

Role of Vitamin D in Cardiovascular Health

Subba Reddy Vanga, MBBS^a, Mathew Good, DO^a, Patricia A. Howard, PharmD^b, and James L. Vacek, MD^{a,*}

Observational studies strongly associate vitamin D deficiency with a variety of cardiovascular diseases beyond defects in bone and calcium metabolism. Vitamin D has multiple mechanisms that potentially may affect cardiovascular health. Because vitamin D deficiency is common, therapies directed at the replacement of vitamin D may be beneficial. To date however, studies evaluating vitamin D supplementation are few and have not consistently shown benefit. It is possible that the lack of benefit in these studies may have arisen from suboptimal levels of vitamin D supplementation or other unknown factors. Nevertheless, the growing body of observational data and consistent findings of relatively high rates of low vitamin D serum levels warrant further well-designed studies to investigate the relation between vitamin D and cardiovascular health. In conclusion, vitamin D is now recognized as important for cardiovascular health and its deficiency as a potential risk factor for several cardiovascular disease processes. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;106:798–805)

Cardiovascular disease is the most common cause of mortality and morbidity in the United States and many other nations. A growing body of evidence suggests a possible association between vitamin D deficiency and many cardiovascular disorders, including hypertension, peripheral vascular disease, diabetes mellitus, metabolic syndrome, coronary artery disease, and heart failure. In this review, we focus on current evidence, potential mechanisms, and the possible role of vitamin D supplementation in cardiac health.

Metabolism of Vitamin D

Vitamin D belongs to a group of secosteroid molecules that are traditionally associated with bone and calcium metabolism. Although 5 forms of vitamin D (D₁ through D₅) are known, vitamins D₂ and D₃ are the most studied forms (Table 1). Ergocalciferol, or vitamin D₂, is principally synthesized in plants and invertebrates. It is typically consumed in the human diet and as supplements or fortified products. Cholecalciferol, or vitamin D₃, is mainly of vertebrate animal origin and commonly consumed in the form of oily fish. Cholecalciferol is also synthesized in human skin after exposure of 7-dehydrocholesterol to solar ultraviolet radiation. Endogenous and consumed vitamin D is stored in fat tissues and released into the circulation (Table 1). Vitamin D₃ is bound to a circulating glycoprotein called vitamin D-binding protein (Figure 1). The liver converts vitamin D to 25-hydroxy (25[OH]) vitamin D. In a rate-limiting step, the kidneys convert 25(OH) vitamin D to its active form 1,25(OH)₂ vitamin D (Figure 2).

^aMid America Cardiology, Division of Cardiovascular Medicine, University of Kansas Medical Center and Hospital, Kansas City, Kansas; and ^bDepartment of Pharmacy Practice, University of Kansas School of Pharmacy, Kansas City, Kansas. Manuscript received February 3, 2010; revised manuscript received and accepted April 20, 2010.

*Corresponding author: Tel: 913-588-9655; fax: 913-588-9773.
E-mail address: jlvacek@mac.md (J.L. Vacek).

The active form of vitamin D (1,25[OH]₂ vitamin D) binds to vitamin D receptors (VDR). The conjugated vitamin D with its receptor forms a heterodimer complex with retinoid X receptor. Together with several other factors and an activator, this complex attaches to vitamin D-responsive elements on deoxyribonucleic acid and alters gene expression (Figure 1).¹ VDRs are prominently present in enterocytes, osteoblasts, parathyroid gland cells, and distal renal tubule cells. Vitamin D increases calcium absorption from gut and renal tubular cells and suppresses parathyroid hormone. It acts on osteoblasts and increases bone mineral density. Recent investigations have also shown a significant presence of VDR in the liver, the immune system, and skeletal and cardiac muscle.²

Sources of Vitamin D and Normal Serum Levels

Cutaneous synthesis of vitamin D₃ from sunlight exposure is the major source (80% to 90%) of vitamin D in humans under natural conditions.³ Total-body sun exposure to 1 minimal erythral dose while wearing a bathing suit provides the equivalent of 250 to 500 μg (10,000 to 20,000 IU) of vitamin D per day.⁴ The dietary supply of vitamin D is minor compared to cutaneous formation but can become an important source of vitamin D with supplementation. Oily fish such as salmon, mackerel, herring, and sardines are rich sources of vitamin D. Fortified milk and juices are fortified to provide ≥100 IU per 8-oz serving in the United States and Canada. Ordinary dietary sources usually provide 2.5 μg (100 IU) of vitamin D per day, and fortified foods may provide up to 5 to 10 μg (200 to 400 IU) of vitamin D daily.⁵

Serum 25(OH) vitamin D is the major circulating metabolite of vitamin D and reflects vitamin D input from cutaneous synthesis and dietary intake. Serum 1,25(OH)₂ vitamin D levels can be normal or even elevated in patients with vitamin D deficiency. The most beneficial serum concentrations of 25(OH) vitamin D are observed at ≥30 ng/ml (≥75 nmol/L). Most experts agree that vitamin D insufficiency is present with 25(OH) vitamin D levels of 21 to 29

Table 1
Classification of vitamin D group of molecules

Class	Chemical Composition	Significance
Vitamin D ₁	Combination of ergocalciferol and lumisterol	
Vitamin D ₂	Ergocalciferol: made from ergosterol or pre-vitamin D ₂	Made by invertebrates, fungus, and plants in response to ultraviolet irradiation; not made by vertebrates
Vitamin D ₃	Cholecalciferol: made from 7-dehydrocholesterol or pre-vitamin D ₃	Made in the skin as a response to ultraviolet B radiation after reacting with 7-dehydrocholesterol
Vitamin D ₄	Dihydroergocalciferol: vitamin D ₂ without 22,23 double bond	Ineffective form of vitamin D
Vitamin D ₅	Sitocalciferol: made from 7-dehydrositosterol	May have antitumor properties

ng/ml, while levels <20 ng/ml (<50 nmol/L) indicate vitamin D deficiency.⁶⁻⁸

Epidemiology of Vitamin D Deficiency

Vitamin D, under ideal conditions, is probably not required in the diet, because most mammals including humans can synthesize it from direct sunlight exposure. However, worldwide, most humans typically expose $\leq 5\%$ of their skin to infrequent periods of unshielded sunlight, a behavior that commonly leads to vitamin D deficiency. This is far less solar exposure than that experienced in most historical human cultures and among free-living primates. In 1 study, 36% of young healthy free-living adults in the United States aged 18 to 29 years had vitamin D deficiency at the end of winter.⁹ In elderly and institutionalized patients, the prevalence of vitamin D deficiency is higher.¹⁰ The Third National Health and Nutrition Examination Survey (NHANES III) reported the prevalence of vitamin D deficiency in United States adults to be 25% to 57%.¹¹ Risk factors for vitamin D deficiency include advanced age, dark skin color, institutionalized or homebound status, increased distance from the equator, winter season, clothing, the use of sunscreen, air pollution, smoking, obesity, malabsorption, renal disease, liver disease, and medications.⁸

Recommended Daily Intake, Toxicity, and Assay of Vitamin D

The present recommended daily dose of vitamin D is 400 IU. It has been estimated that for every 100 IU of vitamin D ingested, the blood level of 25(OH) vitamin D increases by 1 ng/ml (2.5 nmol/L).^{12,13} For many individuals, the present recommended daily allowance may not be sufficient to achieve optimal serum concentrations of vitamin D.¹⁴ African Americans with low sun exposure require 2,100 to 3,100 IU/day of oral vitamin D throughout the year to achieve a serum 25(OH) vitamin D concentration of ≥ 30

mg/ml (≥ 75 nmol/L).¹⁵ Many experts now recommend a daily vitamin D dose of 1,000 to 2,000 IU for most individuals, with higher doses of vitamin D (up to several doses of 50,000 IU) required initially to treat hypovitaminosis.^{3,16}

Hypervitaminosis D, which is extremely rare and typically is caused by prolonged massive doses of oral supplementation, presents with symptoms related to hypercalcemia, including anorexia, nausea, and vomiting, followed by polyuria, polydipsia, weakness, nervousness, pruritus, and eventually even renal failure. Overall, however, evidence suggests that vitamin D is well tolerated over a large intake range.¹⁷ Case reports have shown that 150,000 IU of vitamin D daily for 28 years,¹⁸ and serum concentrations up to 1,126 nmol/L for months to years,¹⁹ did not result in significant hypercalcemia side effects.

Currently, several methods of vitamin D assay are available. Liquid chromatography tandem mass spectroscopy measures all forms of circulating 25(OH) vitamin D and is considered the "gold standard." Other simpler methods, such as radioimmunoassay, enzyme-linked immunoassay, and chemiluminescence assay, may not measure all circulating forms of vitamin D. Clinicians must be aware of the assay methods and normal ranges for their laboratories.

Clinical Conditions Associated With Vitamin D Deficiency

A wide range of cardiovascular disease states have been associated with vitamin D deficiency involving multiple potential mechanisms (Table 2).

Vitamin D and hypertensive vascular disease: Essential hypertension is a major risk factor for cardiovascular disease. Vitamin D appears to be related to blood pressure control via multiple pathways and is inversely related to serum renin activity.^{20,21} Similarly, a decrease in blood pressure was seen in subjects who were exposed to ultraviolet B radiation.²² The effects of vitamin D on the suppression of renin activity may be due to increased intracellular calcium levels.²³ Vitamin D replacement in deficient subjects significantly improved flow-mediated dilatation of the brachial artery, suggesting a role of vitamin D in the sensitivity of vascular smooth muscle cells.²⁴

Initial small retrospective observational studies have shown significant inverse correlations between vitamin D levels and systolic blood pressure.²⁵⁻²⁸ In a small study from Belgium of 25 patients with hypertension, vitamin D levels were inversely correlated with systolic blood pressure, diastolic blood pressure, and calf vascular resistance.²⁵ In a subsequent study involving normotensive men, a similar inverse correlation between 125(OH)₂ vitamin D and systolic blood pressure was observed.²⁶ Conversely, in another study, vitamin D levels did not differ between newly diagnosed patients with hypertension and their matched controls.²⁷

Data from a large cross-sectional national study involving a noninstitutionalized population aged >20 years, NHANES III, were used to evaluate the relation between serum 25(OH) vitamin D concentrations and blood pressure.²⁸ After excluding those who were taking antihypertensive medications, a total of 12,644 patients were included in the analysis. The mean blood pressure varied inversely

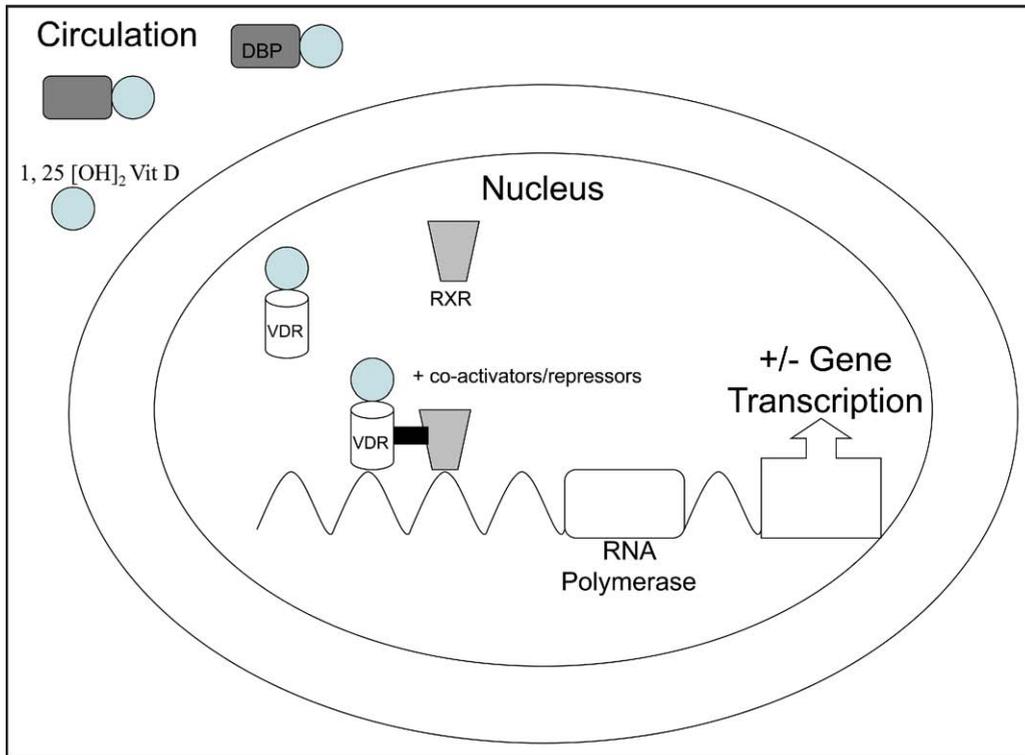


Figure 1. The active form of vitamin (Vit) D (1,25[OH]₂ vitamin D) is bound to vitamin D-binding protein (DBP) in circulation, crosses the cell membrane, and binds to vitamin D receptor (VDR). The conjugated vitamin D with its receptor forms a heterodimer complex with retinoid X receptor (RXR) and with other factors, attaches to vitamin D-responsive elements on deoxyribonucleic acid, and alters gene expression. RNA = ribonucleic acid.

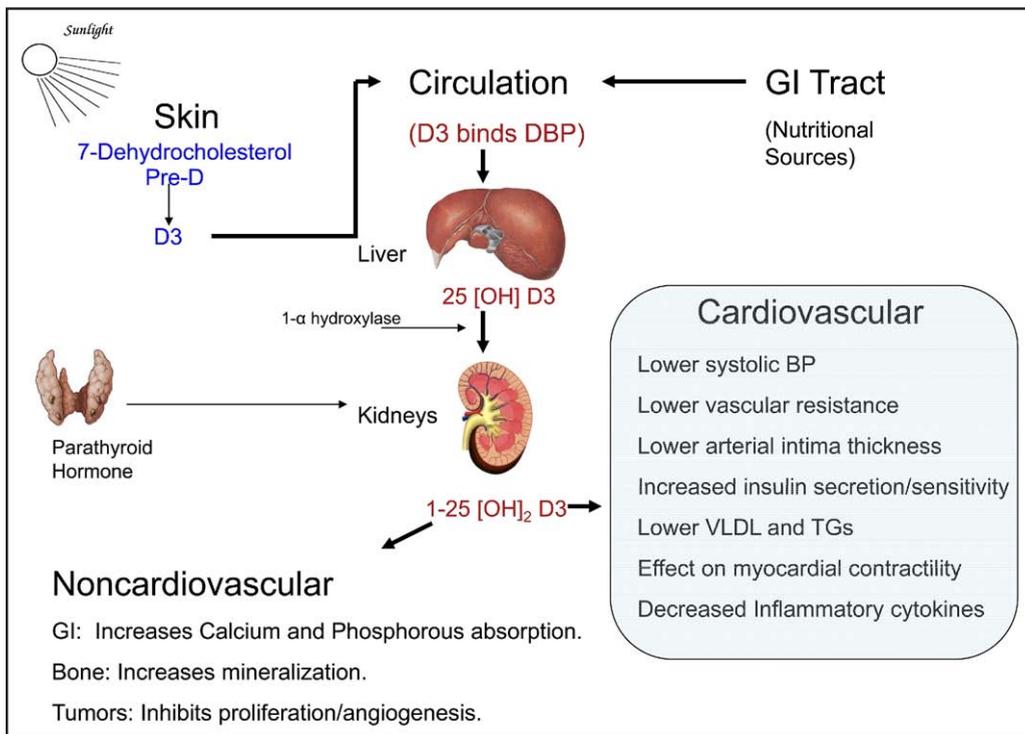


Figure 2. Metabolism and biologic actions of vitamin D. The major biologic form of vitamin D, vitamin D₃, is synthesized in the skin from the precursor (pre-D) under direct sunlight. Vitamin D from cutaneous synthesis and nutritional sources enters the circulation and is bound to vitamin D-binding protein (DBP). A series of enzymatic hydroxylations in the liver and kidneys transform vitamin D to biologically active 1,25(OH)₂ vitamin D. Parathyroid hormone regulates the hydroxylation in kidney. Activated vitamin D exerts multiple cardiovascular and noncardiovascular actions. BP = blood pressure; GI = gastrointestinal; TG = triglyceride; VLDL = very low density lipoprotein.

Table 2
Potential mechanisms through which vitamin D deficiency may affect cardiovascular disease

Pathology	Proposed Mechanism of Action
Hypertensive vascular disease	<ul style="list-style-type: none"> • Increased intracellular calcium leading to decreased renin activity • Calcitriol suppression of renin promoter gene • Alteration of the sensitivity of vascular smooth muscle cells
Peripheral vascular disease	<ul style="list-style-type: none"> • Increased calcification
Diabetes mellitus	<ul style="list-style-type: none"> • Immunomodulatory effects by reducing tumor necrosis factor-α, parathyroid hormone, and interleukin-10 • Decreased insulin receptor expression, leading to peripheral resistance of insulin • Effect on intracellular calcium levels leading to decreased insulin secretion
Lipid metabolism	<ul style="list-style-type: none"> • Increase peripheral insulin resistance, contributing to high lipid profile • Statins may increase vitamin D levels by increasing 7-dehydrocholesterol • Increased vessel free radicals lead to oxidation of low-density lipoprotein and increased engulfment by macrophages, an early sign of atherosclerosis
Coronary artery disease	<ul style="list-style-type: none"> • Indirect effect through risk factor modification • Altering endothelial function • Increased coronary artery calcification
Heart failure	<ul style="list-style-type: none"> • Direct effect on myocardial contractility • Regulation of brain natriuretic peptide secretion • Reduction of left ventricular hypertrophy with effects on extracellular remodeling • Regulation of inflammatory cytokines • Secondary hyperparathyroidism, which leads to vasodilatation and positive inotropic stimulation
Arrhythmias	<ul style="list-style-type: none"> • Direct myocardial substrate modification • Indirectly via calcium levels and metabolism at a cellular level

with serum 25(OH) vitamin D levels, with the association remaining significant after adjustment for age, gender, race or ethnicity, and physical activity. The impact of vitamin D deficiency in the elderly (age >50 years) was highly significant ($p = 0.021$).²⁸

Interventions with vitamin D replacement were attempted to support the hypothesis that changes in vitamin D status affect blood pressure. In a randomized study, women aged >70 years with 25(OH) vitamin D levels <20 ng/ml were randomly assigned to receive supplementation with calcium 1,200 mg/day or calcium 1,200 mg/day plus vitamin D (cholecalciferol) 800 IU/day. Within 8 weeks of treatment, systolic blood pressure in the vitamin D-treated

group had decreased by an average of 13 mm of Hg ($p = 0.02$).²⁹ In a similar randomized study involving patients with diabetes mellitus and serum 25(OH) vitamin D levels <20 ng/ml, patients were randomly assigned to receive a 1-time dose of ergocalciferol 100,000 IU or placebo. Vitamin D supplementation produced a significant decrease in systolic blood pressure.³⁰ Similar benefits of vitamin D on blood pressure were noticed in other small studies.^{22,27}

However, a recent meta-analysis provided little support for a positive effect of vitamin D supplementation on blood pressure.³¹

Vitamin D and peripheral vascular disease: Vitamin D levels have been inversely correlated with calf vascular resistance and positively correlated with calf blood flow.²⁵ Similar associations were identified in the NHANES III study. After multivariate adjustment for demographics, comorbidities, physical activity level, and laboratory measures, low 25(OH) vitamin D levels were associated with a higher prevalence of peripheral arterial disease.³² Vitamin D deficiency is also strongly associated with increased thickness of the intima-media in carotid arteries.³³ One third of the excess risk for peripheral arterial disease in an African American population was attributed to racial differences in vitamin D status.³⁴ Similarly, a high prevalence of vitamin D deficiency with secondary hyperparathyroidism was observed in a nondiabetic population with peripheral vascular disease.³⁵ To date, no interventional studies have examined the specific effect of vitamin D replacement on peripheral vascular disease.

Vitamin D and diabetes mellitus: Pancreatic β -cell dysfunction, peripheral tissue resistance to insulin, and chronic inflammation appear to be possible mechanisms for the role of vitamin D in diabetes mellitus.³⁶ VDRs have been found in pancreatic islets, indicating a possible role for vitamin D in insulin secretion.³⁷ Basal insulin secretion rate was not altered in VDR-knockout mice,³⁸ but insulin secretion rate after a challenge with glucose diet was impaired in vitamin D deficiency.³⁹ Vitamin D may affect intracellular calcium levels in pancreatic cells, which is an important stimulus for insulin secretion. In peripheral tissues, VDRs were found in skeletal muscles and adipose tissue. Vitamin D also has been shown to control insulin receptor expression and insulin responsiveness for glucose transport,⁴⁰ establishing its role in insulin secretion and sensitivity.

Observational human studies examined the seasonal⁴¹ and geographic⁴² variation of type 1 diabetes mellitus and its relation to vitamin D deficiency. The European Community Concerted Action on the Epidemiology and Prevention of Diabetes (EURODIAB) study found a 33% reduction in the risk for developing childhood-onset type 1 diabetes in children who received vitamin D supplementation.⁴³ Seasonal variations of glycemic control attributed to vitamin D level fluctuations were reported.⁴⁴ Replacing vitamin D improves insulin secretion, peripheral insulin sensitivity in patients with type 2 diabetes,^{45,46} and glycosylated hemoglobin levels.⁴⁷ Metabolic syndrome is also prevalent in patients with vitamin D deficiency.⁴⁸

Although the data from observational studies are strong, the expected benefit from replacement of vitamin D on

fasting blood glucose, glucose tolerance, or insulin sensitivity was not observed in some studies.^{49,50} This variance may be due to ethnic differences or VDR gene polymorphisms.^{51–53} Nevertheless, 2 meta-analyses pooling large amounts of data suggest that vitamin D may have a role in the prevention of type 2 diabetes mellitus.^{36,54}

Vitamin D and lipid metabolism: Serum levels of 1,25(OH)₂ vitamin D are inversely correlated with very low density lipoprotein and triglyceride levels.⁵⁵ Vitamin D deficiency may cause an abnormal lipid profile by increasing peripheral insulin resistance and contributing to metabolic syndrome. However, oral supplements of vitamin D₃ in postmenopausal women did not improve total cholesterol, low-density lipoprotein, or high-density lipoprotein levels over 12 months.⁵⁶ Studies have suggested that statin therapy may increase vitamin D levels, a finding that may account for some of the nonlipid pleiotropic actions of statins.^{57–60} It is postulated that the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase enzyme by statins results in increased 7-dehydrocholesterol. This excess 7-dehydrocholesterol is then converted to 25-hydroxycholecalciferol by sunlight or the CYP11A1 enzyme, thereby increasing vitamin D levels (Figure 2).^{58,60,61} Last, a recent study that examined reductions in VDR signaling in patients with diabetes found increased foam cell formation in macrophages, an early sign of atherosclerosis.⁶²

Vitamin D and coronary artery disease: As discussed previously, many coronary risk factors, including hypertension, diabetes mellitus, and lipid levels, are affected by vitamin D. Vitamin D has also been shown to affect endothelial function^{24,29} and decrease vascular calcification.⁶³ Calcification of coronary arteries was inversely correlated with vitamin D levels.⁶⁴ Earlier observations in the 1980s and 1990s found geographic and seasonal differences in mortality from ischemic heart disease.^{56,65} The initial suggestion of vitamin D as a protective factor came from a study in the United Kingdom showing that mortality from ischemic heart disease was inversely proportional to the hours of sunlight.⁵⁶

Larger cross-sectional observations using the NHANES databases found that in a sample of 16,603 men and women aged >18 years, those with ischemic heart disease and stroke had a greater frequency of 25(OH) vitamin D deficiency ($p < 0.0001$).⁶⁶ This was confirmed by a more recent analysis involving 8,351 adults in which the prevalence of vitamin D deficiency was 74% in patients with coronary artery disease and heart failure.⁶ In the general population, the lowest quartile of 25(OH) vitamin D level (<17.8 ng/ml) was independently associated with all-cause mortality.⁶⁷ Together, the findings of these epidemiologic studies suggest that poor vitamin D status is associated with poor cardiovascular outcomes.

Multiple studies evaluated the relation of vitamin D prospectively with long-term cardiovascular outcomes in subjects with no histories of cardiovascular disease. In dialysis patients, those who were vitamin D deficient were at significantly increased risk for early mortality.⁶⁸ Similarly, in healthy male health professionals aged 40 to 75 years with no histories of coronary artery disease, vitamin D

deficiency (25[OH] vitamin D <15 ng/ml) was associated with a twofold increased rate of myocardial infarction over a 10-year period.⁶⁹ In the Framingham Offspring Study, subjects with no histories of cardiovascular disease and severe vitamin D deficiency (25[OH] vitamin D <10 ng/ml) had increased risk for developing a first cardiovascular event after 5 years of follow-up compared with subjects with 25(OH) vitamin D levels >15 ng/ml (hazard ratio 1.80, 95% confidence interval 1.05 to 3.08).⁷⁰ In >3,000 subjects who underwent coronary angiography, those with severe vitamin D deficiency (<10 ng/ml) had 3 to 5 times the risk for death from sudden cardiac death, heart failure, or fatal stroke during a 7-year follow-up period compared to those who had optimal levels (>30 ng/ml).^{71,72}

Although the significance of vitamin D deficiency in coronary artery disease is well established in observational studies, few studies have been conducted to evaluate the impact of vitamin D supplementation on the risk for cardiovascular mortality. In the Women's Health Initiative (WHI) trial, postmenopausal women were randomized to vitamin D 400 IU plus calcium 1,000 mg daily supplementation or placebo and followed for 7 years. The supplements had no significant effect on mortality rates.⁷³ Elderly subjects (aged 65 to 85 years) living in the community were given 100,000 IU oral vitamin D₃ supplementation or matching placebo every 4 months over 5 years. Despite supplementation, the relative risk for total mortality did not change (odds ratio 0.88, 95% confidence interval 0.74 to 1.06, $p = 0.18$).⁷⁴

Vitamin D and heart failure: The major potential mechanisms that may explain a direct protective effect of vitamin D against heart failure include effects on myocardial contractile function, regulation of natriuretic hormone secretion, effects on extracellular matrix remodeling, reduced left ventricular hypertrophy, and the regulation of inflammatory cytokines (Figure 2).^{75–77} Indirectly, vitamin D can also affect cardiac function by altering parathyroid hormone and serum calcium levels. The initial evidence in humans came from dialysis patients. In patients with uremic cardiomyopathy, treatment with 1- α hydroxyl cholecalciferol 1 μ g/day for 6 weeks produced a decrease in plasma parathyroid concentration and an increase in fractional fiber shortening on M-mode echocardiography ($p < 0.025$).⁷⁸

Observational studies have shown that osteoporosis, osteopenia, and low serum 25(OH) vitamin D levels are common in patients with congestive heart failure.⁷⁹ It has been noted that there is ethnic variation in the incidence of heart failure and serum vitamin D levels.⁸⁰ A case-control study demonstrated that patients with heart failure and controls differed in several vitamin D-associated lifestyle factors, such as urban dwelling, sports club membership, and the number of summer holidays during earlier life periods.⁶³ In a study involving African American patients with left ventricular ejection fractions <35%, vitamin D deficiency (≤ 30 ng/ml) was associated with decompensated heart failure and prolonged hospital stays.⁸¹

Heart failure in African American patients is a unique disease that is characterized by greater incidence, disease severity, and overall mortality compared to other populations.^{82–85} Serum parathyroid hormone levels and vitamin

D status may explain some of the differences. Hyperparathyroidism is associated with left ventricular hypertrophy, cardiomyopathy and increased mortality.^{86–88} Vitamin D deficiency leads to increased secretion of parathyroid hormone and activation of the rennin-angiotensin-aldosterone and immune systems. Serum 25(OH) vitamin D levels are inversely correlated with serum parathyroid hormone levels. African American patients are also at risk for developing hyperparathyroidism and cardiomyopathy from other mechanisms, including secondary renin-angiotensin-aldosterone system activation and the use of loop diuretics.^{80,89} Observational studies have shown that vitamin D deficiency and hyperparathyroidism are more common in African American patients⁸⁰ and universally present in patients with heart failure.⁹⁰ Studies have also shown that 30% of African American women remain vitamin D deficient despite oral supplementation.⁹¹ Unrecognized, untreated, or partially treated vitamin D deficiency and associated hyperparathyroidism in African Americans might explain some of their morbidity and mortality associated with heart failure.⁹²

Low vitamin D levels were associated with poor outcomes in patients with end-stage heart failure awaiting heart transplantation.⁹³ A study on VDR gene polymorphisms in patients with end-stage renal disease compared to normal subjects suggested that vitamin D signaling is implicated in the regulation of left ventricular mass and hypertrophy in end-stage renal disease ($p < 0.001$).⁹⁴ Hemodialysis patients with secondary hyperparathyroidism when treated with intravenous vitamin D showed significant reductions in left ventricular wall thickness and left ventricular mass index.⁹⁵ Similarly vitamin D supplementation reduced inflammatory markers in patients with heart failure and improved serum parathyroid hormone levels. However, there was no significant direct survival benefit with vitamin D supplementation.⁹⁶

Vitamin D and arrhythmia: In a recent report, the correction of vitamin D deficiency and hypocalcemia resulted in control of incessant ventricular tachycardia and cardiomyopathy.⁹⁷ A rare case of fetal atrial flutter was reported in vitamin D-resistant rickets.⁹⁸ In an animal study, rats fed a vitamin D-deficient diet for 12 weeks developed significant QT-interval shortening despite normal serum calcium levels compared to normal rats.⁹⁹ These findings suggest a possible role for vitamin D deficiency as a causal factor for arrhythmia and the need for further exploration.

Vitamin D and mortality: Numerous studies and meta-analyses suggest that vitamin D deficiency has a negative association with survival, while supplementation decreases overall mortality.^{16,64,100} A recently announced prospective randomized study plans to enroll 20,000 elderly subjects and examine the potential health benefits of vitamin D and omega-3 supplementation.

1. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004;80:1689S–1696S.
2. Nibelink KA, Tishkoff DX, Hershey SD, Rahman A, Simpson RU. 1,25(OH)₂-vitamin D₃ actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. *J Steroid Biochem Mol Biol* 2007;103:533–537.
3. Pilz S, Tomaschitz A, Ritz E, Pieber TR. Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol* 2009;6:621–630.

4. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999;69:842–856.
5. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr* 2004;80:1710S–1716S.
6. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008;102:1540–1544.
7. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
8. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008;52:1949–1956.
9. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. *Am J Med* 2002;112:659–662.
10. Harris SS, Soteriades E, Coolidge JA, Mudgal S, Dawson-Hughes B. Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population. *J Clin Endocrinol Metab* 2000;85:4125–4130.
11. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone* 2002;30:771–777.
12. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003;77:204–210.
13. Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, Reitz R, Salameh W, Ameri A, Tannenbaum AD. Vitamin D₂ is as effective as vitamin D₃ in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* 2008;93:677–681.
14. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:18–28.
15. Hall LM, Kimlin MG, Aronov PA, Hammock BD, Slusser JR, Woodhouse LR, Stephensen CB. Vitamin D intake needed to maintain target serum 25-hydroxyvitamin D concentrations in participants with low sun exposure and dark skin pigmentation is substantially higher than current recommendations. *J Nutr* 2010;140:542–550.
16. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: bone and beyond, rationale and recommendations for supplementation. *Am J Med* 2009;122:793–802.
17. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85:6–18.
18. Stephenson DW, Peiris AN. The lack of vitamin D toxicity with megadose of daily ergocalciferol (D₂) therapy: a case report and literature review. *South Med J* 2009;102:765–768.
19. Kimball S, Vieth R. Self-prescribed high-dose vitamin D₃: effects on biochemical parameters in two men. *Ann Clin Biochem* 2008;45:106–110.
20. Resnick LM, Muller FB, Laragh JH. Calcium-regulating hormones in essential hypertension. Relation to plasma renin activity and sodium metabolism. *Ann Intern Med* 1986;105:649–654.
21. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002;110:229–238.
22. Krause R, Buhning M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet* 1998;352:709–710.
23. Burgess ED, Hawkins RG, Watanabe M. Interaction of 1,25-dihydroxyvitamin D and plasma renin activity in high renin essential hypertension. *Am J Hypertens* 1990;3:903–905.
24. Tarcin O, Yavuz DG, Ozben B, Telli A, Ogunc AV, Yuksel M, Toprak A, Yazici D, Sancak S, Deyneli O, Akalin S. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. *J Clin Endocrinol Metab* 2009;94:4023–4030.
25. Duprez D, de Buyzere M, de Backer T, Clement D. Relationship between vitamin D₃ and the peripheral circulation in moderate arterial primary hypertension. *Blood Press* 1994;3:389–393.
26. Kristal-Boneh E, Froom P, Harari G, Ribak J. Association of calcitriol and blood pressure in normotensive men. *Hypertension* 1997;30:1289–1294.

27. Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxycholecalciferol concentration in newly detected hypertension. *Am J Hypertens* 1995;8:429–432.
28. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens* 2007;20:713–719.
29. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with type 2 diabetes mellitus and low vitamin D levels. *Diabet Med* 2008;25:320–325.
30. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001;86:1633–1637.
31. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. *J Hypertens* 2009;27:1948–1954.
32. Melamed ML, Muntner P, Michos ED, Uribarri J, Weber C, Sharma J, Raggi P. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. *Arterioscler Thromb Vasc Biol* 2008;28:1179–1185.
33. Targher G, Bertolini L, Padovani R, Zenari L, Scala L, Cigolini M, Arcaro G. Serum 25-hydroxyvitamin D₃ concentrations and carotid artery intima-media thickness among type 2 diabetic patients. *Clin Endocrinol (Oxf)* 2006;65:593–597.
34. Reis JP, Michos ED, von Muhlen D, Miller ER III. Differences in vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease. *Am J Clin Nutr* 2008;88:1469–1477.
35. Fahrleitner A, Dobnig H, Obernosterer A, Pilger E, Leb G, Weber K, Kudlacek S, Obermayer-Pietsch BM. Vitamin D deficiency and secondary hyperparathyroidism are common complications in patients with peripheral arterial disease. *J Gen Intern Med* 2002;17:663–669.
36. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007;92:2017–2029.
37. Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE, Hewison M. Expression of 25-hydroxyvitamin D₃-1 α -hydroxylase in pancreatic islets. *J Steroid Biochem Mol Biol* 2004;89–90:121–125.
38. Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG. Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. *FASEB J* 2003;17:509–511.
39. Bourlon PM, Faure-Dussert A, Billaud B. The de novo synthesis of numerous proteins is decreased during vitamin D₃ deficiency and is gradually restored by 1, 25-dihydroxyvitamin D₃ repletion in the islets of Langerhans of rats. *J Endocrinol* 1999;162:101–109.
40. Maestro B, Campion J, Davila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D₃ of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. *Endocr J* 2000;47:383–391.
41. Karvonen M, Janti V, Muntoni S, Stabilini M, Stabilini L, Tuomilehto J. Comparison of the seasonal pattern in the clinical onset of IDDM in Finland and Sardinia. *Diabetes Care* 1998;21:1101–1109.
42. Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. *Diabetologia* 2008;51:1391–1398.
43. The EURODIAB Substudy 2 Study Group. Vitamin D supplement in early childhood and risk for Type I (insulin-dependent) diabetes mellitus. *Diabetologia* 1999;42:51–54.
44. Ishii H, Suzuki H, Baba T, Nakamura K, Watanabe T. Seasonal variation of glycemic control in type 2 diabetic patients. *Diabetes Care* 2001;24:1503.
45. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D₃ on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int J Clin Pract* 2003;57:258–261.
46. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr* 2004;79:820–825.
47. Schwalfenberg G. Vitamin D and diabetes: improvement of glycemic control with vitamin D₃ repletion. *Can Fam Physician* 2008;54:864–866.
48. Martini LA, Wood RJ. Vitamin D status and the metabolic syndrome. *Nutr Rev* 2006;64:479–486.
49. Fliser D, Stefanski A, Franek E, Fode P, Gudarzi A, Ritz E. No effect of calcitriol on insulin-mediated glucose uptake in healthy subjects. *Eur J Clin Invest* 1997;27:629–633.
50. Tai K, Need AG, Horowitz M, Chapman IM. Glucose tolerance and vitamin D: effects of treating vitamin D deficiency. *Nutrition* 2008;24:950–956.
51. Dilmec F, Uzer E, Akkafa F, Kose E, van Kuilenburg AB. Detection of VDR gene ApaI and TaqI polymorphisms in patients with type 2 diabetes mellitus using PCR-RFLP method in a Turkish population. *J Diabetes Complications* 2009;24:186–191.
52. Malecki MT, Frey J, Moczulski D, Klupa T, Kozek E, Sieradzki J. Vitamin D receptor gene polymorphisms and association with type 2 diabetes mellitus in a Polish population. *Exp Clin Endocrinol Diabetes* 2003;111:505–509.
53. Bid HK, Konwar R, Aggarwal CG, Gautam S, Saxena M, Nayak VL, Banerjee M. Vitamin D receptor (FokI, BsmI and TaqI) gene polymorphisms and type 2 diabetes mellitus: a North Indian study. *Indian J Med Sci* 2009;63:187–194.
54. Danescu LG, Levy S, Levy J. Vitamin D and diabetes mellitus. *Endocrine* 2009;35:11–17.
55. Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. *Am J Hypertens* 1995;8:894–901.
56. Heikkinen AM, Tuppurainen MT, Niskanen L, Komulainen M, Penttila I, Saarikoski S. Long-term vitamin D₃ supplementation may have adverse effects on serum lipids during postmenopausal hormone replacement therapy. *Eur J Endocrinol* 1997;137:495–502.
57. Montagnani M, Lore F, Di Cairano G, Gonnelli S, Ciouli C, Montagnani A, Gennari C. Effects of pravastatin treatment on vitamin D metabolites. *Clin Ther* 1994;16:824–829.
58. Perez-Castrillon JL, Vega G, Abad L, Sanz A, Chaves J, Hernandez G, Duenas A. Effects of atorvastatin on vitamin D levels in patients with acute ischemic heart disease. *Am J Cardiol* 2007;99:903–905.
59. Wilczek H, Sobra J, Ceska R, Justova V, Juzova Z, Prochazkova R, Kvasilova M. Monitoring plasma levels of vitamin D metabolites in simvastatin (Zocor) therapy in patients with familial hypercholesterolemia [article in Czech]. *Cas Lek Cesk* 1994;133:727–729.
60. Yavuz B, Ertugrul DT, Cil H, Ata N, Akin KO, Yalcin AA, Kucukazman M, Dal K, Hokkaomeroglu MS, Yavuz BB, Tutal E. Increased levels of 25 hydroxyvitamin D and 1,25-dihydroxyvitamin D after rosuvastatin treatment: a novel pleiotropic effect of statins? *Cardiovasc Drugs Ther* 2009;23:295–299.
61. Guryev O, Carvalho RA, Usanov S, Gilep A, Estabrook RW. A pathway for the metabolism of vitamin D₃: unique hydroxylated metabolites formed during catalysis with cytochrome P450_{sc} (CYP11A1). *Proc Natl Acad Sci U S A* 2003;100:14754–14759.
62. Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, Proctor BM, Petty M, Chen Z, Schechtman KB, Bernal-Mizrachi L, Bernal-Mizrachi C. 1,25(OH)₂ vitamin d inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation* 2009;120:687–698.
63. Zittermann A, Fischer J, Schleithoff SS, Tenderich G, Fuchs U, Koerfer R. Patients with congestive heart failure and healthy controls differ in vitamin D-associated lifestyle factors. *Int J Vitam Nutr Res* 2007;77:280–288.
64. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL. Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation* 1997;96:1755–1760.
65. Fleck A. Latitude and ischaemic heart disease. *Lancet* 1989;1:613.
66. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 2009;205:255–260.
67. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008;168:1629–1637.
68. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007;72:1004–1013.

69. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008;168:1174–1180.
70. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503–511.
71. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, Marz W. Low vitamin D levels predict stroke in patients referred to coronary angiography. *Stroke* 2008;39:2611–2613.
72. Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, Boehm BO, Dobnig H. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab* 2008;93:3927–3935.
73. LaCroix AZ, Kotchen J, Anderson G, Brzyski R, Cauley JA, Cummings SR, Gass M, Johnson KC, Ko M, Larson J, Manson JE, Stefanick ML, Wactawski-Wende J. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2009;64:559–567.
74. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;326:469.
75. Tishkoff DX, Nibelink KA, Holmberg KH, Dandu L, Simpson RU. Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. *Endocrinology* 2008;149:558–564.
76. Weishaar RE, Kim SN, Saunders DE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. *Am J Physiol* 1990;258:E134–E142.
77. Szabó B, Merkely B, Takács I. The role of vitamin D in the development of cardiac failure [article in Hungarian]. *Orv Hetil* 2009;150:1397–1402.
78. McGonigle RJ, Fowler MB, Timmis AB, Weston MJ, Parsons V. Uremic cardiomyopathy: potential role of vitamin D and parathyroid hormone. *Nephron* 1984;36:94–100.
79. Shane E, Mancini D, Aaronson K, Silverberg SJ, Seibel MJ, Adesso V, McMahon DJ. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. *Am J Med* 1997;103:197–207.
80. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, Burke GL, Lima JA. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med* 2008;168:2138–2145.
81. Laguardia SP, Dockery BK, Bhattacharya SK, Nelson MD, Carbone LD, Weber KT. Secondary hyperparathyroidism and hypovitaminosis D in African-Americans with decompensated heart failure. *Am J Med Sci* 2006;332:112–118.
82. Coughlin SS, Myers L, Michaels RK. What explains black-white differences in survival in idiopathic dilated cardiomyopathy? The Washington, DC, Dilated Cardiomyopathy Study. *J Natl Med Assoc* 1997;89:277–282.
83. Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. *N Engl J Med* 1999;340:609–616.
84. Vaccarino V, Gahbauer E, Kasl SV, Charpentier PA, Acampora D, Krumholz HM. Differences between African Americans and whites in the outcome of heart failure: Evidence for a greater functional decline in African Americans. *Am Heart J* 2002;143:1058–1067.
85. Reusser ME, DiRienzo DB, Miller GD, McCarron DA. Adequate nutrient intake can reduce cardiovascular disease risk in African Americans. *J Natl Med Assoc* 2003;95:188–195.
86. Hagstrom E, Hellman P, Larsson TE, Ingelsson E, Berglund L, Sundstrom J, Melhus H, Held L, Lind L, Michaelsson K, Arnlov J. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. *Circulation* 2009;119:2765–2771.
87. Luboshitzky R, Chertok-Schaham Y, Lavi I, Ishay A. Cardiovascular risk factors in primary hyperparathyroidism. *J Endocrinol Invest* 2009;32:317–321.
88. Yu N, T PD, Flynn Robert WV, Michael JM, Smith D, Rudman A, Graham PL. Increased mortality and morbidity in mild primary hyperparathyroid patients. *Clin Endocrinol (Oxf)*. In press.
89. Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. *J Clin Invest* 1985;76:370–373.
90. Alsafwah S, Laguardia SP, Nelson MD, Battin DL, Newman KP, Carbone LD, Weber KT. Hypovitaminosis D in African Americans residing in Memphis, Tennessee with and without heart failure. *Am J Med Sci* 2008;335:292–297.
91. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Dougherty C, Gunter EW, Bowman BA. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 2002;76:187–192.
92. Wolf M, Betancourt J, Chang Y, Shah A, Teng M, Tamez H, Gutierrez O, Camargo CA Jr, Melamed M, Norris K, Stampfer MJ, Powe NR, Thadhani R. Impact of activated vitamin D and race on survival among hemodialysis patients. *J Am Soc Nephrol* 2008;19:1379–1388.
93. Zittermann A, Schleithoff SS, Gotting C, Dronow O, Fuchs U, Kuhn J, Kleesiek K, Tenderich G, Koerfer R. Poor outcome in end-stage heart failure patients with low circulating calcitriol levels. *Eur J Heart Fail* 2008;10:321–327.
94. Testa A, Mallamaci F, Benedetto F, Pisano A, Tripepi G, Malatino L, Thadhani R, Zoccali C. Vitamin D receptor (VDR) gene polymorphism is associated with left ventricular (LV) mass and predicts LVH progression in end stage renal disease (ESRD) patients. *J Bone Miner Res* 2009;25:313–319.
95. Park CW, Oh YS, Shin YS, Kim CM, Kim YS, Kim SY, Choi EJ, Chang YS, Bang BK. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 1999;33:73–81.
96. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2006;83:754–759.
97. Chavan CB, Sharada K, Rao HB, Narsimhan C. Hypocalcemia as a cause of reversible cardiomyopathy with ventricular tachycardia. *Ann Intern Med* 2007;146:541–542.
98. Vintzileos AM, Neckles S, Campbell WA, Andreoli JW Jr, Kaplan BM, Nochimson DJ. Three fetal ponderal indexes in normal pregnancy. *Obstet Gynecol* 1985;65:807–811.
99. Sood S, Reghunandan R, Reghunandan V, Gopinathan K, Sood AK. Effect of vitamin D deficiency on electrocardiogram of rats. *Indian J Exp Biol* 1995;33:61–63.
100. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007;167:1730–1737.