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## The “Sunshine Deficit” and Cardiovascular Disease

Diane E. Wallis, MD; Sue Penckofer, RN, PhD; Glen W. Sizemore, MD

In past decades, the primary focus on vitamin D was the recognition and treatment of deficiency as it related to metabolic bone disease (rickets, osteomalacia, and secondary hyperparathyroidism). In the last 10 years, however, with the discovery of vitamin D receptors in multiple tissue types has come the recognition that the role of vitamin D extends beyond the musculoskeletal system.<sup>1</sup> The presence of abundant vitamin D receptors in myocardial tissue and vasculature and the observation that hypertension may be ameliorated with vitamin D suggest a greater role for vitamin D in the cardiovascular system.<sup>2</sup> Presently, large numbers of people are found to have hypovitaminosis D (a term chosen for this review to indicate any concentration below normal under substrate-saturated conditions) resulting in part from more indoor activities and the purposeful avoidance of sunshine. This review first describes why vitamin D, parathyroid hormone (PTH), and the skeleton are important to the heart and vasculature, then outlines why the epidemic of hypovitaminosis D deserves further scrutiny by the cardiovascular community, and finally suggests why treatment options for reducing hypovitaminosis D may favorably affect the morbidity and mortality of common cardiovascular disorders.

### Vitamin D and PTH: Basic Biochemistry and Physiology

Vitamin D is both a nutrient and a hormone. It is an essential precursor of calcitriol, 1,25-hydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D], which is necessary for bone development, growth, and mineralization and the maintenance of skeletal integrity. A cascade of steps is needed to cause progression of lesser active nutritionally ingested or synthesized vitamin D to more biologically active forms as depicted in Figure 1.<sup>1</sup> The cascade starts with the photolysis of 7 dehydrocholesterol in the epidermis by solar ultraviolet B (UVB) radiation to previtamin D<sub>3</sub>, which then undergoes thermal isomerization to vitamin D<sub>3</sub>. Vitamin D<sub>3</sub> undergoes primary hydroxylation in the liver to 25-hydroxyvitamin D [25(OH)D] and then undergoes a second hydroxylation, primarily in the kidney, to the highly biologically active 1,25(OH)<sub>2</sub>D.

Calcitriol increases bone resorption, gastrointestinal calcium absorption, renal tubular calcium reabsorption, and renal excretion of calcium. In concert with PTH, it is required for the efficient use of dietary calcium and the maintenance of

calcium-phosphorus homeostasis, and it helps to maintain normal ionized calcium and phosphorus concentrations. PTH secretion is inversely related to ionized calcium concentration; thus, if the ionized calcium concentration drops, PTH secretion increases and restores normal calcium concentration. This is accomplished as the hormone stimulates renal production of calcitriol, increases osteoclastic bone resorption, increases gastrointestinal calcium absorption, and increases renal tubular resorption of calcium. PTH secretion is affected not only by vitamin D but also by disorders of magnesium and phosphorus metabolism, which may occur in conditions of malnutrition, malabsorption, aluminum toxicity, renal disease, and malignancy.<sup>1-3</sup>

### Cardiac Effects of Vitamin D and PTH

The role that vitamin D and PTH play in cardiac function appears greater than previously thought. Table 1 provides a summary of reported vitamin D and PTH effects on the cardiovascular system from in vitro studies. Calcitriol-dependent calcium-binding protein is present on cardiac muscle and endothelial and vascular smooth muscle cells.<sup>4-10</sup> Calcitriol appears to be involved in calcium-dependent cellular processes, including the synthesis of calcium-binding protein, the activation of adenylate cyclase, the rapid activation of voltage-dependent calcium channels, and the influx, reuptake, and release of calcium from the sarcoplasmic reticulum.<sup>4</sup> Calcitriol normalizes the impaired myocardial contractility observed in experimental vitamin D deficiency.<sup>5</sup> The recent discovery that human vascular smooth muscle cells possess the enzyme 25(OH)D-1 $\alpha$ -hydroxylase, which also is upregulated by PTH and estrogenic compounds, underscores the significance of vitamin D in vascular function because it is responsible for the “on-site” conversion of vitamin D precursors into calcitriol.<sup>4,7</sup> Calcitriol regulates myocyte proliferation and hypertrophy, inhibiting ventricular myocyte proliferation in primary cultures of neonatal rat cardiomyocytes.<sup>8</sup> Calcitriol induces prostacyclin in vascular smooth muscle cells, which prevents thrombus formation, cell adhesion, and smooth muscle cell proliferation.<sup>9</sup> Calcitriol is known to suppress the synthesis and secretion of atrial natriuretic peptide.<sup>10</sup> Calcitriol increases matrix  $\gamma$ -carboxyglutamic acid protein (matrix Gla protein), a protein that protects against arterial calcification.<sup>11</sup>

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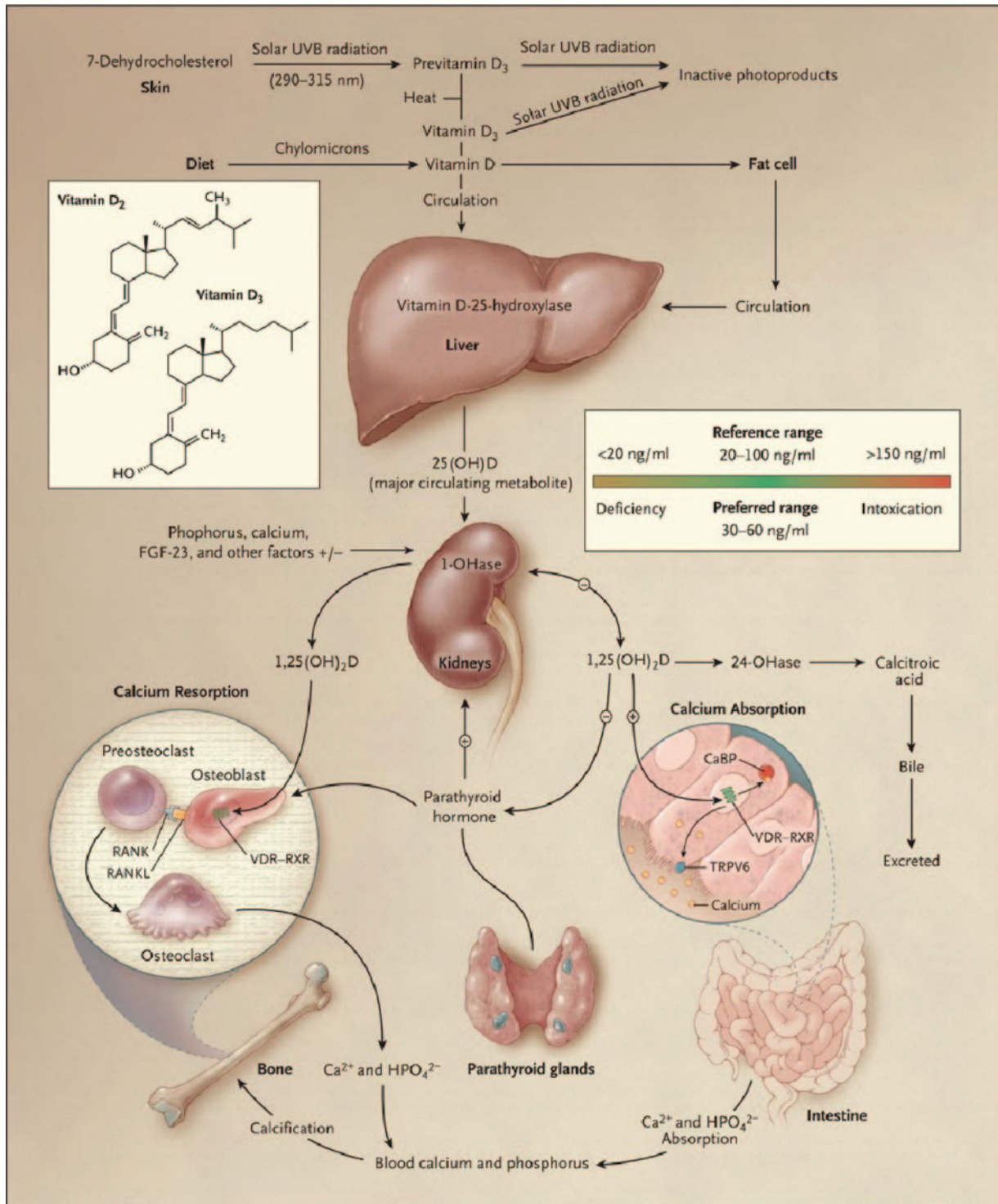
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**Figure 1.** Synthesis and metabolism of vitamin D in the regulation of calcium, phosphorus, and bone metabolism. During exposure to solar UVB radiation, 7-dehydrocholesterol in the skin is converted to previtamin D<sub>3</sub>, which is immediately converted to vitamin D<sub>3</sub> in a heat-dependent process. Excessive exposure to sunlight degrades previtamin D<sub>3</sub> and vitamin D<sub>3</sub> into inactive photoproducts. Vitamin D<sub>2</sub> and vitamin D<sub>3</sub> from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D (hereafter, “D” represents D<sub>2</sub> or D<sub>3</sub>) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D-binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25(OH)D. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. (Although most laboratories report the normal range to be 20 to 100 ng/mL [50 to 250 nmol/L], the preferred range is 30 to 60 ng/mL [75 to 150 nmol/L].) This form of vitamin D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1 $\alpha$ -hydroxylase (1-OHase) to the biologically active form 1,25(OH)<sub>2</sub>D. Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (–) the renal production of 1,25(OH)<sub>2</sub>D. 1,25(OH)<sub>2</sub>D decreases its own synthesis through negative feedback and decreases the synthesis and secretion of PTH by the parathyroid glands. 1,25(OH)<sub>2</sub>D increases the expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)<sub>2</sub>D to the water-soluble,

**Table 1. Vitamin D and PTH Effects on the Cardiovascular System<sup>4-21</sup>**

Vitamin D	
High-affinity receptors in endothelial cells and VSMCs	
Increase in cellular Ca <sup>2+</sup> entry	
Increase in cytosolic free Ca <sup>2+</sup>	
Induction of the expression of contractile proteins	
Acceleration of prostacyclin formation	
Reduced mitogenic response to thrombin, PDGF	
Increased expression of bone proteins	
Control of local production of PTHrP	
Enhanced expression of Ca-ATPase	
Inhibition of myocyte proliferation and hypertrophy	
25(OH)D-1- $\alpha$ hydroxylase in VSMCs	
"On site" activation of 25(OH)D to 1,25(OH) <sub>2</sub> D	
Acceleration of cell migration, cell adhesion, and smooth muscle cell proliferation	
ANP synthesis and secretion suppression	
PTH	
Alteration of automaticity	
Via pacemaker current of the SA node and Purkinje fibers	
Alteration of cellular growth	
Reexpression of fetal-type proteins in cardiomyocytes	
VSMC proliferation via protein kinase C	
Hypertrophic myocyte growth	
Augmentation of MCP-1, collagen, and $\beta$ -1 integrin synthesis	
Permissive role in fibroblast activation via TGF- $\beta$ 1 with intermyocardiocyte fibrosis and collagen deposition in laboratory animals	
Associated with interstitial fibrosis with collagen fiber deposition uremic patients	
Alteration of cellular metabolism	
Decrease in oxidation of fatty acids by heart mitochondria	
Decrease in mitochondrial O <sub>2</sub> consumption	
Inophore for calcium entry into cells	
Increase in myocardial Ca <sup>2+</sup> and Ca <sup>2+</sup> content	
Influence on extracellular Ca <sup>2+</sup> via cAMP-dependent mechanism	
Potent vasodilator	
Coronary, hepatic, and renal arteries via L-type Ca <sup>2+</sup> receptors inhibition	
Stimulation of VSMC adenylate cyclase activity	

VSMC indicates vascular smooth muscle cell; PDGF, platelet-derived growth factor; PTHrP, PTH-related protein; ANP, atrial natriuretic peptide; SA, sinoatrial node; MCP-1, monocyte chemoattractant protein-1; and TGF, transforming growth factor.

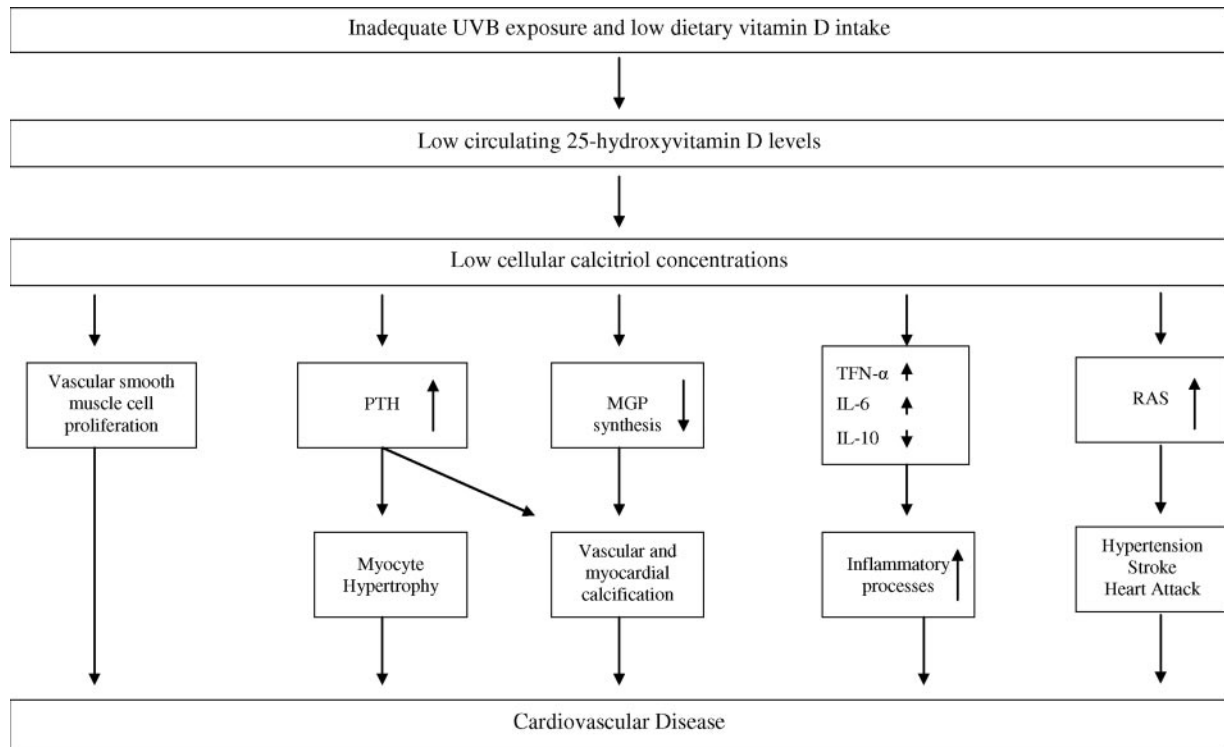
The heart also has receptors for both PTH and PTH-related peptide with actions that influence cardiovascular cell physiology in a way that is different from their influence on classic skeletal target cells.<sup>12</sup> PTH upregulates the same hydroxylase enzyme needed for conversion of D3 to 25(OH)D.<sup>7</sup> PTH-related peptide is produced by vascular smooth muscle cells that regulate the rate of arterial smooth muscle proliferation and has produced positive chronotropic and inotropic effects in isolated cardiomyocytes not found for PTH.<sup>12,13</sup> PTH and PTH-related peptide directly alter the automaticity of the heart by increasing the pacemaker current of the sinoatrial node and Purkinje fibers.<sup>14</sup> PTH causes reexpression of fetal-type proteins in cardiomyocytes, and excess doses cause hypertrophic myocyte growth.<sup>8,12</sup> Excess concentration of PTH impairs the production, transfer, and use of myocardial energy stores by heart mitochondria with increases in myocardial calcium and calcium content, as well as a reduction in phosphate, adenosine triphosphate, and creatine phosphate.<sup>15-17</sup> Animal studies argue for a permissive role of PTH for fibroblast activation and the generation of cardiac fibrosis, possibly via action on transforming growth factor  $\beta$ 1, a promoter of cardiac fibrosis, by the induction of endothelial-mesenchymal transition in adult coronary endothelial cells.<sup>18-20</sup> In vitro studies in adult cardiomyocytes demonstrate that PTH causes calcium influx and modulates contractility by attenuating  $\beta$ -adrenoceptor stimulation indirectly via protein kinase C-dependent pathways.<sup>21</sup>

## The Skeleton and the Heart

### The Osteoprotegerin/Receptor Activator of Nuclear Factor- $\kappa$ B Ligand/Receptor Activator of Nuclear Factor- $\kappa$ B System

Studies in cell biology suggest a link among the vascular system, coagulation, inflammatory proteins, and the skeleton. Bone proteins such as osteopontin, osteocalcin, bone morphogenetic protein-2, matrix  $\gamma$ -carboxyglutamic acid protein, receptor activator of nuclear factor- $\kappa$ B (RANK) ligand (RANKL), and osteoprotegerin are expressed by vascular cells and are found in atherosclerotic plaques and calcified valves.<sup>22</sup> Osteoprotegerin also is produced in many tissues, including the normal artery wall, coronary smooth muscle cells, and endothelial cells; modulates inflammatory responses; and exerts antiapoptotic effects.<sup>23,24</sup> Osteoprotegerin, RANKL, and the ratio of RANKL to osteoprotegerin have been implicated in atherosclerotic plaque destabilization and rupture, vascular calcification, and heart failure, even after adjustment for other known predictors of mortality and cardiovascular events.<sup>24-27</sup> In a recent review of osteoprotegerin/RANK/RANKL in vascular pathophysiology, Kiechl and colleagues<sup>26</sup> highlighted numerous studies consistently

**Figure 1 (Continued).** biologically inactive calcitroic acid, which is excreted in the bile. 1,25(OH)<sub>2</sub>D enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor-retinoic acid x-receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel (transient receptor potential cation channel, subfamily V, member 6 [TRPV6]) and calbindin 9K, a calcium-binding protein (CaBP). 1,25(OH)<sub>2</sub>D is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of RANKL. RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood. Adequate Ca<sup>2+</sup> and phosphorus (HPO<sub>4</sub><sup>2-</sup>) levels promote the mineralization of the skeleton. Reproduced with permission from Holick M. Vitamin D deficiency. *N Engl J Med.* 2007;357:266-281. Copyright © 2007 Massachusetts Medical Society. All rights reserved.



**Figure 2.** Hypothetical associations between vitamin D insufficiency and cardiovascular disease. MGP indicates matrix Gla protein; RAS, renin-angiotensin system. Adapted with permission from Zittermann et al.<sup>11</sup> Copyright © 2005, Cambridge University Press.

reporting higher serum osteoprotegerin concentrations in patients with diabetes mellitus, with the highest concentrations of osteoprotegerin correlating with poor glycemic control, renal disease, microvascular disease, and severity of coronary atherosclerosis.

### Proposed Pathophysiology of Hypovitaminosis D

Zittermann and colleagues<sup>11</sup> have proposed several mechanisms by which hypovitaminosis D may contribute to cardiovascular disease (Figure 2). Matrix Gla protein, synthesized by chondrocytes and vascular smooth muscle cells and increased by calcitriol, has been shown to be a strong inhibitor of vascular calcification. Inflammatory processes play an important role in the development of adverse vascular events. Interleukin-6 and tumor necrosis factor- $\alpha$ , physiological stimulants of C-reactive protein, are suppressed by calcitriol, whereas the antiinflammatory interleukin-10 is upregulated. The renin-angiotensin system, which regulates blood pressure, electrolytes, and volume status, is tempered by calcitriol via the reduction in plasma renin activity and angiotensin II concentration.<sup>11</sup>

In addition to these mechanisms, PTH and vitamin D are significantly involved in the osteoprotegerin/RANKL/RANK pathway, which may provide the missing link between the skeleton and cardiovascular diseases.<sup>28</sup> As a membrane-bound cytokine member of the tumor necrosis factor receptor superfamily, RANKL also induces the expression of myriad inflammatory cytokines that also have been implicated in the pathogenesis of acute vascular insults.<sup>29</sup> Jabbar and colleagues<sup>30</sup> have demonstrated an inverse relationship between 25(OH)D and osteoprotegerin and RANKL concentrations. In

another study, the correction of hypovitaminosis D significantly decreased serum RANKL production.<sup>31</sup> As PTH concentrations increase in response to vitamin D deficiency, immature cells in the osteoblast lineage upregulate RANKL binding to its osteoclastic receptor, RANK.<sup>30</sup> Increased levels of osteoprotegerin have been proposed as a compensatory response to any increased osteoclastic activity. Calcitriol reduces the expression of osteoprotegerin.<sup>32</sup>

## Vitamin D Deficiency and Cardiovascular Disease

### Cardiovascular Risk Factors and Morbidity and Mortality Studies

Vitamin D deficiency links to cardiovascular disease can be found in a number of studies demonstrating a 30% to 50% higher cardiovascular morbidity and mortality associated with reduced sun exposure caused by changes in season or latitude.<sup>33–36</sup> Conversely, the lowest rates of heart disease are found in the sun-drenched Mediterranean coast and in southern versus northern European countries.<sup>36–39</sup> Cardiac death has been reported to be the highest during winter months.<sup>40</sup>

A number of studies have attempted to correlate levels of 25(OH)D with cardiovascular events. Scragg and colleagues<sup>39</sup> reported that myocardial infarction patients had lower mean 25(OH)D concentrations than control subjects, with a relative risk of myocardial infarction of 0.43 (95% confidence interval [CI], 0.27 to 0.69) for those above compared with those below the median. The case-control differences were greatest in the winter and spring. In the National Health and Nutrition Examination Survey III survey

of 15 000 subjects, the prevalence of hypertension, diabetes mellitus, and hypertriglyceridemia was significantly higher in those with the lowest concentrations of 25(OH)D ( $P<0.001$ ).<sup>41</sup> Wang and colleagues<sup>42</sup> studied 1739 Framingham offspring and reported that the 28% of subjects found to have a 25(OH)D concentration of  $<15$  ng/mL experienced a 62% greater incidence of cardiovascular events compared with those with higher concentrations (95% CI, 1.11 to 2.36) in multivariable-adjusted analysis. In studies involving cerebrovascular disease, stroke patients were found to have 25(OH)D concentrations substantially lower than those in control subjects.<sup>43</sup>

Epidemiological studies of primary hyperparathyroidism have demonstrated that morbidity and mortality are associated primarily with an increased risk of cardiovascular disease rather than the consequences of bone disease or hypercalcemia.<sup>44</sup> A 7-year national registry of 4461 patients with primary hyperparathyroidism reported a risk ratio for cardiovascular disease death of 1.71 for men (95% CI, 1.34 to 2.15) and 1.85 for women (95% CI, 1.62 to 2.11).<sup>45</sup> Kamycheva and colleagues<sup>46</sup> reported that coronary heart disease was highest in those with the highest concentrations of PTH (men: relative risk, 1.67; 95% CI, 1.26 to 2.23; women: relative risk, 1.78; 95% CI, 1.22 to 2.57).

After parathyroidectomy, excess all-cause mortality rate gradually declines to that of the general population with a statistically significant mortality advantage only for the mildly hypercalcemic patients.<sup>47</sup> Mortality benefits are not limited to patients with primary hyperparathyroidism, however. Parathyroidectomy also was associated with lower long-term mortality rates in patients receiving long-term dialysis, estimated at 10 to 15% lower than nonsurgical matched control subjects.<sup>48</sup>

Statins have been recognized as having pleiotropic effects, with benefits extending beyond their lipid-lowering effects. It has been hypothesized that this is related in part to their effects on vitamin D.<sup>49,50</sup> Pérez-Castrillón and colleagues<sup>51</sup> found that atorvastatin produced a statistically significant increase in baseline 25(OH)D concentrations in 83 patients with acute ischemic syndrome and a decrease in vitamin D deficiency by 57% to 75% after 12 months of treatment. The relationship between statins and the skeleton has recently been explored. In primary human osteoblasts, statins increase the level of osteoprotegerin messenger RNA and decrease RANKL messenger RNA. Observational studies indicate that the level of soluble RANKL is lower in those on statin therapy than in those not on statin therapy.<sup>26</sup> Women taking statins have a higher bone density than those who do not.<sup>52</sup> In experimental rabbit aortic valve calcification, bone-matrix deposition is reduced by atorvastatin.<sup>53</sup>

### Congestive Heart Failure

Severe vitamin D deficiency and secondary hyperparathyroidism are common in patients with heart failure.<sup>54</sup> Diuretic-induced losses of calcium and phosphorus activate the renin-angiotensin-aldosterone system, which causes secondary hyperparathyroidism, bone resorption, and calcium overloading of peripheral blood mononuclear cells and cardiac tis-

sue.<sup>55</sup> Primary aldosteronism is characterized by secondary hyperparathyroidism in the majority of cases.<sup>56</sup> Shane and colleagues<sup>57</sup> reported severe deficiency [ $25(\text{OH})\text{D} \leq 9$  ng/mL] in 17% of patients with New York Heart Association functional class III or IV heart failure. Elevated concentrations of PTH ( $\geq 65$  pg/mL) were found in 30% of subjects. Zittermann and colleagues<sup>54</sup> demonstrated an association between low vitamin D status, exercise intolerance, and heart failure severity. Heart failure patients had reduced concentrations of 25(OH)D ( $P<0.001$ ) and calcitriol ( $P<0.001$ ) and significantly increased serum concentrations of N-terminal pro-atrial natriuretic peptide ( $P<0.001$ ), serum phosphate concentrations, albumin-corrected calcium concentrations, and PTH concentrations compared with control subjects. Patients with the lowest 25(OH)D concentrations had the lowest peak  $\dot{V}\text{O}_2$  ( $6.7 \pm 1.2$  versus  $11.5 \pm 1.1$  mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>;  $P=0.01$ ), with exercise tolerance correlating with vitamin D stores ( $r=0.393$ ,  $P=0.008$ ). Those who could not exercise at all had the lowest concentrations of vitamin D compared with those who could ( $P=0.007$ ).<sup>54</sup>

A randomized placebo-controlled trial of vitamin D supplementation (cholecalciferol or placebo) taken for 9 months by patients with congestive heart failure demonstrated a significant decline in PTH and a significant increase in the antiinflammatory cytokine interleukin-10 in the treated group and prevented an increase in the proinflammatory cytokine tumor necrosis factor- $\alpha$ .<sup>58</sup> More recently, osteoprotegerin is being explored for its role in the pathogenesis of heart failure. Higher levels of osteoprotegerin were reported in patients with aortic stenosis who have heart failure that was independent of age, sex, and the presence of coronary artery disease.<sup>24</sup>

### Hypertension and Myocardial Hypertrophy

The prevalence of hypertension has a similar relationship to latitude changes in UVB radiation.<sup>59–61</sup> Vitamin D plays an important role in the regulation of renin biosynthesis and blood pressure homeostasis in animal studies. Disruption of vitamin D signaling in mice leads to activation of the renin-angiotensin system, high blood pressure, and cardiac hypertrophy.<sup>62–64</sup> Forman and colleagues<sup>65</sup> examined the association between 25(OH)D concentrations and the risk of incident hypertension in men who participated in the Health Professionals Follow-Up Study and women in the Nurses Health Study who did not have hypertension at baseline. They reported that in individuals who had the lowest 25(OH)D concentrations ( $<15$  ng/mL), the relative risk of incident hypertension was 6.13 (95% CI, 1.00 to 37.8) for men and 2.67 (95% CI, 1.05 to 6.79) for women after adjustment for age, body mass index, physical activity, race, and menopausal status.

Hypertension also has been shown to respond to treatment with vitamin D. Patients with mild hypertension were randomized to exposure of vitamin D–producing UVB spectrum of light or the placebo arm of ultraviolet A rays 3 times weekly for 6 weeks. A fall in systolic and diastolic blood pressures of 6 mm Hg occurred, and a mean increase in 25(OH)D concentration of 162%.<sup>66</sup> Park and colleagues<sup>67</sup> reported that pharmacological doses of calcitriol reversed

hypertension and insulin resistance without causing significant changes in serum calcium or PTH. Pfeifer and colleagues<sup>68</sup> demonstrated that calcium and vitamin D supplements compared with calcium alone demonstrated a 9% decrease in systolic blood pressure after 6 weeks in 148 severely vitamin D–deficient women who had baseline 25(OH)D concentrations of 10 ng/mL. This is even more significant because only modest concentrations of 25(OH)D were achieved after treatment (26 ng/mL).

It is unclear what the relative contribution of vitamin D is compared with the effects of even modest but chronic elevations of PTH on hypertension and myocardial hypertrophy. Intravenous calcitriol produces a significant regression of the left ventricular mass index with concomitant reductions in plasma PTH, angiotensin II, and atrial natriuretic peptide.<sup>67</sup> Prolonged PTH infusion results in significant and sustained but reversible hypertension in normal human subjects.<sup>69</sup>

PTH is an independent predictor of left ventricular mass in the general population in subjects without known cardiovascular disease or hypertension.<sup>70,71</sup> Left ventricular hypertrophy, be it symmetric, asymmetric, or obstructive, has been shown to be almost invariably associated with hyperparathyroidism,<sup>72</sup> leading Symons and colleagues<sup>73</sup> to recommend that PTH be measured in all patients with left ventricular hypertrophy. Stefanelli and colleagues<sup>74</sup> reported that left ventricular hypertrophy was present in 81% of 123 consecutive patients undergoing parathyroidectomy for primary hyperparathyroidism and was a strong and independent predictor of cardiovascular morbidity and mortality. They also reported that left ventricular hypertrophy was reversible in years 1 to 4 after surgery, particularly in normotensive patients. Similar regression of myocardial hypertrophy has been found in patients with secondary hyperparathyroidism caused by chronic renal failure.<sup>75</sup>

### Metabolic Syndrome

Vitamin D receptors are present in the pancreas, modulating insulin secretion and sensitivity. Human pancreatic islet cells possess 1 $\alpha$ -hydroxylase capable of calcitriol production.<sup>6</sup> Hypovitaminosis D has been associated with insulin resistance, type 1 and 2 diabetes mellitus, and the metabolic syndrome.<sup>76–81</sup> One study demonstrated a 60% improvement in insulin sensitivity resulting from vitamin D treatment, a treatment more potent than with either troglitazone or metformin.<sup>76</sup>

### Vitamin D Replacement Studies

Several clinical trials have examined the effectiveness of vitamin D replacement on heart disease outcomes or all-cause mortality but generally included replacement dosages now considered inadequate to achieve physiological concentrations of 25(OH)D.<sup>82</sup> In the Women's Health Initiative, >36 000 postmenopausal women were randomized to calcium carbonate with vitamin D 200 IU twice daily or placebo. No significant differences were found in coronary or cerebrovascular risk between the treatment and placebo groups over a 7-year period.<sup>83</sup> Another randomized controlled trial compared cholecalciferol (100 000 IU every 4 months for 5 years) with placebo in >2600 persons (32% women) 65 to 85

years of age.<sup>84</sup> The primary outcomes studied were total mortality and fracture incidence. Trivedi et al<sup>84</sup> reported that the group taking vitamin D had lower all-cause mortality, yet the difference was not statistically significant. They concluded that although the concentration of vitamin D in the treatment group was 40% higher than placebo, it still did not achieve physiological concentrations.

Most recently, Autier and Gandini<sup>85</sup> performed a meta-analysis of 18 randomized controlled trials including 57 000 participants of vitamin D supplementation and total mortality. Daily vitamin D supplements ranged from 300 to 2000 IU with a mean adjusted dose of 528 IU. The summary relative risk reduction for all-cause mortality was 0.93 (95% CI, 0.87 to 0.99).

Patients with chronic kidney disease lack the ability to manufacture calcitriol and often are deficient in its substrate. Vitamin D and analogs given to treat calcium and phosphate metabolic abnormalities of associated secondary hyperparathyroidism have demonstrated a striking reduction in cardiovascular death and all-cause mortality.<sup>86–89</sup> Teng and colleagues<sup>87</sup> reported a 2-year survival rate of 75.6% versus 58.7%, a mortality rate of 13.8 versus 28.6 per 100 person-years ( $P < 0.001$ ), and lower PTH concentrations in a historical cohort study of 51 037 dialysis patients receiving intravenous calcitriol or paricalcitol. Even after adjustment for potential confounders, a 20% lower mortality remained (hazard ratio, 0.80; 95% CI 0.76 to 0.83).

## Recognition and Treatment Guidelines

### Groups at Risk and Symptoms of Vitamin D Deficiency

Many patient-specific and environmental factors are associated with chronic vitamin D deficiency. They range from sunlight and dietary deficits and drugs to common medical conditions, including malabsorption and liver and chronic kidney disease. Absorption of UVB depends on latitude, season, and time of day. UVB rays do not penetrate clothes, smog, or window glass. A variable response to UVB radiation even despite abundant sun exposure has been demonstrated, causing some to have a low vitamin D status despite abundant sun exposure.<sup>90</sup> Aging is associated with depletion of provitamin D3 in the epidermis, decreasing the capacity of skin to produce vitamin D3 and reducing the conversion to activated vitamin D by the kidney.<sup>91</sup> Melanin is an effective absorber of UVB radiation, with lighter skin pigmentation decreasing the time to achieve equilibrium up to 10-fold. Commercially available vitamin D dietary supplements and food supplementation are currently not regulated by the Food and Drug Administration. Over-the-counter vitamin D3 usually is taken in combination with calcium supplements. Calcium supplements have been shown to be poorly absorbed in individuals with gastric hypochlorhydria and in those who take histamine receptor blockers or proton pump inhibitors.<sup>82</sup> Many patients taking vitamin D–containing supplements remain severely deficient.<sup>92</sup> Little evidence exists that fortified milk is sufficient to provide adequate concentrations of 25(OH)D in a population in which 70% of adults are lactose intolerant<sup>93</sup>

**Table 2. Groups at Risk for Vitamin D Deficiency**<sup>1,90–93,94</sup>

Malabsorption syndromes
Inflammatory bowel disease
Hepatic failure
Cystic fibrosis
Bowel resection
Adult celiac disease
Gastrojejunostomy (gastric bypass)
Chronic diarrhea
Pancreatitis
Sun deprived
Institutionalized
Skin barriers (SPF 9 or higher, clothing, etc)
House staff
Alterations in synthesis
Chronic renal disease
Chronic hepatic disease
Age-related decline in epidermal 7-dehydrocholesterol
Pharmaceuticals
Steroids
Rifampin (phenobarbital)
Cholestyramine
Xenical

SPF indicates sun protection factor.

(Table 2).<sup>1,90–94</sup> Additionally, vitamin D concentrations in milk may not be reliable. In one study, milk analyzed in the United States and Canada did not contain any of the labeled amounts of vitamin D in 14% of samples, and half the samples contained <80% of what was stated on the label.<sup>95</sup>

Most patients with vitamin D deficiency diagnosed on the basis of screening blood tests are generally considered to be asymptomatic because symptoms of bone and muscle pain, gait disturbance, seasonal depression, muscle weakness, and neuropathy may be attributed to other conditions such as myalgias in conjunction with statin drugs, fibromyalgia, and aging.<sup>92,96,97</sup> Weakness of the quadriceps muscle groups may lead to gait disturbances, falls, and fractures, and at its most extreme, severe myopathy caused by hypovitaminosis D can lead to immobility.<sup>98</sup> Common conditions such as psoriasis, osteoporosis, multiple sclerosis, autoimmune disorders, sarcoidosis, and breast, prostate, or colon cancer have recently been attributed to vitamin D deficiency.<sup>1</sup>

### Normal Concentrations of Vitamin D

Many authorities believe that hypovitaminosis D is the point at which PTH concentrations increase or reach a stable, normal concentration in a calcium-replete individual. This point appears to be at a minimum concentration of 25(OH)D >30 ng/mL.<sup>99–103</sup> Measurement of PTH alone, however, is not recommended as a reliable indicator of vitamin D adequacy, particularly in those with chronic renal failure or calcium insufficiency.<sup>88</sup> Furthermore, chronic vitamin D deficiency causes parathyroid hyperplasia, with PTH elevations remaining high for prolonged periods. Persistent eleva-

tions of PTH concentrations are probably best managed in conjunction with endocrine or nephrology specialists.

### Treatment Guidelines

Vitamin D2 (Drisdol) is available by prescription and is our preferred method of replacement. Produced by ultraviolet irradiation of the yeast sterol ergosterol, it is available by prescription as a 50 000-IU capsule. D2 is converted to D3 in vivo and is effective in raising the concentration of 25(OH)D to goal, usually ranging from weekly to monthly. Treatment guidelines according to various populations and conditions have been published.<sup>1</sup> Vitamin D3 is produced by irradiating 7-dehydrocholesterol from lanolin in sheep's wool and is available in many nonprescription preparations.<sup>1</sup>

Some replacement caveats are important. First, physician-guided monitoring is essential because each patient must be treated individually. "One size" therapy does not fit all. We have found that vitamin D requirements may be higher in the elderly, the obese, and nonwhite patients. Thus, in the initial treatment stages, 25(OH)D and intact PTH are measured at intervals of 3 to 6 months until stable. Second, attention must be paid to serum and urinary calcium concentrations. Hypocalcemia may be precipitated in patients taking bisphosphonates if calcium is not adequately replaced, and hypercalcemia may be unmasked in patients with chronic granulomatous or lymphoproliferative diseases. Adequate calcium replacement is present if 24-hour urinary calcium is >50 mg/mL. Although data are limited, treatment can theoretically increase urinary calcium excretion because of the direct effect of vitamin D on renal excretion of calcium. For patients with a history of nephrolithiasis, urinary calcium excretion exceeding 4.5 mg/kg should be avoided, with concentrations of <1.5 mg/kg preferred for these individuals. Finally, measuring 1,25(OH)<sub>2</sub>D to determine substrate sufficiency is not useful given that those with low 25(OH)D may have normal 1,25(OH)<sub>2</sub> values because PTH stimulates 1 $\alpha$ -hydroxylase.<sup>1,102</sup>

### Conclusions and Future Perspectives

The evidence suggests that chronic and often decades-long vitamin D deficiency and secondary hyperparathyroidism are important in the pathophysiology of ischemic heart disease, hypertension, myocardial hypertrophy, diastolic heart failure, and the metabolic syndrome. Further study of the osteoprotegerin/RANK/RANKL system and its relationship to cardiovascular disease is needed, particularly because future therapies for treatment may target this system. The influence of PTH and PTH-related peptide on myocardial hypertrophy and diastolic function also needs further investigation. Randomized trials should be designed to target specific physiological concentrations of 25(OH)D and PTH to confirm epidemiological observations that the provision of a simple, well-tolerated, and inexpensive correction of hypovitaminosis D could favorably affect the morbidity and mortality of the most common cardiovascular diseases.

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## Disclosures

None.

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KEY WORDS: calcium ■ heart diseases ■ hyperparathyroidism ■ nutrition ■ vitamin D deficiency