

Vitamin D Deficiency and Supplementation and Relation to Cardiovascular Health

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Recent evidence supports an association between vitamin D deficiency and hypertension, peripheral vascular disease, diabetes mellitus, metabolic syndrome, coronary artery disease, and heart failure. The effect of vitamin D supplementation, however, has not been well studied. We examined the associations between vitamin D deficiency, vitamin D supplementation, and patient outcomes in a large cohort. Serum vitamin D measurements for 5 years and 8 months from a large academic institution were matched to patient demographic, physiologic, and disease variables. The vitamin D levels were analyzed as a continuous variable and as normal (≥ 30 ng/ml) or deficient (< 30 ng/ml). Descriptive statistics, univariate analysis, multivariate analysis, survival analysis, and Cox proportional hazard modeling were performed. Of 10,899 patients, the mean age was 58 ± 15 years, 71% were women ($n = 7,758$), and the average body mass index was 30 ± 8 kg/m². The mean serum vitamin D level was 24.1 ± 13.6 ng/ml. Of the 10,899 patients, 3,294 (29.7%) were in the normal vitamin D range and 7,665 (70.3%) were deficient. Vitamin D deficiency was associated with several cardiovascular-related diseases, including hypertension, coronary artery disease, cardiomyopathy, and diabetes (all $p < 0.05$). Vitamin D deficiency was a strong independent predictor of all-cause death (odds ratios 2.64, 95% confidence interval 1.901 to 3.662, $p < 0.0001$) after adjusting for multiple clinical variables. Vitamin D supplementation conferred substantial survival benefit (odds ratio for death 0.39, 95% confidence interval 0.277 to 0.534, $p < 0.0001$). In conclusion, vitamin D deficiency was associated with a significant risk of cardiovascular disease and reduced survival. Vitamin D supplementation was significantly associated with better survival, specifically in patients with documented deficiency. © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;xx:xxx)

Cardiovascular disease is the most common cause of mortality and morbidity, accounting for nearly 30% of deaths in 2003 worldwide. Although multiple risk factors for coronary artery disease are well established, novel risk factors continue to emerge, in accordance with the findings from various epidemiologic studies. In particular, a growing body of evidence has identified vitamin D deficiency as a potential widespread risk factor for cardiovascular disease.^{1–11} In addition to its well-defined role in bone and calcium metabolism, vitamin D has been identified as an important factor in cardiovascular health. Recent evidence supports an association of vitamin D deficiency with hypertension, peripheral vascular disease, diabetes mellitus, the metabolic syndrome, coronary artery disease, and heart failure. The Third National Health and Nutrition Examination Survey reported the prevalence of vitamin D deficiency in the United States to be 25% to 57% of adults.¹² Similar studies have shown that a prevalence of vitamin D deficiency of 30% to 50% in the general population.^{3,13,14} Although epidemiologic evidence for an association be-

tween vitamin D deficiency and several cardiovascular diseases is strong, the effect of vitamin D supplementation on patient outcomes is largely unknown. We studied the association of vitamin D deficiency and cardiovascular morbidity and mortality, as well as the effect of supplementation on survival.

Methods

This was an observational retrospective study using a cohort of patients followed up by a cardiovascular practice at a large academic medical center. Patients seen by the service from January 1, 2004 and October 8, 2009 with documented serum vitamin D levels were eligible for the present study.

Serum vitamin D measurements were performed by the clinical laboratory at the University of Kansas Hospital, Kansas City, Kansas. The laboratory uses the DiaSorin (Stillwater, Minnesota) chemiluminescence immunoassay method to measure the total serum vitamin D (both 25-hydroxyvitamin D₂ and D₃ forms of vitamin D). The laboratory assay did not change during the study period. The optimal concentration of 25[OH] vitamin D was defined as ≥ 30 ng/ml and vitamin D deficiency as a 25[OH]D level of < 30 ng/ml.

The abstracted patient data included demographics, medical history, medications (including statins, vitamin D supplementation, and aspirin), and physiologic and disease state variables obtained from the electronic cardiovascular

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Table 1
Baseline characteristics

Variable	Vitamin D Deficient		p Value
	No (n = 3,234)	Yes (n = 7,665)	
Age (years)	60 ± 15	58 ± 15	<0.0001
Women	2,503 (77%)	5,255 (69%)	<0.0001
Body mass index (kg/m ²)	28 ± 7	31 ± 8	<0.0001
Coronary artery disease (>70% stenosis of ≥1 coronary artery)	306 (9%)	830 (11%)	0.03
Cardiomyopathy (clinical diagnosis of dilated, hypertrophic or restrictive myocardial disease)	95 (3%)	288 (4%)	0.03
Hypertension (blood pressure >140/90 mm Hg)	938 (29%)	2,795 (36%)	<0.0001
Diabetes mellitus	294 (9%)	1,436 (19%)	<0.0001
Valvular heart disease (stenosis or regurgitation greater than moderate or valve replacement)	181 (6%)	487 (6%)	NS
Atrial fibrillation	201 (6%)	398 (5%)	0.03
Ejection fraction (%)	58 ± 10	57 ± 10	NS
Aspirin use	997 (31%)	2,254 (29%)	NS
Angiotensin-converting enzyme inhibitor use	725 (22%)	2,089 (27%)	<0.0001
Statin use	1,098 (34%)	2,611 (34%)	NS
Calcium (mg/dl)	9.17 ± 0.59	9.31 ± 0.49	<0.0001
Creatinine (mg/dl)	1.38 ± 0.29	1.58 ± 0.28	NS
Total cholesterol (mg/dl)	166 ± 43	171 ± 54	0.02
High-density lipoprotein cholesterol (mg/dl)	52 ± 18	47 ± 16	<0.0001
Low-density lipoprotein cholesterol (mg/dl)	92 ± 33	97 ± 39	0.002
Triglycerides (mg/dl)	115 ± 80	140 ± 126	<0.0001
Vitamin D (ng/ml)	40 ± 11	17 ± 7	<0.0001
Vitamin D supplement use	689 (21%)	2,423 (32%)	<0.0001
Vitamin supplement (any)	1,097 (34%)	2,992 (39%)	<0.0001
Death	43 (1%)	293 (4%)	<0.0001

All data are expressed as mean ± standard deviation.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant at p = 0.05 level.

database at the medical center. The diagnoses were derived from the patient problem list documented in the patients' electronic medical record and using the *International Classification of Diseases, 9th Revision* codes. Vitamin D supplementation was defined as an active prescription for vitamin D or its analogs or patient-reported use of vitamin D supplements. Not all doses of vitamin D were reported; however, the usual reported doses ranged from 1,000 IU/day to 50,000 IU biweekly (sample mean 2254 ± 316 IU). The use of multivitamins was not considered vitamin D supplementation. All-cause mortality data were obtained from the Social Security Death Index.

Statistics were performed using SAS, version 9.1.3 software (SAS Institute, Cary, North Carolina). The serum

Table 2
Univariate analysis: odds ratio of death and major cardiovascular events if vitamin D deficient

Event	OR	95% CI	p Value
Death	2.95	2.135–4.073	<0.001
Coronary artery disease	1.16	1.012–1.334	0.03
Atrial fibrillation	0.83	0.693–0.984	0.03
Diabetes mellitus	2.31	2.018–2.633	<0.001
Cardiomyopathy	1.29	1.019–1.633	0.03
Hypertension	1.40	1.285–1.536	<0.0001

CI = confidence interval; OR = odds ratio.

Table 3
Logistic regression analysis for death as dependent variable

Predictor	OR	95% CI	p Value
Coronary artery disease	2.71	2.062–3.573	<0.0001
Vitamin D deficiency	2.64	1.901–3.662	<0.0001
Diabetes mellitus	1.45	1.114–1.891	0.006
Cardiomyopathy	3.29	2.359–4.596	<0.0001
Hypertension	1.53	1.183–1.969	0.001

Abbreviations as in Table 2.

vitamin D levels were analyzed as both a continuous variable and a dichotomous variable (normal [≥ 30 ng/ml] vs deficient [< 30 ng/ml]). Most analyses were done with vitamin D deficiency as a dichotomous variable, except as noted. However, repeating the analyses with continuous vitamin D levels did not change the outcomes. Descriptive statistics, univariate analysis (unpaired *t* tests for continuous variables, chi-square analysis for categorical variables), multivariate logistic regression analysis for odds ratios (OR) and 95% confidence intervals (CIs), survival analysis, and Cox proportional hazard modeling were performed. Interaction between vitamin D deficiency and supplementation was studied by development of an interaction variable for retesting the outcomes models, with confirmation using the Wald statistic and likelihood ratio test and proportionality testing. A 0.05 level of significance was used throughout.

Results

During the study period, a total of 24,895 samples from 14,261 unique patients were tested for vitamin D concentrations in the University of Kansas Hospital laboratory. The lowest recorded value for patients with multiple measurements was used for analysis. Database query yielded information for 11,017 matching patients. After excluding patients who were <18 years old, 10,899 patients were available for analysis.

The baseline characteristics for the patients with and without vitamin D deficiency are listed in Table 1. The cohort's mean age was 58.3 ± 14.9 years, 71% were women (n = 7,758), and the mean body mass index (BMI) was 29.9 ± 7.7 kg/m². The mean left ventricular ejection fraction (by echocardiogram) was 57 ± 10%. The mean and median serum vitamin D value was 24.1 ± 13.6 ng/ml and 22.5 ng/ml, respectively. A total of 3,234 patients (29.7%) were in the predefined normal range for vitamin D (≥ 30 ng/ml) and 7,665 (70.3%) patients were deficient (< 30 ng/ml).

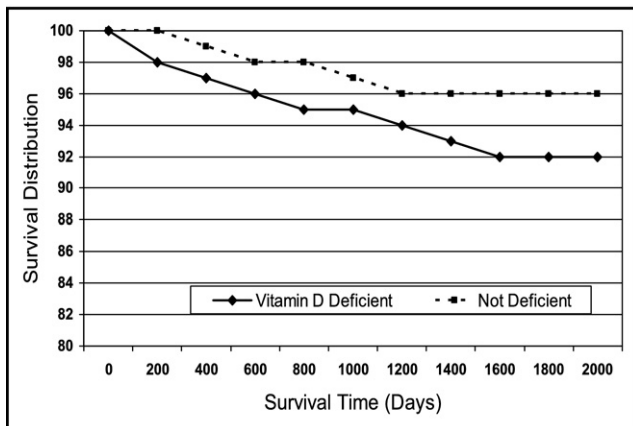


Figure 1. Survival in vitamin D deficient versus not deficient subjects.

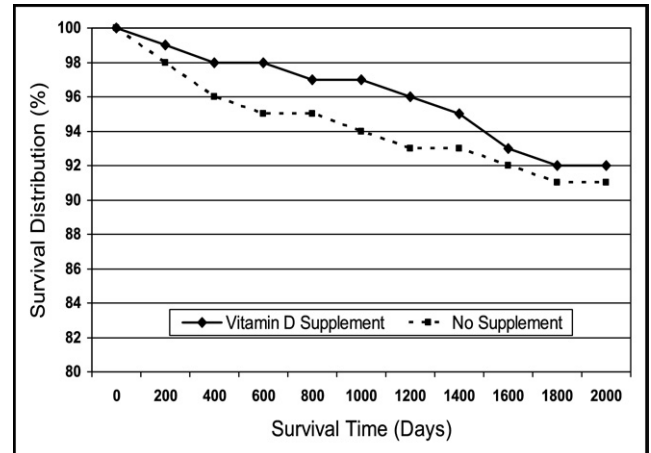


Figure 2. Survival stratified by vitamin D supplementation in deficient subjects.

Table 4

Logistic regression analysis for death as dependent variable with vitamin D supplementation added

Predictor	OR	95% CI	p Value
Coronary artery disease	2.45	1.852–3.245	<0.0001
Diabetes mellitus	1.67	1.281–2.172	0.0001
Cardiomyopathy	3.09	2.189–4.355	<0.0001
Hypertension	1.62	1.249–2.091	0.0003
Vitamin D supplement	0.44	0.335–0.589	<0.0001
Atrial fibrillation	2.13	1.543–2.929	<0.0001

Abbreviations as in Table 2.

On univariate analysis, vitamin D deficiency as a dichotomous variable was significantly associated with an increased risk of several cardiovascular disease states, including coronary artery disease (OR 1.16, 95% CI 1.012 to 1.334), diabetes (OR 2.31, 95% CI 2.018 to 2.633), cardiomyopathy (OR 1.29, 95% CI 1.019 to 1.633), and hypertension (OR 1.40, 95% CI 1.285 to 1.536) and all-cause death (OR 2.95, 95% CI 2.135 to 4.073). In contrast, vitamin D deficiency was negatively associated with the risk of atrial fibrillation (OR 0.83, 95% CI 0.693 to 0.984; Table 2). On stepwise multivariate logistic regression analysis, vitamin D deficiency (dichotomous variable) was a strong independent predictor of all-cause death (OR 2.64, 95% CI 1.901 to 3.662, $p < 0.0001$; Table 3).

Survival was calculated using the interval between the date of sample collection and the date of death or the end of study period. The survival curve is shown in Figure 1 ($p < 0.0001$ for homogeneity of strata). Hazard ratios using the Cox proportional hazards model were calculated, with vitamin D deficiency as a dichotomous variable showing a hazards ratio of 2.48 ($p < 0.0001$) for reduced survival. Hazard function analysis with additional predictive variables (disease states, age, BMI, ejection fraction, gender) was then performed with overall $p < 0.0001$; vitamin D deficiency remaining a significant independent predictor of decreased survival. Vitamin D deficiency remained the variable with the highest OR (2.29).

Vitamin D supplementation improved survival overall but to a significant degree only in deficient patients. On univariate analysis, the overall risk of all-cause death was reduced for subjects taking vitamin D supplements with an

OR of 0.62 (95% CI 0.469 to 0.806, $p = 0.0004$). On stepwise regression analysis for death, the OR for vitamin D supplementation was 0.44 ($p < 0.0001$; Table 4), suggesting an association with a significantly lower occurrence of death. In a hazard model, the hazard ratio for death was 0.40 (95% CI 0.335 to 0.576) for subjects receiving supplementation ($p < 0.0001$). This strong relation persisted in additional models with the clinical variables added.

The use of vitamin D supplementation was more common in vitamin D-deficient patients, with 31.6% of deficient patients receiving supplements versus 21.3% of patients with normal vitamin D levels (OR 1.71, $p < 0.0001$). The effect of vitamin D supplementation was studied using death versus vitamin D deficiency, stratified by vitamin D supplementation. Vitamin D deficiency and supplementation were highly associated. With supplementation, the OR for death in the vitamin D-deficient subjects was 1.46 (95% CI 0.760 to 2.799; $p = \text{NS}$). Without supplementation, the OR for death was 3.72 (95% CI 2.563 to 5.396; $p < 0.0001$). Controlling for vitamin D supplementation, the common OR for death in the deficient subjects was 3.07 (95% CI 2.222 to 4.228; $p < 0.0001$; Cochran-Mantel-Haenszel analysis). The Breslow-Day test for homogeneity of the ORs was significant ($p = 0.01$). An indication was found for an important interaction between vitamin D deficiency and supplementation when the interaction variable was added to the models, with significant differences in survival seen only for the vitamin D-deficient patients ($p < 0.0001$) on repeat separate modeling stratified by deficiency (Figure 2). Nondeficient subjects had no survival advantage with vitamin D supplementation.

Linear regression analysis with vitamin D levels as a continuous variable showed a highly significant negative association ($\beta -0.3134$, $p < 0.0001$) with BMI, indicating a greater BMI was associated with lower vitamin D levels. Similarly, the association between vitamin D levels and low-density lipoprotein cholesterol showed a significant negative association ($\beta -0.1956$, $p = 0.0005$), and high-density lipoprotein cholesterol had a significant positive association ($\beta 0.1734$, $p < 0.0001$). The vitamin D levels were associated with the triglyceride measurements (β

–1.126, $p < 0.0001$); for every 1-U increase in vitamin D, the triglyceride levels decreased by >1 U.

Discussion

Vitamin D has important physiologic functions beyond bone and calcium metabolism. Because vitamin D receptors are involved in the expression of nearly 3,000 human genes, a deficiency could potentially affect numerous disease processes.¹⁵ Cardiovascular, oncologic, and immunologic disorders have been associated with vitamin D deficiency. Our study showed an association between vitamin D deficiency and many cardiovascular disease states, including hypertension,^{16–19} coronary artery disease,^{7,20,21} cardiomyopathy,²⁰ and cardiovascular risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia.

Numerous studies and meta-analyses have suggested that vitamin D deficiency has a negative association with survival; however, the effect of vitamin D supplementation on overall mortality has not been studied. Our findings are consistent with these previous studies, suggesting poorer patient outcomes for patients with vitamin D deficiency.^{22–24} In addition, our data further extend these findings by demonstrating better survival with vitamin D supplementation. The benefits of vitamin D supplementation on survival were significant for those patients with a documented deficiency. This benefit was independent of the concomitant use of other cardioprotective drugs such as aspirin or statins.

These findings could have clinical implications for the usual recommended daily allowance for vitamin D. The regular intake of the recommended 400 IU/day might be adequate to avoid deficiency in many people,¹ and supplementation of $\geq 1,000$ IU/day might be required to achieve optimal levels.

When included in survival and hazard models with several disease states, vitamin D deficiency is a strong independent predictor of all-cause death. Several studies have reported on the association between obesity and low vitamin D levels,^{8–10} which we also observed in our study cohort. Because the prevalence of obesity is increasing in the United States, as well as in many other developed and emerging nations, vitamin D deficiency could be increasingly common in the future. In addition, our study showed an association between vitamin D deficiency and unfavorable serum lipid values.

Because vitamin D deficiency is widespread, strategies directed at population-based supplementation programs could prove beneficial.⁶ To date, however, prospective studies evaluating vitamin D supplementation are few and have not consistently shown benefit. It is possible that the lack of benefit in these studies resulted from suboptimal levels of vitamin D supplementation or other unknown factors. Many previous studies of vitamin D supplementation have used doses of 400 to 800 IU, which might not be adequate to ensure optimal serum levels, with more appropriate daily supplement doses suggested as 1,000 to 2,000 IU.^{6,25} Nevertheless, the growing body of observational data demonstrating relatively high rates of low vitamin D serum levels warrant additional well-designed studies to investigate the relation between vitamin D and cardiovascular health.

Additional investigation with long-term prospective studies of various vitamin D dosage levels in both healthy and diseased populations are indicated to firmly establish the role of vitamin D supplementation on overall outcomes and mortality. Our study suggests a significant association of vitamin D supplement use and improved survival in deficient subjects, supporting the potential benefit of this intervention. Recent guidelines for the evaluation and treatment of vitamin D deficiency have been published that can help the clinician with patient treatment.²⁶

This was a retrospective, observational study with a selected population, introducing possible selection bias. The study population was derived from patients who had had their vitamin D levels measured at a hospital laboratory and who were patients in a cardiovascular practice and included in its electronic medical records. Extrapolation to other populations might not be appropriate. Also, isolated vitamin D measurement might not reflect long-term levels. We made an arbitrary decision to use the lowest vitamin D measurement for analysis because this value was thought to most likely represent the subjects' baseline nonsupplemented level. We were unable to accurately associate the timing of vitamin D measurement and supplement initiation. The dose and duration of vitamin D supplementation were not analyzed, and patient compliance was not measured. Inclusion of vitamin D in multivitamin supplements was not considered.

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