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Is vitamin D deficiency a risk factor for ischemic heart disease in patients with established cardiovascular disease? 10-year follow-up of the Nova Scotia Health Survey

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Recent studies have reported that low serum vitamin D levels are associated with a variety of diseases, including cardiovascular disease and in particular ischemic heart disease (IHD). Possible mechanisms underlying this association include increased inflammation, renin-angiotensin system upregulation, insulin resistance, altered lipid metabolism, and altered vascular smooth muscle growth and function that lead to hypertension, diabetes, dyslipidemia and atherosclerosis.[1][2]

However, few longitudinal studies have explored the association between vitamin D levels and incident IHD. A nested case-control study of male health care professionals found an approximately doubled risk of incident myocardial infarction associated with lower vitamin D levels.[3] Other studies have identified trends between vitamin D levels and incident

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myocardial infarction but no statistically significant associations, [4][5][6] at least in part due to small sample sizes or short follow-up.

The association between vitamin D levels and recurrent IHD has been studied even less frequently. A cohort study among patients referred for coronary angiography for suspected coronary artery disease found a statistically significant association between low vitamin D levels and risk of cardiovascular mortality.[7] A cohort study among patients with a history of IHD found no significant association between vitamin D levels and risk of secondary cardiovascular disease including IHD, ischemic stroke, or other cardiovascular disease.[8] No study has specifically tested the population-based relation between vitamin D levels and ischemic heart disease among patients with prior cardiovascular disease. In the current study, we hypothesized that an inverse association exists between vitamin D level and risk of IHD would be detected in patients with established cardiovascular disease.

We studied a randomly selected, population-based sample of participants in the Canadian Nova Scotia Health Survey 1995 (NSHS95) who underwent plasma vitamin D quantification, consented for linkage of their NSHS95 data and subsequent hospitalization or death data, and had a prior history of cardiovascular disease – IHD, peripheral vascular disease, or stroke. To identify these conditions, the following International Classification of Disease (ICD) codes were included: ICD-9 codes V12.5, V45.81, V49.7x, 250.70, 410-414.xx, 415.05, 430-432, 433-435.xx, 440.xx, 441-442.xx, 443.21, 444.xx, 447.xx, 459.9, 593.81, 707.xx, 785.4; or ICD-10 codes E11.5, E10.5, E13.5, E14.5, G45.xx, L98.4, L97, N28.0, R02, T82.3, Z86.7, Z89.x, Z95.x, 120-125.xx, 160-166.xx, 167.0, 170-174.x, 177.x, 179.2, 199. The design of and data collection for NSHS95 has been described elsewhere. [9]

25-hydroxyvitamin D (25(OH)D) quantification of serum is the established method of determining a patient's vitamin D status.[10] and was measured with the Diasorin radioimmunoassay method (Stillwater, MN). [11]

Data for IHD events during the 10-year period beginning with a subject's baseline NSHS95 interview date were provided by the provincial health care registry (hospitalization data) and Statistics Canada (mortality data, including deaths outside of a hospital). Time to event is days from NSHS enrollment to IHD event.

Cox regression analyses were performed to evaluate the association between vitamin D level and IHD events. Covariates in the analyses included season during which plasma was collected (for vitamin D quantification), age, and cigarette smoking. The analyses were sex-stratified. Diabetes, hypertension, obesity, and cholesterol were not included as covariates because they are hypothesized to be in the causal pathway.

In the NSHS95 database of 1844 patients, 244 subjects met our selection criteria.

25(OH)D level was not transformed given its normal distribution as ascertained during exploratory analysis. 25(OH)D level was divided into three categories for analysis: <15 ng/mL, 15 to <30 ng/mL, and ≥30 ng/mL. The 30 ng/mL cutoff distinguishes between vitamin D sufficiency and insufficiency or deficiency.[12][13] A 25(OH)D level above this cutoff is considered optimal for several health outcomes.[14][15] 25(OH)D levels below this cutoff are associated with elevated parathyroid hormone(PTH) levels, [16] indicating vitamin D insufficiency. Although several different cutoffs have been used to distinguish vitamin D insufficiency and deficiency, 15 ng/mL has been used in multiple studies.[17][3][18]

13 subjects (5.3%) had vitamin D levels of <15 ng/mL, 140 (57.4%) had levels of 15 to <30 ng/mL, and 91 (37.3%) had levels of ≥30 ng/mL. The subjects' characteristics are detailed in Table 1.

114 IHD events occurred during the 10-year follow-up. The figure below show the predicted Cox regression equations for IHD events according to vitamin D level. In men and women combined, levels of <30 ng/mL were associated with a hazard ratio of 1.33 (p=.172) for IHD events compared to levels ≥30 ng/mL. Levels of <15 ng/mL were associated with a hazard ratio of 2.30 (p=.035) for IHD events compared to levels ≥30 ng/mL (see Figures 1a and 1b).

Our study's objective was to expand on the thus far limited literature exploring the association between vitamin D levels and incident or recurrent IHD. We have shown that among patients with prior cardiovascular disease (including IHD, peripheral vascular disease, or stroke), marked vitamin D deficiency is associated with an increased risk of IHD events.

Growing evidence indicates that low vitamin D levels may underlie established cardiovascular risk factors, perhaps making it in and of itself a cardiovascular risk factor. Early hypotheses relating vitamin D and IHD stemmed from ecological studies showing increased IHD incidence or mortality at increased latitude,[19][20] during winter months [21][22][23], and lower altitude [24] – presumably due to decreased sun exposure and thus lower vitamin D levels. Indeed, two case-control studies found lower vitamin D levels among myocardial infarction patients versus controls, with the greatest differences existing according to season. [25][26]

Specific mechanisms underlying the vitamin D--IHD association have since been explored. The pathophysiology initially became evident in studies of end-stage renal disease patients. [27][28] This population's high IHD burden has been attributed to decreased production of the active metabolite 1,25-dihydroxyvitamin D (calcitriol) as well as consequent secondary hyperparathyroidism, both of which lead to atherosclerosis via altered lipoprotein metabolism and altered vascular smooth muscle growth and function.[1] Low vitamin D levels may also lead to increased vessel calcification via increased PTH,[1] which would help explain associations even in non-renal failure populations between low vitamin D levels and more extensive vascular calcification[29] including incident coronary artery calcification.[30]

Additional mechanisms have been elucidated. Inflammation and hypertension are both risk factors for IHD. Low vitamin D levels lead to increased inflammation via increased TNF- α and IL-6[31] and decreased IL-10.[32] Low vitamin D levels result in upregulation of the renin-angiotensin system, increasing blood pressure.[2] In fact, low vitamin D levels are associated with hypertension[33][34][35][18] and vitamin D supplementation has been shown to decrease systolic blood pressure.[36] Low vitamin D levels are also associated with other IHD risk factors, including diabetes, obesity, and dyslipidemia.[33][34][18] Mechanisms underlying these associations include increased insulin resistance and altered lipid metabolism leading to decreased high-density lipids and increased very low-density lipids.[1]

It is important to understand how the association found in our study could influence clinical practice. Once the association is confirmed in larger, more diverse populations, the effect of vitamin D supplementation on IHD in cardiovascular disease patients should be explored. A recent meta-analysis of randomized controlled trials involving various patient populations found that vitamin D supplementation caused decreased total mortality.[37] In cohort studies, dialysis patients receiving vitamin D supplementation have had decreased mortality

from cardiovascular disease, including IHD;[38][39] the caveat being that dialysis patients receive a different vitamin D formulation compared to that typically given to the non-renal failure population. Therefore, the potential for vitamin D to provide health benefits, and specifically to reduce the incidence of IHD events in cardiovascular disease patients, may exist.

Limitations of this study include its observational design and its geographically limited population. Not all NSHS survey participants underwent vitamin D quantification or consented for linkage of their survey and subsequent hospitalization or death data, introducing further selection bias. Also, this analysis relies on medical records in which ICD-9/10 coding may not always be accurate; however, obtaining data from a universal healthcare system for the general population is more representative and complete than other methods. It is also conceivable that vitamin D status simply reflects outdoor physical activity, making it a surrogate marker for exercise rather than an independent risk factor for IHD.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.[40]

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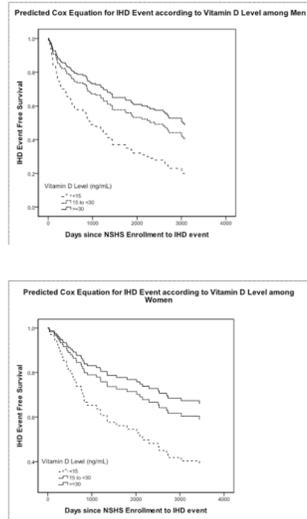


Fig. 1.

Table 1

Baseline Characteristics of the Patients According to Vitamin D Level

Characteristic	Vitamin D Level			p-value
	<15 ng/mL	15 to <30 ng/mL	>=30 ng/mL	
Age	72.1 ± 11.0	65.6 ± 14.5	66.2 ± 15.4	0.315
% Female	53.8%	47.9%	37.4%	0.228
% Smokers	23.1%	27.9%	26.4%	0.919
% Diabetic	23.1%	10.0%	13.2%	0.340
Systolic Blood Pressure (mmHg)	137.1 ± 17.0	134.5 ± 18.0	138.3 ± 20.8	0.331
Body Mass Index (kg/m ²)	26.5 ± 6.3	28.1 ± 6.0	27.4 ± 5.6	0.520
Cholesterol (total:HDL)	4.7 ± 1.6	5.1 ± 1.5	5.1 ± 1.4	0.514
% Previous IHD	69.2%	55.7%	62.6%	0.434
% Previous stroke	15.4%	17.1%	15.4%	0.936
% Previous PVD	41.7%	45.7%	34.1%	0.215
Season (quarter of plasma collection)				0.492
January 1 – March 31	23.1%	11.4%	6.6%	0.146
April 1 – June 30	53.8%	53.6%	50.6%	0.900
July 1 – September 30	7.7%	16.4%	33.0%	*0.005
October 1 – December 31	15.4%	18.6%	9.9%	0.201