Hypovitaminosis D and Valvular Calcification in Patients With Dilated Cardiomyopathy

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Abstract: *Background:* In patients with dilated (idiopathic) cardiomyopathy (DCM), little is known about the presence of valvular calcification and its association with hypovitaminosis D, which may predispose affected tissues to calcification. Our objectives were 2-fold: to conduct a retrospective assessment of echocardiographic evidence of valvular calcification in patients with DCM who were known to have hypovitaminosis D (25(OH)D <30 ng/mL) and to conduct a prospective assessment of serum 25(OH)D in patients with DCM, who had demonstrated echocardiographic evidence of valvular calcification. *Methods:* The retrospective study consisted of 48 African American patients (34 men, 14 women; 52.3 ± 1.5 years) having DCM and ejection fraction <35% with serum creatinine <2.0 mg/dL and 25(OH)D <30 ng/mL; and 20 white patients in the prospective study (20 men; 71.0 ± 3.0 years) having DCM and ejection fraction <35% with serum creatinine <2.0 mg/dL and echocardiographic evidence of valvular calcification. In the retrospective study, a transthoracic echocardiogram was obtained to address mitral valvular and annular calcification, aortic valvular calcification, and sinotubular calcification; whereas in the prospective study, serum 25(OH)D level was monitored in patients with known valvular calcification. Serum parathyroid hormone (PTH) was monitored in both studies. *Results:* In the retrospective study, hypovitaminosis D was found in 19 patients (31%) with valvular calcification and in whom serum PTH was increased (83 ± 8 pg/mL). In the prospective study, 15 of 20 elderly patients (80%) with known DCM and valvular calcification were found to have hypovitaminosis D (25(OH)D <30 ng/mL), whereas serum PTH was normal (43 ± 4 pg/mL). *Conclusions:* In patients with DCM without marked renal dysfunction, valvular calcification was seen more frequently and associated with hypovitaminosis D, whereas in elderly patients with valvular calcification, hypovitaminosis D is common, suggesting that the duration of vitamin D deficiency may determine the extent of valvular calcification. The role of hypovitaminosis D in the appearance of valvular calcification deserves further study.

Key Indexing Terms: Hypovitaminosis D; Valvular calcification; Dilated cardiomyopathy; Echocardiography. **[Am J Med Sci 2009; 337(5):312–316.]**

The prevalence of vitamin D deficiency (ie, hypovitaminosis D) is relatively high in the United States and worldwide.[1] Levels of the principal storage form of vitamin D, 25-hydroxyvitamin D (25(OH)D), are low in up to one half of otherwise healthy adults.[2,3] The causes of hypovitaminosis D are multifactorial and most importantly include inadequate exposure to sunlight.

The vital role of calcium and vitamin D in the maintenance of skeletal health has been well established. There is cumulative evidence that vitamin D has extraosseous manifestations. Clinical studies have demonstrated multiple associations between hypovitaminosis D and plasma renin activity, blood pressure, and calcification involving the coronaries and other vascular beds.[4] Furthermore, ecological studies have revealed an increased incidence of hypertension and cardiovascular disease as the latitude from the equator rises, a phenomenon attributed to a higher prevalence of vitamin D deficiency in regions with less sunlight exposure.[4]

Even though vitamin D is most recognized for its effects on the skeletal system, vitamin D receptors have demonstrated versatility in their expression in various tissues, including the endothelium, vascular smooth muscle cells, and cardiomyocytes.[5] *In vitro*, activated 1,25-dihydroxyvitamin D (1,25-$(OH)D_2$) regulates the growth of vascular smooth muscle cells and cardiomyocytes, directly suppresses renin gene expression, and inhibits cytokine release from lymphocytes.[4] Of particular clinical relevance, the principal biologic effect of vascular smooth muscle cells is the production of inhibitors of calcification.[5] These roles reflect the variability and versatility of vitamin D on the cardiovascular system.

Vascular calcification occurs in patients with atherosclerosis, ischemic cardiomyopathy, osteoporosis, and chronic kidney disease. In each of these conditions, vascular calcification is independently associated with increased cardiovascular risk.[5] In the general population, presence of vascular calcification carries a poor 5-year prognosis.[6] It has been suggested that valvular calcification may be another potential manifestation of hypovitaminosis D.[7] Similarities have been shown between vascular atherosclerosis and chronic degenerative changes in the aortic and mitral valves.[8,9] Related to atherosclerosis, the initiating event for valvular disease is thought to be injury or endothelial dysfunction.[10] Boon et al[11] found an association of both mitral and annular calcification, as well as aortic valvular calcification with age and vascular risk factors. Age, female sex, diabetes mellitus, hypertension, and hypercholesterolemia were strongly associated with mitral and aortic valvular calcification, with odds ratios between 2.2 and 2.8.[11] Little is known regarding the relationship between hypovitaminosis D and valvular calcification in patients with dilated cardiomyopathy (DCM).

The aforementioned clinical and experimental findings led us to hypothesize that DCM, valvular calcification, and hypovitaminosis D must be correlated. Our objectives were 2-fold: (1) to conduct a retrospective assessment of echocardiographic evidence of valvular calcification in patients with

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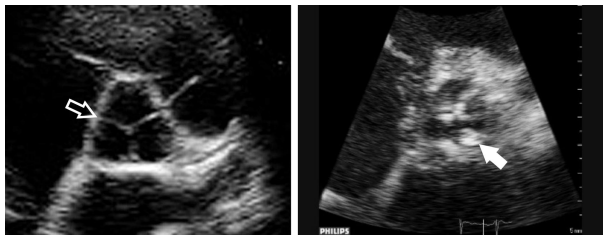

FIGURE 1. Parasternal short-axis view on a transthoracic echocardiogram showing a normal appearing aortic valve with clearly defined leaflets (open arrow) and calcification in the margins of aortic valve leaflets with lack of crisp definition (solid arrow).

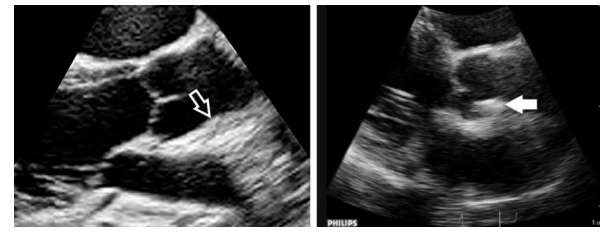

FIGURE 3. Parasternal long-axis view on a transthoracic echocardiogram showing normal appearing aortic root and sinotubular junction (open arrow) and calcification of the sinotubular junction (solid arrow).

DCM and who were known to have hypovitaminosis D (defined as 25(OH)D <30 ng/mL) and (2) to conduct a prospective assessment of serum 25(OH)D in patients with DCM who had known echocardiographic evidence of valvular calcification.

METHODS

Data were collected both retrospectively and prospectively. The patient populations included in this study, approved by the respective institutional review boards at the University of Tennessee Health Science Center and Veterans Affairs Medical Center, consisted of 48 patients in the retrospective study and 20 patients in the prospective study.

Retrospective Study

The 48 patients (34 men, 14 women; 52.3 ± 1.5 years) in the retrospective study were inpatients and outpatients treated by the Cardiology Service at the Regional Medical Center in Memphis, TN. Demographic and clinical data were obtained from the patients' records. Each of these patients had DCM with an ejection fraction (EF) <35%, serum creatinine <2.0 mg/dL, and clinically established hypovitaminosis D (defined as a serum 25(OH)D level <30 ng/mL). Three experienced echocardiologists interpreted the echocardiograms for evidence of valvular calcification. Valvular calcification (see Figures 1–3) was defined by the presence of echodense calcium on the mitral valve or annulus, on the aortic valve or annulus, or in the sinotubular junction as previously reported.[12] No tricuspid or pulmonary valvular or annular calcification was documented. All of these patients were African American and none were obese.

Prospective Study

The 20 patients (20 men; 71.0 ± 3.0 years) in the prospective study were inpatients and outpatients at the Veterans Affairs Hospital in Memphis, TN, who had DCM and echocardiographic evidence of valvular calcification. The aforementioned definition for the echocardiographic presence of calcification was also pertinent to this study. Serum 25(OH)D levels were subsequently obtained in these patients. Patients in this group were all men and predominantly white. All patients had a serum creatinine <2.0 mg/dL.

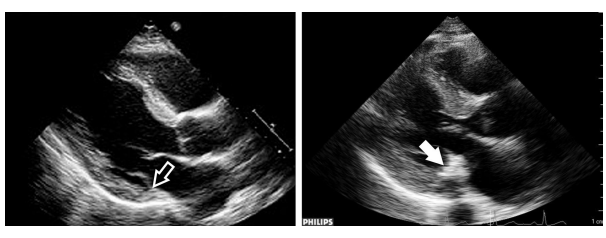

FIGURE 2. Parasternal long-axis view on a transthoracic echocardiogram showing a normal appearing posterior mitral annulus (open arrow) and calcification of the posterior mitral annulus, extending into the base of the posterior mitral leaflet (solid arrow).

Exclusion Criteria

In both groups, none of the patients was receiving therapies that could have altered the hypothalamic-pituitary axis, and consequently parathyroid function and vitamin D levels. None was receiving growth hormone, insulin, thyroxin, estrogen, or a glucocorticoid, and none had any disorder affecting bone metabolism, including rheumatoid arthritis, osteomalacia, primary hyperparathyroidism, Paget disease, hyperthyroidism, osteogenesis imperfecta, gastric resection, inflammatory bowel disease, or a history of fragility fractures.

We did not adjust for comorbid states, such as hyperlipidemia, diabetes mellitus, or hypertension. Furthermore, no adjustments were made for body mass index, cigarette smoking, or specific medical or pharmacologic treatments.

The lowest recordable 25(OH)D level, below the limits of detection, was <7.0 ng/mL for both groups. For calculation purposes, in those patients in whom a level of <7.0 ng/mL was obtained, a value of 6.9 ng/mL was used. Serum parathyroid hormone (PTH) was monitored by standard methodology.

RESULTS

Retrospective Study

The retrospective study consisted of 48 younger patients (52.3 ± 1.5 years) with DCM and hypovitaminosis D. In this population of middle-aged African Americans, we would not implicate senescent skin and its reduced efficiency in generating vitamin D. Nineteen (31%) patients were found to have valvular calcification of whom 9 had calcification involving the aortic valve or annulus, 8 had calcification of the mitral valve or annulus, and 4 had calcification localized to the sinotubular ridge. Of the 19 patients with echocardiographic calcification, 2 patients had calcification involving both the aortic and mitral valves.

Ninety-six percent of patients had hypovitaminosis D as defined by a 25(OH) vitamin D level <30 ng/mL. The average 25(OH)D for the entire group was 13.2 ng/mL (range <7–54.1). There was no 25(OH)D data available on 12 patients—5 patients with calcification versus 7 patients without calcification. The mean 25(OH)D level in patients with calcification was 11.7 ng/mL versus 23.6 ng/mL in those without calcification. Two patients had a 25(OH)D level >30 ng/mL (mean 42.5). Neither of those patients had any echocardiographic