ABSTRACT
Aimal studies have revealed that the biologically active metabo-
lite of vitamin D—1,25 dihydroxy-vitamin D (1,25(OH)2D)—
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 athero-
sclerosis. 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 encour-
gaged to increase their sun exposure, because vitamin D—
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 guide-
lines for increasing sun exposure without increasing the risk of
skin cancer.

INTRODUCTION
The role and function of Vitamin D are detailed else-
where in this Journal. Briefly, it is a steroid hormone
whose primary function is to maintain calcium homeo-
- stasis by enhancing calcium absorption from the intestinal
tract, promoting osteoblast differentiation, and inhibiting
osteoclast activity. By supporting calcium homeo-
- stasis, 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)2D), binds with the vitamin D receptor
(VDR), a steroid hormone nuclear receptor that partici-
pates 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 prolif-
eration, promote cell differentiation, modulate immune
activity, and influence blood pressure (BP).

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

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.7 The
coexistence of risk factors for HD and vitamin D insuf-
ficiency 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 pos-
sibility 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 fill-
ning or ejection.8 Diastolic HF is, in part, associated with
impaired ventricular relaxation, as in cardiac fibrosis or
hypertrophy. Systolic HF occurs when impaired myo-
cardial contractility results in reduced stroke volume
and cardiac output.8,9 Preliminary evidence of vitamin
D’s influence on the size, character, and contractility of
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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 D₃ (cholecalciferol), the form produced in the skin on exposure to sunlight, reduces the risk of cardiac hypertrophy. Studies in rats suggest that the VD₃R acts synchronously with retinoic acid receptors on cardiomyocytes and vascular smooth muscle cells to reduce cell size, and that 1,25(OH)₂D₃ inhibits the maturation of cardiomyocytes. Support for its role in preventing hypertrophy has also been provided by animal studies in which vitamin D₃ deficiency led to cardiac hypertrophy characterized by a significant increase in collagen-filled extracellular space and an increase in myofibrillar area.

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. Vitamin D may limit this hypertropic 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 D₃ deficiency in the neonatal rat heart have suggested an inverse correlation between serum 1,25(OH)₂D₃ levels and the myosin isozyme concentration in ventricular myocytes, and studies in adult animals suggest that the 1,25(OH)₂D₃ level only needs to be restored to normal to achieve maximum contractility. 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.

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.

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, particularly by promoting the formation of intra-arterial plaque. By suppressing PTH activity, vitamin D₃ may reduce the risk of calcification and stenosis in the coronary vessels.

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.

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. The addition of NE activity may increase the risk of damage to the myocardial cell, given its ability to increase myocardial contractility. If serum NE (and Ang II) levels are not regulated, the result could be an arrhythmia or possibly a myocardial infarction. Vitamin D₃ may have a preventive effect, given that 1,25(OH)₂D₃ 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)₂D₃
vitamin D and the heart

blocked ANP production in the presence of an extremely potent vasoconstrictor, endothelin, 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)2D3 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)2; 2) inhibiting substances that block osteoblast activity, such as Ang II (e.g., ACE inhibitors) and NE (e.g., beta blockers)3; 3) preventing the loss of calcium in the urine (thiazide diuretics)4; 4) inhibiting the production of prostaglandins by platelet cyclo-oxygenases (COX, especially COX-2) to prevent bone loss (e.g., aspirin).21

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. 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 ≥1000 IU/d of vitamin D3 may be necessary to achieve the highest serum levels possible.1

Because of the potential benefits of vitamin D3 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 D3 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 D3 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) 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.

REFERENCES