ORIGINAL ARTICLE

Association of vitamin D deficiency and coronary artery disease with cardiovascular risk factors

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Background: Vitamin D deficiency is a prevalent condition in many countries.The aim of this study is to elucidate whether deficient vitamin D status is associated with coronary artery disease considering cardiovascular risk factors. **Materials and Methods:** We measured 25 (OH) D serum levels in 57 patients that were diagnosed with coronary artery disease upon coronary angiography and 62 individuals in the control group who were matched for age and sex with the patients and examined the association between serum 25 (OH) D and coronary artery disease with regard to cardiovascular risk factors. **Results:** The odds ratio of being affected by coronary artery disease in individuals with vitamin D deficiency (25 (OH) D < 30 ng/ml) was 5.8 (1.77 - 18.94) after adjustment with cardiovascular risk factors, i.e., blood pressure, diabetes, smoking, obesity, physical activity and high blood cholesterol in comparison with the control group. **Conclusion:** Low levels of 25 (OH) D are associated with prevalent coronary artery disease independent of cardiovascular risk factors. Further investigations could demonstrate the need for vitamin D supplementations in order to prevent atherosclerosis.

Key words: Cardiovascular disease, coronary artery disease, risk factor, vitamin D deficiency

INTRODUCTION

Vitamin D deficiency is prevalent in most parts of the world. Vitamin D exists in two forms: Ergocalciferol (D2) and cholecalciferol (D3). Ergocalciferol is made in herbal resources and cholecalciferol through UVB (Ultraviolet B) radiation to the body skin. Generally, humans receive vitamin D by being exposed to the sun light or dietary intake, such as fish oil and nutritional supplements.[1]

Although 1,25 (OH) 2D is the active form of vitamin D, it is not suitable for measuring vitamin D serum level. 25(OH) D has a longer half – life and it can more precisely show the food intake and skin production of vitamin D. A serum level of less than 20 ng/ml ($50 \frac{n\ mol}{L}$) 25 (OH) D is considered as vitamin D deficiency, between 20-30 ng/ ml as its insufficient level and higher than 30 ng/ml as its desirable level.[2]

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Most body cells, including cardiomyocytes and vascular smooth muscles and also the endothelium of the vessels have vitamin D receptors.[3-5]

Recent studies are indicative of a relation between vitamin D deficiency and cardiovascular disease, increased blood pressure, increased insulin resistance, heart failure and fatal strokes.[6-10]

Also mortality rate due to Ischemic heart disease has been associated inversely with the sunshine hours in winter when vitamin D is at the lowest level.[11,12]

The mechanism which causes the protective effect of vitamin D against cardiovascular diseases is not fully understood but several mechanisms have been proposed such as the effect of the vitamin D on the renin-angiotensin system, vessel compliance, blood pressure, parathyroid hormone level and also glycemic control. In addition, vitamin D has anti-inflammatory effects and prevents cholesterol removal by macrophage and foam cell formation on vessels walls. Also an inverse relation has been seen between vitamin D serum level and coronary artery calcification.[13]

The prevalence of cardiovascular disease is increasing in the world. Stable angina, which is the first sign of ischemic heart disease (IHD) in 50% of patients, is common in 213 out of each 100000 people above

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30 years old.[14] Accordingly, in Iran, statistics are indicative of increased mortality due to cardiovascular disease and in a research conducted in Isfahan, a high percentage of men and women had definite coronary artery disease.[15]

Previous studies indicate moderate to severe vitamin D deficiency in a significant percentage of Iranians, the highest percent being relevant to Tehran and the lowest percent to Mashhad and Bushehr.[16,17]

Considering the high prevalence of vitamin D deficiency in Iran and increased coronary heart disease and the relation between these two subjects, more investigations appear to be essential to prove this relation. The aim of this study is to investigate the association between ischemic heart disease and vitamin D deficiency after adjustment with cardiovascular risk factors.

MATERIALS AND METHODS

This was a cross sectional study that was conducted in Isfahan Khorshid Hospital from March 2010 to March 2011. Detailed description of the methods have been mentioned elsewhere.[18]

The cases were selected by convenient sampling method from the patients over 40 years admitted to the hospital with the diagnosis of angina pectoris and whom the existence of coronary artery disease had been proved upon angiography.

The control group was family or friends of the patients which were matched with them for sex and age and didn't have any history of angina pectoris upon clinical evaluation. The exclusion criteria of the study were unwillingness to cooperate or chronic renal diseases. Written consent was obtained from the participants.

Study variables including age, sex, education, smoking status, usage of antihyperlipidemic, antidiabetic and antihypertensive drugs were gathered through checklist. The Level of physical activity was collected by a standard questionnaire (Rapid assessment physical activity questionnaire) and the participants were divided to five categories according to the score they obtained by this questionnaire: Without activity, low activity, light activity, moderate activity and appropriate activity. Weight, height and also the blood pressure of the participants were measured by the standard protocol. The blood pressure was measured two times with a five minute interval in a sitting position and from the right brachial artery. Then the mean blood pressure was calculated.

Then 2.5 cc of patients and control group blood samples were obtained after 8 hrs of fasting and centrifuged, and was frozen at -20 c in capped plastic pipes. The levels of 25(OH)D, Cholesterol and Fasting blood sugar were measured in the laboratory.

BMI (Body Mass Index) was calculated as weight/height*height(kg/m^2).

Vitamin D deficiency was considered as 25 (OH) D levels<30 ng/ml.(2)

Diabetes was considered as FBS levels ≥126 mg/dl or the consumption of antidiabetic drugs.[1]

Hypertension was considered as blood pressure≥140/90 or the consumption of antihypertensive drugs.[1]

Hypercholesterolemia was considered as blood cholesterol ≥240 mg/dl or the consumption of antihyperlipidemic drugs.[19]

Statistical tests used were Chi–square, independent *t* test and log regression.

The gathered information were analyzed by the statistical software SPSS version 19 (IBM corporation, USA) and $P < 0.05$ was considered significant.

RESULTS

57 Patients with angina pectoris and 62 healthy individuals participated in this study from whom 30 were females and 89 were males ($P = 0.674$).

Table 1 shows the base line characteristics of the participants. There was no significant difference in the age and sex between the two groups ($P > 0.05$).

Smoking status, Obesity, high blood cholesterol and also the amount of physical activity was significantly different between the patients and the control group ($P < 0.05$). Despite the higher percentage of the individuals with hypertension in the patient group, the difference between the two groups was not significant. Vitamin D deficiency (25 (OH) D < 30 ng/ml), was significantly higher in the patients ($P < 0.05$).

In Table 2, the odds ratio for coronary artery disease in individuals with vitamin D deficiency has been presented. Without adjustment, the chance of being affected by coronary artery disease in individuals with vitamin D deficiency is 3.49 (1.59-7.64) times in comparison to those with normal vitamin D and after adjustment with risk factors, i.e., blood pressure, diabetes, smoking, obesity, physical activity and high blood cholesterol, this chance becomes 5.8 times (1.77-18.94).

DISCUSSION

The results of our study demonstrates that vitamin D deficiency increases the chance of coronary artery disease and the association between ischemic heart disease and vitamin D deficiency remains significant even after adjustment for cardiovascular risk factors such as diabetes, smoking, obesity, physical activity, high blood cholesterol.

In addition to calcium metabolism vitamin D has other physiological roles. There are vitamin D receptors in the brain, skeletal muscles, the pancreas, blood vessels and immunity cells such as T cells, B cells and monocytes. Production of the active form of vitamin D is dependent on the serum level of 25 (OH) D and 1α- hydroxylase enzyme which acts by binding to its intranuclear receptor in tissues in the form of autocrine and paracrine that causes angiotensin–renin system inhibition and induces or inhibits cell apoptosis and proliferation and development of cells as well. So, vitamin D deficiency can be effective on the occurrence of many disorders such as cardiovascular diseases and malignancies and Immune system diseases.[20]

During a Framingham–Off spring study on 1739 participants who were followed up within 5.4 years Wang and colleagues revealed that vitamin D deficiency is associated with cardiovascular disease. However in the mentioned study levels lower than 15 ng/ml were considered as vitamin D deficiency while we considered levels lower than 30 ng/ml as vitamin D deficiency.[10]

A research conducted on the Europeans who underwent coronary artery angiography, showed that those with serum levels of 25(OH)D in the lowest quartile had the highest mortality rate by any reason and after adjustment with risk factors.[1]

Another study that divided 2910 patients with coronary artery disease history (acute myocardial infarction-unstable angina- stable angina) to three groups on the basis of their angiography results showed that although vitamin D deficiency is prevalent in all groups, it is more prevalent in patients with stable angina and also it is indicative of a worse prognosis (such as death, MI, cerebral stroke, or the need to revascularization) in them.[20]

Studies conducted on adolescents, revealed that the low level of vitamin D is obviously accompanied by abdominal obesity, elevated hypertension, and high fasting blood sugar (FBS) and metabolic syndrome.[21] Previous studies also showed that vitamin D deficiency is associated with cardiovascular risk factors such as hypertension, hypercholesterolemia, obesity and diabetes mellitus.[10,21,22] This may suggest that the vitamin D status in individuals would be a marker of unhealthy lifestyle but our study demonstrated that even after adjustment with common cardiovascular risk factors the chance of being affected by coronary heart disease remained unchanged.

The limitation of our study is that we used cross sectional method and so the casual relation between vitamin

Table 1: The baseline characteristics of the studied individuals

Studied variables	Patient %(*N*)	Control %(*N*)	*P* value
Sex			
Male	77.2 (44)	72.6 (45)	0.674
Female	22.8 (13)	27.4 (17)	
Age			
40-49	22.8 (13)	11.3 (7)	
50-59	26.3 (15)	37.1 (23)	0.306
60-69	29.8 (17)	27.4 (17)	
Over 70	21.1 (12)	24.2 (15)	
BMI			
30≤	12.3 (7)	0 (0)	0.005
<30	87.7 (50)	100 (62)	
Physical activity[1]			
1	22.8 (13)	1.6 (1)	
2	21.1 (12)	0 (0)	
3	31.6 (18)	75.8 (47)	0.000
4	8.8 (5)	14.5 (9)	
5	15.8 (9)	8.1 (5)	
Hypertension	64.9 (37)	50 (31)	0.072
Diabetes	47.4 (27)	27.4 (17)	0.019
Smoking			
Current	26.3 (15)	16.1 (10)	
Past	7 (4)	0 (0)	0.031
Never	66.7 (38)	83.9 (52)	
High cholesterol	68.4 (39)	29 (18)	0.000
Vitamin D statue			
<30 ng/ml	75.4 (43)	46.8 (29)	0.002

1:1=Non active ,2=Low activity, 3=Low weekly activity, 4=Moderate weekly activity, 5=Optimal activity

Table 2: Odd ratios (95% confidence interval) of coronary artery disease if vitamin D deficient

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
25 (OH) D<30 ng/ml	3.49 (1.59-7.64)	3.53 (1.59-7.79)	3.83 (1.7-8.67)	3.37 (1.52-7.47)	3.23 (1.44-7.24)	4.48 (1.63-12.27)	6.152 (2.33-16.22)	5.80 (1.77-18.94)	5.87 (1.76-19.53)
P value	0.002	0.002	0.001	0.003	0.004	0.004	0.000	0.004	0.004

"1"Each model was adjusted with assigned variables as following: Model 1=Without adjustment; Model 2=Adjusted for hypertension; Model 3=Adjusted for diabetes; Model 4=Adjusted for smoking; Model 5=Adjusted for body mass index(BMI), Model 6=Adjusted for physical activity; Model 7=Adjusted for high cholesterol; Model 8=Adjusted for hypertension, diabetes, smoking, body mass index, physical activity and high cholesterol; Model 9=Adjusted for all of the risk factors, age and sex

D deficiency and ischemic heart disease could not be confirmed, also our sample size was small because we selected our cases from individuals that their atherosclerosis were confirmed by carotid artery angiography.

In conclusion this study suggests that low levels of 25(OH)D are associated with prevalent coronary artery disease independent of cardiovascular risk factors. Further investigations could demonstrate the need for vitamin D supplementations in order to prevent atherosclerosis.

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