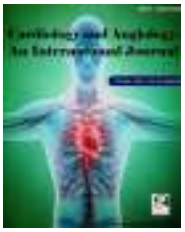

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The Association of Vitamin D Levels with the Extent and Severity of Coronary Artery Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SI, OE and MHD designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors BHI, TF and GK managed the analyses of the study. Authors YSS and AB managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Vitamin D is known for its primary role in calcium and bone homeostasis and regulation of parathyroid hormone (PTH) secretion. There is increasing evidence for health benefits accomplished by activated vitamin D, that go beyond these classical functions. Previous studies have suggested that lower Vitamin D levels are associated with increased cardiovascular disease (CVD) risk. Therefore, we aimed to evaluate relationship between vit D levels and extent and severity of coronary artery disease.
Study Design: Cross-sectional.
Place and Duration of Study: Sample: Department of Cardiology, Bagcilar Training and Research Hospital between November 2009 and march 2010.
Methodology: We evaluated 135 patients who underwent elective coronary angiography between November 2009 and march 2010. Patients with renal failure(GFR less than 60ml/min per 1.73m2), history of malignancy within the past 5 years, any predominant non-cardiac disease, patients using any vitamin D supplement or with hyperparathyroidism or hypercalcemia were excluded.
The severity and extent of CAD were determined using the Gensini score. And, patients were classified as having advanced (≥40) or mild (<40) CAD according to the Gensini scores.

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Results: The mean 25-OH D concentration was 18.7ng/mL. The overall prevalence of 25-OH D less then 15ng/mL was 34,8%(n=47), with 11% having 25-OH D less then 10ng/mL. Multivariate analysis revaeled that smoking, presence of hyperlipidemia, higher CRP levels, higher ALP levels and low levels of 25-OH D concentrations were significantly associated with higher Gensini Scores.
Conclusion: In our study, we found significant correlation between low vitamin D levels and higher Gensini scores.

Keywords: Vitamin D; atherosclerosis; coronary artery disease; gensini score.

1. INTRODUCTION

Vitamin D is known for its primary role in calcium and bone homeostasis and regulation of parathyroid hormone (PTH) secretion. There is increasing evidence for health benefits accomplished by activated vitamin D through interaction with the vitamin D receptor (VDR) that go beyond these classical functions. The VDR is expressed by many tissues and is present in, for instance, arteries, heart, the immune system and endocrine organs [1].

Although the best-characterized sequelae of vitamin D deficiency involves the musculoskeletal system, a growing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system [2]. Vitamin D in the form of 1,25(OH)2D is a hormone, because it is produced primarily in one organ (the kidney) and then circulates throughout the body, where it exerts wide ranging effects. Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle [3,4], endothelium [5], and cardiomyocytes [6]. In addition, both vascular smooth muscle and endothelial cells may have the ability to convert 25(OH)D to 1,25(OH)2D [7].

Clinical studies have reported cross-sectional associations between lower vitamin D levels and plasma renin activity [8], hypertension [9,10], coronary artery calcification [11,12], and prevalent cardiovascular disease [13-15]. Some studies have suggested that lower 25(OH)D levels are associated with increased cardiovascular disease (CVD) risk [16-18]. Epidemiologically, such an effect is also supported by associations observed between 25(OH)D deficiency and many CVD risk factors, including hypertension, diabetes mellitus, obesity, and high serum triglyceride levels [19].

As 25(OH) D deficiency has been identified as a potential novel cardiovascular disease risk factor, we aimed at evaluating relationship between 25(OH) D levels and extent and severity of coronary artery disease. Because, vitamin D deficiency is easy to screen for and easy to treat with supplementation.

2. MATERIALS AND METHODS

We evaluated 135 patients who underwent elective coronary angiography between november 2009 and march 2010 (during winter period). Sunlight is the most important source of vitamin D, and is estimated to provide 90% of vitamin D in humans. Therefore, we conducted the study during winter period to make a clinical judgement on the freguency of vitamine D deficiency as sunlight is limited in this season.

Indications for coronary angiography were commonly chest pain or non-invasive tests in which myocardial ischaemia was suspected. Patients with renal failure (GFR less than 60ml/min per 1.73m2), history of malignancy within the past 5 years and any predominant non-cardiac disease were not enrolled. Also patients using any vitamin D supplement or with hyperparathyroidism or hypercalcemia were excluded.

Coronary angiograms were evaluated by two experienced interventional cardiologist who were blinded to study protocol. The severity and extent of CAD were determined using the Gensini score [20]. The Gensini score is calculated as a sum of stenosis scores and functional significance scores calculated for each segment of the coronary artery tree. Stenosis score expresses the percentage of the reduction in the diameter of the coronary artery lumen (the score was given from 1 to 32 for complete occlusion). The functional significance score illustrates the regional importance of the lesion's position (the score was given from 0.5 to 5). Gensini score>40 was defined as advanced CAD.

Venous blood sampling was performed in the morning before coronary angiography and complete blood count, urea, Creatine, electrolytes, lipid profile, calcium, phosphate and alkaline phosphotase (ALP) were immediately determined, whereas remaining blood samples were snap frozen for further determinations and stored at -80C until analysis. Intact PTH was determined in serum by Electro Chemi Luminescence Immunoassay (ECLIA) on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany), with a normal range of 15–65pg/mL and an inter-assay coefficient of variation of 5.7–6.3%. Serum concentrations of 25(OH) D were measured by a radioimmunoassay (DiaSorin Antony, France; Stillwater, USA) with an intra- and inter-assay coefficient of variation of 8.6 and 9.2%, respectively.

Hypertension was defined as blood pressure 140/90mm Hg or greater, or if patient had a history of antihypertensive drug usage. Hyperlipidemia was defined as low-density lipoprotein cholesterol, 140mg/dL or greater, or if the patient was taking a hypolipidemic drug.

On the basis of the experimental evidence, we postulated that 25-OH D deficiency was associated with higher cardiovascular risk and that this association observed a threshold. Previous clinical studies suggest that the association of vitamin D deficiency with other sequelae, such as hyperparathyroidism and hyperglycemia, is nonlinear [21,22]. Thus, in our primary analysis, we modeled vitamin D status using a categorical variable. All cut points were chosen a priori, based on previous studies [21-23]. We used the 25-OH D cut point of 15ng/mL in our primary analyses, in keeping with cross-sectional studies in Framingham [23] and hospital-based (21) samples. For additional analyses, we defined "severe" vitamin D deficiency as 25-OH D ≤10ng/mL, which approximates the lowest thresholds used in prior studies [21,24].

We divided our patients into 2 groups according to GensiniScores. Patients with advanced CAD (Gensini Score ≥40), and mild CAD (Gensini Score<40). Study was given approval by an institutional review committee and that informed consent was given by the subjects.

2.1 Statistical Analysis

Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software. The data are presented as mean±SD with 95% confidence intervals (CI). The Student t-test was used for continuous variables between groups. Categorical variables were compared using the chi-square test and one-way Anova. In addition, univariate and

multivariate binary logistic regression analysis was performed to detect independent factors affecting severity of CAD. The baseline variables for which evident significance ($p<0.10$) by univariate analysis were included in multivariate logistic regression analysis. The results of the model were reported as 95% Confidence Interval and p values. All p values were two-sided in the tests and p values less than 0.05 were considered to be statistically significant. Categorical variables were noted as presence or absence of a related variable and continous variables were used accordingly to their levels.

3. RESULTS

The baseline demographic and clinical characteristics of the patients are summarized in (Table 1). The mean age was 56±9.1, ranging from 26 to 88 years and 71 patients (52.6%) were male. Nearly 40% of the patients had a history of hypertension and 36,3% of the patients were diabetic. On the 44,4% of the patients, advanced coronary artery disease was observed (Gensini score ≥40). The mean 25-OH D concentration was 18.7ng/mL. The overall prevalence of 25-OH D less then 15ng/mL was 34,8%(n=47), with 10,6% (7 patients) having 25-OH D less then 10ng/mL. The clinical and biochemical features of patients with Gensini Scores of ≥40 and <40 were shown on (Table 2). Smoking, presence of hyperlipidemia, higher CRP levels, higher ALP levels and low levels of 25-OH D concentrations were significantly associated with higher Gensini scores (Table 3). Nineteen of 135 patients (14%) had normal coronary arteries and the average 25-OH-D concentration was 28.3ng/ml in this group of patients.

Table 1. Baseline demographic characteristics, clinical features and laboratory results of the patients

Variables	(n:135)
Age (years)	56±9.1
Range;	26-88years
Sex	
Male	52.6%(71)
Female	47.4% (64)
Presence of diabetes mellitus	36,3%(49)
Presence of hypertension	39,3%(53)
Creatinine (mg/dl)	0.97±0.17
BMI	27±3.76
CRP	3,37±1.87
Calcium (mg/dl)	9.70±1,21
ALP(mg/dl)	95.7±54.8
Parathormone (ng/ml)	28,3±6.82
Phosphate (mg/dl)	3.57±0.79
Alcohol consumption	31.8 %(43)
25(OH) D levels(ng/ml)	18,7±7,3
Gensini score	54.7±39.3
Advanced coronary artery disease (Gensini score>40)	44,4 %(60)

BMI: Body mass index, ALP: Alkalane phosphatase

Table 2. Distribution of clinicalanddemographiccharacteristics of the patients according to angiographic severity of coronary artery disease

Variables	Gensini≥40N=60	Gensini≤40N=75	*P*
Age (years)	59.3±9.6	53.8±12.0	0.001
Sex			0.02
Male	53.52%(38)	51.56%(33)	
Female	46.48%(33)	48.44 %(31)	
Presence of diabetesmellitus	45 %(27)	29.3 3%(22)	0.001
Presence of hypertension	41.66%(25)	37.33%(28)	0.47
Presence of hyperlipidemia	68.3%(41)	46.6%(35)	<0.001
Calcium(mg/dl)	9.8±1.21	9.14±0.68	<0.001
Creatinine(mg/dl)	1.01±0.35	0.92±0.27	0.01
Parathormone	28.1±6.83	29.3±6.56	0.24
Smoking	58.33%(35)	37.33%(28)	<0.001
BMI	28.7±3.45	27.1±3.17	0.26
Phosphate(mg/dl)	3.45±0.88	3.42±0.60	0.17
ALP(mg/dl)	103.8±63.7	84.4±39.6	<0.001
CRP	3.57±1.23	2.96±0.79	<0.001
25(OH) D	15.9±8.1	21.3±9.4	<0.001
Gensiniscore	75.4±31.4(49)	22.8±14.8(18)	<0.001
Total	70.0 %(329)	30.0 %(141)	

ALP: Alkaline phosphatase, BMI:Bodymassindex; P<0.05 is indicated as significant

Table 3. Univariate and multivariated logistic regression analysis for the determinants of advanced coronary artery disease which defined as Gensini score>40

Dependantvariable: advanced coronary artery disease	Univariate analysis		Multivariate analysis		OR
	95% CI	*p*	95% CI	*P*	
Age	0.326;0.764	0.001	0.282;1.475	0.29	0.978
Sex	0.362;0.918	0.02	0.483;2.138	0.96	0.845
Presence of hyperlipidemia	0.103;0.253	<0.001	0.094;0.385	<0.001	0.308
Presence of hypertension	0.997;1.007	0.47			
Smoking	0.946;0.985	<0.001	0.960;1,173	0.01	1.024
Creatinine(mg/dl)	1.195;5.138	0.01	0.300:3.110	0.95	1.245
Presence of diabetesmellitus	0.937;1.332	0.21	0.998;1.006	0.37	0.768
Parathormone	1.019;1.348	0.24	0.950;1.364	0.16	1.026
Calcium	1.644;2.306	<0.001	0.995;1.793	0.05	1.324
Phosphate	0.487;0,523	0,17			
ALP	1.223;1.622	0,001	0,945;1,187	0,01	0.978
BMI	0.851;1.802	0.26			
CRP	1.008;1.021	<0.001	1.003;1.023	0.01	0.972
25(OH)D	0.838;0.904	<0.001	0.867;0.949	<0.001	0.913

BMI: Body massindex, CRP: C-reactive protein , ALP: Alkalanephosphatase OR: Oddsratio; P<0.10 is indicated as significant in univariateanalysis,; P<0.05 is indicated as significant in multivariateanalysis

4. DISCUSSION

In this study, we found a significant association between lower 25(OH) D levels and advanced coronary artery disease as assesed by Gensini score.

A growing body of evidence from experimental, clinical, and epidemiological studies suggests a possible association between vitamin D deficiency and several indices of vascular function, including the development and progression of atherosclerotic cardiovascular disease [25]. As we stated before, Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle [26,27], endothelium [28], and cardiomyocytes [29]. Circulatory 1,25(OH)2D crosses the cell membrane and cytoplasm and reaches the nucleus, where it binds to the VDR. The VDR-bound 1,25(OH)2D in turn binds to the retinoic acid x-receptor and serves as a nuclear transcription factor, altering gene function and inducing protein synthesis [30]. Directly or indirectly, 1,25(OH)2D regulates over 200 genes, including those involved in renin production in the kidney, insulin production in the pancreas, release of cytokines from lymphocytes, production of cathelicidin in macrophages, and growth and proliferation of both vascular smooth muscle cells and cardiomyocytes [31].

Vitamin D stimulates the production of prostacyclin by vascular smooth muscle cells, which prevents thrombus formation, cell adhesion, and smooth muscle cell proliferation [32]. Vascular smooth muscle cells and endothelial cells express receptors for vitamin D and could convert 25- hydroxyvitamin D3, the major circulating metabolite of vitamin D3, to 1,25-dihydroxyvitamin D3(1,25(OH)2D)[33]. In addition, Al Mheid et al. [34] reported that vitamin D insufficiency was associated with increased arterial stiffness and endothelial dysfunction in healthy humans. It was recently demonstrated that vitamin D supplementation significantly improves endothelial function, both in patients with diabetes [35] and in healthy vitamin D insufficient adults [36]. 25(OH)D has been inconsistently found to be associated with early signs of atherosclerosis, such as increased intima-media thickness and maximal carotid plaque thickness [37,38]. Vitamin D deficiency has also been associated with endothelial dysfunction in patients with chronic kidney disease [39].

Vitamin D deficiency triggers secondary hyperparathyroidism. Parathyroid hormone (PTH) promotes myocyte hypertrophy [40] and vascular remodeling [41,42]. Classic PTH effects on bone and kidney are important for the control of calcium homeostasis, but PTH receptors are also expressed in the vessel walls and the myocardium suggesting direct effects on the cardiovascular system [43]. Parathyroid hormone level is associated with mortality and cardiovascular events in patients undergoing coronary angiography [44]. In our study, we found normal levels of PTH in both group of patıents with 25-OH D vit levels <15ng/mL and >15ng/mL. We excluded patients with hyperparathyroidism from the study to avoid bias. So, there was not hyperparathyroidism interfering with our results.

Deficient or insufficient serum 25(OH)D levels have been documented in patients with myocardial infarction [45], stroke [46], heart failure [47], diabetic CV disease [48], and peripheral arterial disease [49]. Additionally, vitamin D deficiency predisposes to insulin resistance, pancreatic beta cell dysfunction [50], and the metabolic syndrome [50,51]. Recently, the relationship between CV risk factors and 25(OH)D levels was explored among the 15088 subjects from the NHANES III national cohort registry. In this cross-sectional study, 25(OH)D levels were inversely associated with hypertension, diabetes mellitus, hypertriglyceridemia, and obesity [52].

Vitamin D deficiency also predispose to calcification of heart valves, mitral annulus, and myocardium, especially in patients with moderate or severe chronic kidney disease [53]. Calcification is a common feature of atherosclerosis, and nearly all angiographically significant lesions are calcified [54]. Calcification of coronary arteries has been associated with increased risk of MI [55] and poorer 5-year survival [56]. Atherosclerotic calcification is a

process regulated in ways similar to skeletal osteogenesis [57]. A significant association exists between osteoporosis and vascular calcification, suggesting that osteoregulatory mechanisms related to bone development may affect calcification in the vasculature. Levels of 1,25-dihydroxyvitamin D have been shown to be inversely associated with vascular calcification [57], suggesting that vitamin D may affect MI risk through its effects on vascular calcification.

In a group of 173 patients at moderately high risk for coronary heart disease who underwent Electron beam tomography (EBT) scanning of their coronary arteries, Watson et al. found that serum 1,25(OH)2 D levels were inversely correlated with the extent of coronary calcification [57]. However, another study by Arad et al. found no correlation between serum 1,25(OH)2D levels and coronary calcification in 50 patients undergoing coronary angiography [58]. Their findings might be explained by the differentiating effect on cells and the anti-inflammatory effect of 1,25(OH)2D found by others [59-61]. In a study population of old Amish people, the association between vitamin D deficiency and subclinical vascular disease was investigated. EBT was used to detect coronary artery calcification (CAC) and the results fail to show an association between CAC and vitamin D deficiency [62].

A recent prospective cohort study measured the vitamin D levels in 3,258 German adults who were undergoing elective cardiac catheterization. During a mean follow-up of 7.7 years, individuals in the lowest quartile for baseline serum 25-hydroxyvitamin D [25(OH)D] had a risk-adjusted 2-fold increased risk of death, especially CV death, compared with those in the highest quartile of vitamin D [18].

Another mechanism explaining the effects of vitamin D and its metabolites on CVD may be their anti-inflammatory actions [59]. Several studies have shown an inverse relationship between vitamin D levels and inflammation [63-65].

Epidemiologic studies have also recently linked vitamin D deficiency with increased risk of major adverse CV events [17]. A study of male health professionals showed a 2-fold risk of myocardial infarction (MI) in subjects who were vitamin D deficient compared with those in the sufficient range [66]. The exact cause of this poor survival is not clear.

Recently, in their study, Akin et al. demonstrated that serum 25(OH)D levels are inversely associated with coronary lesion severity established by coronary angiography. Their data suggests that vitamin D may play a role in the development and progression of atherosclerosis [67].

A recent study, namely the ‘MROS sleep study’ failed to show an association between 25(OH) vitamin D and risk of CVD [68].

As we stated before, vitamin D deficiency increases the risk of hypertension. But, the results of recent interventional studies that investigated the potential benefit of vitamin D supplementation on blood pressure have not been promising. Further studies are needed to find out if and when vitamin D supplementation should be used for treating patients with hypertension. It is apparent that vitamin D supplementation may be appropriate for populations that are most vulnerable to hypovitaminosis D. But it is not clear what degree of vitamin D deficiency may activate the renin-angiotensin system (RAS) and trigger an increase in blood pressure [69].

In Heart and Soul Study, authors identified 946 participants with stable cardiovascular disease in San Francisco, California, and followed them prospectively for cardiovascular events (heart failure, myocardial infarction, stroke, or cardiovascular death). They then examined the extent to which the association was attenuated by adjustment for poor health behaviors, comorbid health conditions, and potential biological mediators [70]. During a median follow-up period of 8.0 years (through August 24, 2012), 323 subjects (34.1%) experienced a cardiovascular event. Following adjustment for socio demographic factors, season of blood measurement, health behaviors, and comorbid conditions, 25-hydroxyvitamin D levels under 20ng/mL remained independently associated with cardiovascular events (hazard ratio=1.30, 95% confidence interval: 1.01, 1.67).

In a recent systematic review and meta-analysis of observational cohort and randomised intervention studies, it is concluded that, evidence from observational studies indicates inverse associations of circulating 25-hydroxyvitamin D with risks of death due to cardiovascular disease, cancer, and other causes. Supplementation with vitamin D3 significantly reduces overall mortality among older adults; however, before any widespread supplementation, further investigations will be required to establish the optimal dose and duration and whether vitamin D3 and D2 have different effects on mortality risk [71].

5. CONCLUSION

In our study, we found significant correlation between lower vitamin D levels and higher Gensini scores. Therefore, our data suggest that vitamin D may play a role in the development and progression of atherosclerosis. This is important because, screening for Vit D deficiency may have an importance for coronary artery disease in the future as data accumulates in this era. The mechanistic role of vitamin D deficiency on development of coronary artery diseases hold be clarified with new prospective and higher volume studies.

CONSENT

All authors declare that written informed consent was obtained from the patients (or other approved parties).

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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