailed elsewhere in this Journal.<sup>1</sup> Briefly, it is a steroid hormone whose primary function is to maintain calcium homeostasis by enhancing calcium absorption from the intestinal tract, promoting osteoblast differentiation, and inhibiting osteoclast activity. By supporting calcium homeostasis, vitamin D inhibits substances that are activated by low serum calcium levels—including parathyroid hormone (PTH)—most of which promote bone resorp-

tion as a means of restoring normal calcium levels. Its biologically active metabolite, 1,25 dihydroxy-vitamin D (1,25[OH]<sub>2</sub>D), binds with the vitamin D receptor (VDR), a steroid hormone nuclear receptor that participates in the regulation of gene transcription. Because of the virtually ubiquitous nature of the VDR, vitamin D can affect a myriad of functions in body tissues, including intracellular signaling pathways that block cell proliferation, promote cell differentiation, modulate immune activity, and influence blood pressure (BP).

Its potential cardiovascular benefits are associated with its ability to inhibit PTH,<sup>2</sup> which is involved in the pathogenesis of several conditions that increase the risk for heart disease (HD); and with its effects on the vasculature, including improved calcium uptake,<sup>3</sup> inhibition of platelet aggregation, enhanced nitric oxide synthase production, inhibition of abnormal thrombotic activity and, possibly, the regulation of vasomotor reactivity to neural input.<sup>4-6</sup>

Unfortunately, Vitamin D deficiency is common and commonly overlooked, particularly among hospital inpatients, including those with several risk factors for HD such as hypertension and diabetes mellitus.<sup>7</sup> The coexistence of risk factors for HD and vitamin D insufficiency certainly does not establish a cause-and-effect relationship, but given the preliminary evidence of a role for vitamin D in normal cardiovascular activity, the possibility of such a relationship is worth exploring.

## VITAMIN D: POTENTIAL MECHANISMS OF ACTION IN THE HEART

### Vitamin D and the Risk of Heart Failure

Heart failure (HF) is characterized by disordered heart structure and function that interferes with normal filling or ejection.<sup>8</sup> *Diastolic HF* is, in part, associated with impaired ventricular relaxation, as in cardiac fibrosis or hypertrophy. *Systolic HF* occurs when impaired myocardial contractility results in reduced stroke volume and cardiac output.<sup>8,9</sup> Preliminary evidence of vitamin D's influence on the size, character, and contractility of

myocardial tissue suggests that it may have a beneficial effect in either type of HF.

#### Effect on risk of hypertrophy

There is some evidence that vitamin D<sub>3</sub> (cholecalciferol), the form produced in the skin on exposure to sunlight, reduces the risk of cardiac hypertrophy. Studies in rats suggest that the VD<sub>3</sub>R acts synchronously with retinoic acid receptors on cardiomyocytes and vascular smooth muscle cells to reduce cell size, and that 1,25(OH)<sub>2</sub>D<sub>3</sub> inhibits the maturation of cardiomyocytes.<sup>10,11</sup> Support for its role in preventing hypertrophy has also been provided by animal studies in which vitamin D<sub>3</sub> deficiency led to cardiac hypertrophy characterized by a significant increase in collagen-filled extracellular space and an increase in myofibrillar area.<sup>12</sup>

Cell size is also regulated indirectly through protein kinase C (PKC), which can be activated by norepinephrine (NE), angiotensin II (Ang II), or PTH to contribute to cell enlargement. Studies in mouse myocardial cells have shown that increased PKC activity can result in left ventricular hypertrophy.<sup>13</sup> Vitamin D may limit this hypertrophic response by inhibiting PTH activity, thereby preventing it from activating PKC.

#### Effect on cardiac contractility

Animal studies have provided evidence of a role for vitamin D in supporting normal heart muscle contractility. Studies of vitamin D<sub>3</sub> deficiency in the neonatal rat heart have suggested an inverse correlation between serum 1,25(OH)<sub>2</sub>D<sub>3</sub> levels and the myosin isozyme concentration in ventricular myocytes,<sup>11</sup> and studies in adult animals suggest that the 1,25(OH)<sub>2</sub>D<sub>3</sub> level only needs to be restored to normal to achieve maximum contractility.<sup>14</sup> There may be a second mechanism for vitamin D's support of cardiac contractility: calcium homeostasis. By inhibiting PTH-induced mobilization of calcium from bone, vitamin D reduces the risk of calcification of heart valves and coronary vessel walls.<sup>15</sup>

#### Vitamin D and the Risk of Arrhythmias

Its ability to promote calcium homeostasis may also enable vitamin D to prevent arrhythmias. Cardiac action potentials are generated by the movement of calcium through calcium channels in nodal tissue. Intracellular calcium modulates the activity of sodium channels--which transmit these action potentials throughout the myocardial tissue—to keep the heart rate under control. If calcium homeostasis is disrupted, an arrhythmia or

mechanical dysfunction (i.e., reduced cell contractility) may develop, which, if uncorrected, could result in cell injury or death. Studies in rats have shown that vitamin D also stimulates the uptake of calcium by ventricular myocardial cells to help maintain calcium homeostasis in the heart.<sup>16</sup>

#### Vitamin D vs Ischemic Heart Disease

Clinical studies suggest that PTH contributes to changes in the structure and function of blood vessel walls that increase the risk of atherosclerosis,<sup>2</sup> particularly by promoting the formation of intra-arterial plaque. By suppressing PTH activity, vitamin D<sub>3</sub> may reduce the risk of calcification and stenosis in the coronary vessels.<sup>17</sup>

Vitamin D may also help maintain normal vascular activity by supporting the production of nitric oxide synthase. This effect has also been suggested by the observation that VDR knockout mice exhibit a significant increase in platelet aggregation, and suppression of gene products necessary for antithrombin activity.<sup>4</sup>

#### Vitamin D vs Hypertension

Four key contributors to hypertension are Angiotensin II, Norepinephrine, natriuretic peptide (ANP), and calcium.

#### The angiotensin II/NE connection

Ang II, a product of the renin-angiotensin system, induces arteriolar constriction and raises both diastolic and systolic BP. In rats, when myocardial cells stretch in response to increased filling, Ang II production increases to help restore normal vascular tone. An increase in Ang II levels stimulates the release of NE, thereby enhancing its own vasoconstrictive effect.<sup>13</sup> The addition of NE activity may increase the risk of damage to the myocardial cell, given its ability to enhance myocardial contractility. If serum NE (and Ang II) levels are not regulated, the result could be an arrhythmia or possibly a myocardial infarction.<sup>8</sup> Vitamin D<sub>3</sub> may have a preventive effect, given that 1,25(OH)<sub>2</sub>D<sub>3</sub> has been shown to control renin activity and, thus, may be able to modulate the release of Ang II. The consequent reduction in serum Ang II (and, consequently NE) levels might prevent BP from rising excessively and reduce the risk of an arrhythmia.

#### The ANP connection

ANP is released by atrial myocardial cells and acts on receptors in the kidney to oppose Ang II activity and reduce BP. In a recent animal study, 1,25(OH)<sub>2</sub>D<sub>3</sub>

blocked ANP production in the presence of an extremely potent vasoconstrictor, endothelin,<sup>10</sup> and, thus, helped prevent hypotension. This effect contrasts with its hypotensive effect through control of renin activity. The fact that it may be able to inhibit Ang II through its effect on renin, while also “disinhibiting” Ang II (possibly by opposing ANP) suggests that the effect of vitamin D on BP may be modulatory, rather than strictly inhibitory. Further study is warranted to determine which is most responsible for the effect observed in the ANP study: 1,25(OH)<sub>2</sub>D<sub>3</sub> or endothelin.

#### The calcium connection

Up to one third of individuals with hyperparathyroidism develop hypertension as well as hypercalcemia, and the hypertension disappears when the calcium levels are corrected. This suggests that vitamin D may be able to prevent or reverse hypertension through its ability to suppress PTH activity.

#### VITAMIN D AND THE TREATMENT OF HEART DISEASE

Vitamin D may lend itself to at least 2 therapeutic approaches to HD: pharmacotherapy and diet. A third approach—increased physical activity—is not likely to change the patient’s need for vitamin D significantly from the recommended intake for healthy individuals.

##### Pharmacotherapeutic Approach to HD: A Role for Vitamin D?

Drugs commonly used in various types of HD appear to enhance the effects of vitamin D on bone by 1) promoting osteoblast differentiation (e.g., calcium channel blockers verapamil and diltiazem)<sup>18</sup>; 2) inhibiting substances that block osteoblast activity, such as Ang II (e.g., ACE inhibitors) and NE (e.g., beta blockers)<sup>18,19</sup>; 3) preventing the loss of calcium in the urine (thiazide diuretics)<sup>20</sup>; 4) inhibiting the production of prostaglandins by platelet cyclo-oxygenases (COX, especially COX-2) to prevent bone loss (e.g., aspirin).<sup>21</sup>

##### Dietary Approach to HD: A Role for Vitamin D?

Patients who require a sodium-restricted diet may find it difficult to maintain an adequate vitamin D intake because of reduced access to vitamin D-rich foods—which are already few in number.<sup>1</sup> This may become critical in patients with severe HF or with fluid accumulation in the presence of diuretic therapy, who may need to limit their sodium intake to 1 g daily (compared with a normal intake of 6-10 g/d). Such stringent salt restriction cannot be accomplished without eliminating at least two important sources of vitamin D: milk and

fortified cereals. For these patients, supplementation is crucial.

#### READY TO PRESCRIBE VITAMIN D FOR HEART DISEASE?

Let’s hope not.

Evidence for vitamin D’s role in maintaining normal cardiovascular activity is, at best, still preliminary. The only role that appears to be relevant is that of maintaining calcium homeostasis. At this point, the best you can do is advise patients with HD to follow current guidelines for an adequate intake: 400 IU daily is usually recommended, although  $\geq 1000$  IU/d of vitamin D<sub>3</sub> may be necessary to achieve the highest serum levels possible.<sup>1</sup>

Because of the potential benefits of vitamin D<sub>3</sub> in HD, one of the best things you could add to a patient’s treatment plan is a prescription for sunshine. Increased sun exposure is especially important for elderly patients with HD, who often present with poor balance, fatigue, muscle weakness, and other symptoms that could be due to HD or vitamin D insufficiency. These individuals often avoid the sun because of physical limitations that keep them indoors or a fear of developing skin cancer. We need to teach them current guidelines for safe sun exposure—5 to 10 minutes of sunscreen-free exposure between the hours of 10 AM and 3 PM 2 to 3 times a week in a temperate climate—to achieve maximal vitamin D<sub>3</sub> production with minimal skin cancer risk. We should also evaluate their vitamin D status regularly, perhaps during routine exams.

#### CONCLUSION

Vitamin D appears to play an important role in maintaining normal cardiovascular activity through its ability to modulate BP, prevent calcification of the heart and blood vessels, support normal cardiovascular contractility, and reduce the risk of thrombosis. Vitamin D<sub>3</sub> in particular appears to maintain normal cardiac contractility and prevent cardiac hypertrophy, and thus may be helpful in preventing or managing HD. These effects should be explored further to determine whether vitamin D has a therapeutic role in HD, but until that role is firmly established, we can still encourage patients with HD to consume adequate amounts of vitamin D-rich foods, to take a supplement, and to increase their sun exposure by following current guidelines for doing so without increasing their risk of skin cancer. This three-pronged approach is especially helpful for elderly patients with HD, who often have symptoms that could be caused by

HD or by vitamin D insufficiency. By monitoring their vitamin D status, the physician may be able to rule out one or another cause, to make an accurate diagnosis, to select the most effective treatment available, and, thus, to give the patient the best chance for an optimal recovery.

\*Tables: 4 Tables that accompany this article have been posted on our website ([www.jlgh.org](http://www.jlgh.org)) with this article.

Table 1. Nutritive Values of Selected Foods: Vitamin D and Calcium.  
Table 2. Clinical Signs Reported for Specific Serum 25(OH)D Levels.  
Table 3. Risk Factors for Reduced Bone Mass.  
Table 4. Common Conditions That Can Induce Secondary Osteoporosis.

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