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Original Article

Internal Medicine Section

Evaluation of Correlation between Serum Levels of Vitamin D and Coronary Artery Disease: An Existing Debate

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ABSTRACT

Introduction: Coronary Artery Disease (CAD) is the global leading cause of death. Previous studies have been controversial on whether lower serum vitamin D levels could enhance the risk of CAD or its extent.

Aim: To evaluate the association between serum vitamin D levels and CAD by using a novel and promising angiographic index the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score.

Materials and Methods: In the present cross-sectional study, 227 consecutive patients with suspected CAD referred for Coronary Angiography (CAG) were included. The patient's clinical and demographic data were recorded. Blood sample was taken from each subject to measure serum 25-Hydroxy vitamin D (25(OH)D) concentration at the time of admission. Then CAG was performed and patients were divided according to their degree of CAD. Stenosis more than 50% in at least one main coronary artery was defined as significant CAD. Among the patients with significant CAD, the severity of the disease was assessed using the SYNTAX score. Statistical analyses were performed using chi-square and independent t-test. Analysis of Variance (ANOVA and Spearman's correlation coefficient (ρ) and scatter plot were also used to detect the relationship between quantitative variables.

Results: The mean serum vitamin D concentration of the participants was 32.1±21 ng/mL. CAG confirmed 150 patients had significant and 77 had non-significant CAD. Mean serum vitamin D concentration was higher among the non-significant CAD group than the other group, but not statistically significant (p=0.94). In patients with significant CAD, the mean SYNTAX score was 11.7±6.8 and mean serum vitamin D was 30.3±12.4 ng/mL. Correlation analysis revealed a weak and not significant inverse correlation (r=-0.037, p=0.67) between serum vitamin D levels and the SYNTAX score.

Conclusion: The CAD and its severity may not be associated with serum vitamin D levels. Future large investigations will reveal more detailed results.

Keywords: 25-hydroxyvitamin, Coronary angiography, SYNTAX score

INTRODUCTION

The impact of vitamin D and its serum levels on various human conditions has been a hot topic of research during recent years. Considering the multiple vital roles of this micronutrient in different body organs, an estimated one billion people around the world with inadequate serum vitamin D levels can only add to the importance of this substance [1]. Numerous studies have linked higher levels of serum vitamin D with lower prevalence of CVD, especially CAD, and their associated risk factors such as hypertension, Diabetes Mellitus (DM) and dyslipidaemia [2]. If such an association is proved by strong evidence, screening and improving the patient's vitamin D profiles could greatly help prevent or even treat CAD (the current global leading cause of death and morbidity) [3,4].

To identify whether a patient does really have CAD and to effectively determine the extent of the disease, a standard scoring system seems necessary. The SYNTAX score is an effective, angiography-based method to evaluate the severity of coronary lesions in patients with CAD. It takes into account anatomical changes or abnormalities in coronary arteries that may trigger or contribute to the development of CAD [5,6].

Measuring serum levels of 25(OH)D is the best assessment of an individual's vitamin D status. A 25(OH)D is a reliable indicator of both the amount of dietary vitamin D intake and the amount produced by the body itself as a result of exposure to sunlight. Accordingly, vitamin D status is commonly divided into three categories based on the musculoskeletal system's requirements: sufficient (serum level >20 ng/mL), insufficient (12-20 ng/mL) and deficient (<12 ng/mL) [7]. While it is worth mentioning some guidelines suggest slightly different serum levels, the more important issue of proposing an optimal level required to maintain the possible protective effects of vitamin D on the cardiovascular system remains unresolved [8].

The studies on the association between serum vitamin D levels and CVD have been controversial. Though, many research articles support the idea that sufficient serum vitamin D levels may lower the risk of CVD and its risk factors, some studies deny such a relationship. The discussion is particularly strong in the case of CAD, where there are lack of adequate solid evidences. In present study, authors tried to investigate this correlation by using SYNTAX score and help conclude the existing debate.

MATERIALS AND METHODS

In the present cross-sectional study, consecuetive adult patients referred to Modarres Hospital from December 2015 to September 2017 to undergo CAG due to a suspected CAD were included. The study protocol was approved by the Institutional Review Board of Cardiovascular Research Center of Shahid Beheshti University of Medical Sciences and Ethical Committee. All patients signed an informed written consent before participating in the study. The clinical diagnosis and the subsequent need to undergo CAG was made and confirmed by a cardiologist according to accepted guidelines [9,10]. Those who were on multi-vitamin or vitamin D supplements and the patients with any known metabolic or bone disorder involving calcium and vitamin D balance in the body (e.g., hyperparathyroidism) were

excluded as well as those with any underlying disorder including infection, acute or chronic inflammatory diseases, renal or hepatic failure, or a known malignancy. All patients with an estimated eGFR higher than 60 mL/minute per 1.73 m^2 were eligible to exclude the effect of chronic kidney disease on vitamin D. The presence of hypertension, DM, dyslipidaemia and any familial history of cardiovascular diseases were assessed in each patient on admission. Additionally, a blood sample was taken from each subject to measure serum 25(OH)D concentration at the admission time before CAG. CAG was then performed using the standard Judkins technique. Angiographic data including the percentage of artery stenosis and the location of all the coronary lesions in the index coronary angiogram were obtained from reviewing the angiogram. A certified cardiologist who was blinded to the study protocol performed the angiographic analysis afterwards. Stenosis more than 50% in at least one main coronary artery was defined as significant CAD. Among the patients who actually had confirmed CAD on the angiogram, the severity of the disease was assessed using the SYNTAX score [11,12]. The SYNTAX score is an inclusive angiographic scoring system centred on coronary anatomy and lesion characteristics and was originally developed to define the extent of CAD and lesion complexity; it was derived from the summation of the individual scores for each distinct lesion described as ≥50% luminal obstruction in vessels ≥1.5 mm. The SYNTAX score was considered as a tool in the decision-making practice and, later on, its utility was developed as a forecasting score of major adverse cardiac events in patients who underwent coronary revascularisation.

Based on the number of the involved main coronary arteries, we divided these subjects into three groups: One-vessel; two-vessel; and three-vessel.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM SPSS Statistics version 23.0. Chi-square and independent t-test were used for analysing qualitative and normally distributed quantitative variables, respectively. ANOVA used to extract differences between groups. Spearman's correlation coefficient (ρ) and scatter plot were also used to detect the relationship between quantitative variables.

RESULTS

A total of 227 patients were included in the present study; consisted of an almost equal proportion of both genders. The demographic data of the patients in detail are shown in [Table/Fig-1]. According to these data, male gender, smoking and DM were directly correlated with having CAD.

Demographic variables	All subject (n=227)	Subjects with CAD (n=150)	Subjects without CAD (n=77)	p-value*
Age (year), mean (SD)	58.98 (11.04)	60.57 (10.44)	55.87 (11.59)	0.38
Male, n (%)	114 (50.2%)	91 (40.1%)	23 (10.1%)	<0.01
DM, n (%)	74 (32.6%)	62 (27.3%)	12 (5.3%)	<0.01
HTN, n (%)	134 (59%)	90 (39.6%)	44 (19.4%)	0.67
Dyslipidaemia, n (%)	69 (30.4%)	43 (18.9%)	26 (11.5%)	0.42
Cigarrete Smoking, n (%)	63 (27.8%)	52 (29.2%)	11 (4.8%)	<0.01
Positive FH, n (%)	57 (25.1%)	42 (18.5%)	15 (6.6%)	0.16
Vitamin D Level, mg/dL, mean (SD)	32.14 (20.99)	30.28 (21.44)	35.78 (19.71)	0.91

[Table/Fig-1]: Demographic information of subjects, recruited into the study.
*p-value is calculated between subjects with CAD and without CAD. For qualitative variables, p-value was calculated using chi-square test and for quantitative variables, by independent t-test.
CAD: Coronary artery disease; DM: Diabetes mellitus; FH: Family history; HTN: Hypertension

In general, the mean serum vitamin D concentration of all patients was 32.1±21 ng/mL (minimum=6 and maximum=140). We weren't able to allocate a SYNTAX score to 77 patients, (i.e., non-significant CAD group) since, they had either normal coronary arteries or only mild CAD. Mean serum vitamin D concentration was 35.8±19.7 among these patients-slightly higher than the total mean. Among the remaining 150 (i.e., significant CAD group), 53 had single-vessel involvement, 31 had two-vessel and 66 subjects had three-vessel involvement [Table/Fig-2]. In these 150 patients, we found the mean SYNTAX score to be 11.7±6.8 and their serum vitamin D levels had a mean of 30.3±12.4 ng/mL. In these patients, correlation analysis revealed a weak inverse correlation (r=-0.037) between serum vitamin D levels and the SYNTAX score that was not statistically significant (p=0.67) [Table/Fig-3].

Level	SVD (N=53)	2VD (N=31)	3VD (N=66)	F	p-value*
Vitamin D Level, mg/dL, mean (SD)	30.85 (21.24)	30.71 (20.74)	29.62 (22.21)	0.055	0.94

[Table/Fig-2]: Different levels of vitamin D in patients with coronary artery disease.
*p-value was calculated using ANOVA test. There is no significant difference between different groups of patients with coronary artery disease.
SVD: Single-vessel disease; 2VD: Two-vessel disease; 3VD: Three-vessel disease

Level	Spearman's correlation coefficient (ρ)	p-value
Vitamin D Level, mg/dL	-0.037	0.67

[Table/Fig-3]: Correlation between SYNTAX score and vitamin D level in patients with coronary artery disease.

Interestingly, when we compared the mean serum vitamin D levels between significant (n=150) and non-significant (n=77) CAD groups by means of independent t-test, the difference showed no statistical significance (p=0.94).

DISCUSSION

One cannot question the high importance of CAD, as it is now the leading cause of death in addition to forcing a huge economic burden by causing a high rate of disability worldwide. Previous studies have suggested serum vitamin D can affect the cardiovascular system via various mechanisms. Vitamin D Receptors (VDR) and 1-α-hydroxylase, an enzyme converting vitamin D into its active form, both have been reported to be existent in cardiovascular tissues. By activating VDRs in heart cells, vitamin D can start a cascade of events that are eventually helpful to maintain a balance in the cardiac connective and muscular tissues. In the vascular system, vitamin D has been shown to have a role in lowering the risk of arterial endothelial dysfunction, calcification and stiffness-all potential risks for CVDs. It can also reduce the activity of the Renin-Angiotensin-Aldosterone System (RAAS) and help control the blood pressure [8].

A quick review of the existing literature shows a high proportion of studies referring to low serum vitamin D as a risk factor for CAD. In a large study on 1739 patients, Wang TJ et al., reported those with low serum vitamin D levels are about two thirds more likely to develop heart disease compared with those who have higher levels [13]. However, there is also some opposing evidence indicating no link between serum vitamin D levels and CAD at all [14-16]. Therefore, whether this association is overrated is still among debate.

In the present study, we used the SYNTAX score since it has proven itself to be an effective indicator of the severity of CAD and also a proper predictor of long term adverse cardiovascular events in previous investigations [11,12]. Among the studies that are for the idea of a correlation between vitamin D (serum 25(OH) vitamin D) and CAD, there are some that are brilliant but did not use an effective scoring system as good as the SYNTAX to categorise the extent of the disease in patients. For instance, Akin F et al., used the GENSINI score-which is of less clinical value than the SYNTAX score-to evaluate the severity of CAD [17,18]. Syal SK et al., also supported

the association in their study on an Indian population, but did not use a reliable scoring system to assess the extent of CAD [19]. In a case-control study of 140 CAD patients and 101 controls, Kumar M et al., mentioned somehow similar results by reporting vitamin D to be an independent risk factor for CAD with an odds ratio of 2.695 [20]. But in addition to not mentioning precisely how they assessed CAD in their study population, their study had a low sample size, making it impossible to draw a concrete conclusion [20]. The positive correlation results were replicated in another investigation on 130 CAD cases and 195 controls in Saudi Arabia [21].

However, multiple similar studies have taken the SYNTAX score into consideration, the first of which was probably the one by Chen WR et al., in 2013 [22]. They conducted a study on 347 patients undergoing CAG with a mean SYNTAX score of 27.8±8.5 and found that "low vitamin D" (according to their classification) two-fold increases the risk of having high SYNTAX scores (i.e., more severe CAD) [22]. The study had two prominent limitations, however. First, they selected a relatively young population and unintentionally overlooked the effect of age. Second, the majority of their patients had severe CAD; so, they could not evaluate the effect of vitamin D on other extents of the disease.

Baktir AO et al., performed a prospective study on 113 patients with acute Myocardial Infarction (MI), including both ST-segment Elevation Myocardial Infarction (STEMI) and Non-STEMI (NSTEMI). The authors defined SYNTAX>22 as "high SX" and ≤22 as "low SX". The authors concluded that serum 25(OH) D levels were significantly lower in both STEMI and NSTEMI patients. The author also reported a significant correlation between low serum 25(OH) D levels and the complexity of CAD [23].

While several studies supported the concept of an association between serum 25(OH)D and CAD, there are many that are against it. In a study on 224 Iranian patients undergoing CAG, Mostafavi A et al., clearly stated that low serum 25(OH)D levels were not related in any way to the prevalence or complexity of CAD and its risk factors [16]. Another investigation on 315 patients revealed that vitamin D deficiency was frequent among CAD patients, but didn't have an association with the intensity of the disease [15].

Degerud E et al., did an interesting investigation on the role of patient's vitamin D status in one-year progression of CAD. To assess the relationship between 25(OH)D levels and stenotic changes in coronary arteries, they performed baseline CAG or Percutaneous Coronary Intervention (PCI) on 348 patients followed by a second CAG 302±79 days later and found no such association in the end [14]. Alani A et al., used Coronary Artery Calcium Score (CACS) in their study and reported no correlation between this score and serum 25(OH)D levels in 303 patients who were mainly Caucasians [24].

Because of the lack of a subtle cut-off for vitamin D sufficiency in association with the amount needed for cardiovascular health, most of the mentioned studies have used the popular categorisations of serum 25(OH)D levels that are mainly based on studies on the musculoskeletal system. We did not take into account those reference values, which in turn gave us more freedom to report the correlation between 25(OH)D and CAD directly and on a pure cardiovascular basis. One of the most important findings of the present study was that among the patients with significant CAD, those with higher extents of coronary involvement had lower serum vitamin D levels. However, this correlation should be interpreted with caution as it is statistically insignificant and one cannot simply deduct a clear fact based on it. More importantly, we found that patients with non-significant CAD had slightly higher amounts of 25(OH)D compared with those with the significant form of the disease. However, the p-value for this difference was not statistically significant, rejecting an actual association between serum vitamin D levels and CAD. Nevertheless, these findings illustrate that the controversy still remains and further evidence and larger studies are absolutely vital for a final conclusion.

LIMITATION

To determine the patient's vitamin D status, we only took one sample of blood from each of them which is obviously not the most meticulous long term assessment of serum vitamin D. This was perhaps the most important limitation of present study along with a low study population. Factors such as different amounts of sunlight exposure due to the traditional type of clothing in Iran could also affect the study results.

CONCLUSION

The current study shows that neither developing CAD nor its extent is associated with serum vitamin D levels. Present analysis opposes such a correlation, indicating it might be too soon to recommend prescribing vitamin D supplements to prevent or treat CAD.

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