Association between Vitamin D Level and Ischemic Heart Disease

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Abstract

Background- Vitamin D deficiency has been associated with many cardiovascular diseases and mortality. In this study, we aimed to investigate whether low levels of 25 hydroxy vitamin D concentrations associate with ischemic heart disease (IHD) in patients who referred for coronary angiography.

Methods- We included 293 subjects: 133 without IHD (normal reported angiography) and 163 with ischemia (70% or more stenosis of at least one coronary artery documented by angiography). Basal concentrations of serum vitamin D, fasting blood sugar, triglyceride, cholesterol, LDL, and HDL were measured in both groups.

Results- The two groups had no significant difference in respect to their age (56.55 vs. 61.45 years), blood pressure (123.03/73.88 vs. 123.68/73.98 mm Hg), fasting blood sugar (114.97 vs. 121.49 mg/dl), and lipid profile (P< 0.05). The medians of vitamin D concentration in the case and control groups were 40.80 and 40 nmol/lit, respectively, with the difference not constituting statistical significance (P< 0.05). After adjusting for other risk factors (age, sex, blood pressure, fasting blood sugar, and lipid profile), the association between vitamin D and ischemia remained non-significant (adjusted OR: 0.83, 95% CI: 0.37-1.85).

Conclusion- This study was unable to demonstrate an association between low levels of vitamin D and IHD (Iranian Heart Journal 2012; 13 (1):40-45).

Keywords: Vitamin D■Ischemic heart disease■Cardiovascular disease
Considering that the vitamin D receptor and the 1-α-hydroxylase enzyme that converts 25-hydroxyvitamin D (25(OH)D) to its active form 1,25-di hydroxyvitamin D have been found in tissues throughout the body, it is likely that vitamin D is important for more than the recognized association between vitamin D and bone growth. Accordingly, vitamin D status has been linked with a wide variety of disorders, including cancers, multiple sclerosis, and diabetes mellitus and more recently with cardiovascular disease, and cardiovascular disease risk factors such as hypertension, obesity, and dyslipidemia.4-8 Indeed, vitamin D was shown to make a significantly decrease in all-cause mortality as was reported by a recent meta analysis. A report from the National Health and Nutrition Examination Survey (NHANES) involving nearly 5,000 participants found that low levels of vitamin D were associated with an increased risk of peripheral artery disease.9 Reports from the same organization showed a significant inverse association between serum 25 (OH) D₃ levels and blood pressure, presenting even after variable adjustment.10 In a study by Douglas et al., the incidence and mortality rates of coronary heart disease showed a seasonal pattern with higher occurrence rates in winter, when vitamin D levels were lowest.11 The mechanism by which vitamin D can influence the risk of cardiovascular disease has not been clearly understood, but suppressive effects on rennin-angiotensin system, vascular calcification, and endothelium dysfunction, inflammation, and effects relating to PTH have been proposed as the possible mechanisms.12-13

In line with these observations, in this study we aimed to investigate the association between vitamin D status and ischemic heart disease (IHD) in patients referred for coronary angiography.

**Methods**

This case-control study enrolled 294 patients who were referred for coronary angiography between January 2010 and June 2010. The inclusion criteria were defined as the adult subjects, aged between 40 and 75 years. Patients who had documented malignancy, renal failure, hyperparathyroidism, taking vitamin D supplements, or any drug that affects serum vitamin D levels were excluded from the study. Data were gathered by using a questionnaire that was comprised of information about family history of IHD, smoking, diabetes mellitus, menopause, and hypertension. Diabetes mellitus was defined as the use of insulin or hypoglycemic medications or a fasting blood sugar (FBS) ≥ 126 mg/dl. HTN was defined as a self-reported history of HTN accompanied with blood pressure >140/90 mm Hg detected during study examination or positive history of anti-hypertensive medication consumption. A signed written informed consent was obtained from all the participants. The protocol of the study was approved by the Ethics Committee of the Endocrine and Metabolism Research Center of Tehran University of Medical Sciences. The patients were divided into two groups of ischemic (n=161) and non-ischemic (n=133) according to their angiographic reports performed by an expert cardiologist. The ischemic patients were those with 70% or more stenosis of at least one coronary artery estimated by visual analysis and the non-ischemic patients were the ones with normal angiographic findings. The two groups were matched frequently based on their age. Blood pressure was measured in sitting position after 5-10 minute rests.

**Laboratory measurement**

A fasting serum sample was obtained before coronary angiography. The serum was separated and stored at -20°C until all the samples were ready to process. The serum levels of FBS, triglyceride (TG), cholesterol, low-density lipoprotein (LDL) cholesterol,
high-density lipoprotein (HDL) cholesterol, and 25 (OH) D were measured. FBS, HDL cholesterol, and TG were determined enzymatically. Fasting LDL cholesterol levels were measured directly by immunoturbidimetry method. All of these were performed using Randox laboratories kit (Hitachi 902). Serum vitamin D (25-hydroxy vitamin D3) was measured via radioimmunoassay using an IDS kit (England, Immunodiagnostics Systems Limited). The inter and intra assay coefficients of variation were 8.7% and 4.9%, respectively. The sensitivity of the kit was 5 nmol/L. Vitamin D deficiency was defined as serum levels of 25 (OH) D < 75 nmol/lit.

Statistical analysis
All the statistical analyses were performed using SPSS version 16 for Windows. The t-test and/or Man-Whitney test was used for the continuous data and the Chi square test for the categorical data. Multiple logistic regression (MLR) model was fitted to the data to adjust the association between vitamin D status and ischemia for confounders (age, sex, dyslipidemia, diabetes mellitus, and HTN). The result of the logistic regression was presented as odds and 95% confidence interval. A p value < 0.05 was considered statistically significant.

Results
Totally, 294 patients (161 cases and 133 controls) were interviewed. The mean age of all the participants was 59.32±10.55 years. Of the study population, 54.8% were male and approximately 31% were smokers. Distribution of the baseline characteristics by cases and controls is shown in Table I.

The two groups had no significant difference with respect to their baseline FBS, TG, cholesterol, LDL cholesterol, and HDL cholesterol (P>0.05).

The association between vitamin D deficiency and ischemia in the univariate analysis was not statistically significant (crude OR: 0.62, 95% CI: 0.33-1.17). After MLR analysis for the other risk factors (age, sex, blood pressure, FBS, and lipid profile), the association between vitamin D deficiency and ischemia remained non-significant (adjusted OR: 0.83, 95% CI: 0.37-1.85)

Table I. Demographic and clinical characteristics of the ischemic and non-ischemic patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ischemic</th>
<th>Non-ischemic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=161</td>
<td>n=133</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male; %</td>
<td>115 (71.4%)</td>
<td>46 (28.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (year)</td>
<td>61.45±10.11</td>
<td>56.5±10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123.08 (16.5)</td>
<td>123.03 (17.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75.98 (9.9)</td>
<td>73.88 (10.83)</td>
<td>NS</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>121.49 (43.06)</td>
<td>114.97 (30.19)</td>
<td>NS</td>
</tr>
<tr>
<td>25 (OH)D (nmol/lit)</td>
<td>40.80 (33.10)</td>
<td>40 (41.33)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>158.3 (80.2)</td>
<td>157.1 (83.6)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>98.4 (28.8)</td>
<td>95.8 (25.9)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>41.83 (10.16)</td>
<td>43.2 (11.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>67 (41.9)</td>
<td>24 (18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data for gender and smoking are presented as numbers (%)
**Data for vitamin D are presented as medians (interquartile range); and for all the other variables, the data are presented as mean (SD).

Discussion
In this study, we found no remarkable association between the serum levels of 25(OH) D and coronary artery disease in patients who were referred for angio-
Here, we measured the serum level of 25(OH)D because it reflects vitamin D produced cutaneously and that obtained from food (exogenous and endogenous sources of vitamin D) and has a fairly long circulating half life of 15 days, while the circulating 1,25(OH)2D is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and its levels are not decreased unless vitamin D deficiency is severe. \(^\text{14}\) Vitamin D is classically known for its crucial role in calcium and bone metabolism. However, recent advances in research have introduced the new roles for vitamin D in the pathogenesis of many chronic diseases, including cardiovascular disorders. \(^\text{15}\) Several experimental and epidemiological studies have studied the relation between vitamin D and vascular disease. Evidence is accumulating, that vitamin D may exert various direct and indirect effects on the cardiovascular system. \(^\text{13-16-17}\) Several prospective studies, including the Intermountain Heart Collaborative (IHC) Study, which included >40,000 individuals from a general health care population, have evaluated this risk. In this study, individuals with low serum concentrations of 25(OH)D were at significantly increased risk for future cardiovascular diseases, in particular for heart failure and cerebrovascular events. \(^\text{18}\) Significant associations between low 25(OH)D levels and increased risk of fatal cardiovascular events, and in particular sudden cardiac death, were also observed elsewhere in patients referred for coronary angiography. \(^\text{19}\) It is worthy of note that the association between vitamin D and heart disease in some studies was not in line with the above observations. In a systematic review conducted to quantitatively and qualitatively summarize the available evidence regarding the possible cardiovascular harms and benefits of vitamin D, \(^\text{20}\) 51 eligible trials with moderate quality were studied and as yet there is no consensus over a statistically significant effect of vitamin D on important cardiovascular events. In another study performed by Michos and his colleagues, no significant correlation was observed between 25(OH)D levels and coronary artery calcification or carotid intimal medial thickness (as an indicator of sub clinical vascular disease). \(^\text{21}\) Lack of a close association between low vitamin D status and coronary artery disease and also serum levels of both 25(OH)D and 1,25(OH)2D with fatal myocardial infarction in the study of Pilz et al. \(^\text{19}\) is indeed in line with our findings. Similarly, the Pilz et al. study suggested that vitamin D deficiency might be more related to the pathogenesis of myocardial disease with non-ischemic origins than those with ischemic origins. What should also be taken into account is the fact that the cut-off of level of vitamin D could influence the result of these studies. Indeed, Grandi et al. found that the risk of cardiovascular mortality was increased in individuals with 25(OH)D levels below a cut-off ranging from ~25 to 50 nmol/Lit. \(^\text{22}\) In this context, it could be argued that the high levels of vitamin D cut-off may account for the absence of an association between ischemia and vitamin D levels in our study. On the other hand, it is possible that overall low levels of plasma vitamin D in our study population may account, at least partially, for the absence of such correlation. Several possible confounders were adjusted in our analysis, and still no correlation of ischemic status and vitamin D levels was found. We need to point out that we cannot exclude the existence of other unconsidered or unmeasured factors which could potentially affect the ischemic status and thereby influence the relation between vitamin D and coronary vascular disease in our study. Our study population had generally low levels of plasma 25(OH)D with a median of 40.80 nmol/Lit in the ischemic and 40 nmol/Lit the in non-ischemic group. More than 78% of our subjects suffered from vitamin D deficiency. In accordance with our observation, in a recent study performed by Heshmat et al. \(^\text{3}\), the
prevalence of moderate to severe vitamin D deficiency among male and female subjects resident in Tehran and aged between 50 and 60 years, was reported to be high and reach 58.5% in the males and 51.5% in the females. It should be noted that in their study, the levels of vitamin D below 63 nmol/Lit was considered as vitamin D deficiency, which was still lower than that of our cut-off limit of 70 nmol/Lit. This may explain why the occurrence of vitamin D deficiency was higher in our study. No general consensus has yet emerged on the blood level of 25(OH)D, defined as vitamin D deficiency. Generally, the 25(OH)D level below which PTH levels start to rise (~75 nmol/L) is frequently used for the definition of a sufficient vitamin D status.

In our study, the occurrence of the major factors that could influence the ischemic disease was assessed; and except for smoking status, the prevalence of other diseases was similar between the two groups of ischemic and non-ischemic patients. Diabetes mellitus, HTN, and dyslipidemia are known as the traditional risk factors for IHD. One reason for the lack of difference in the percentile of these risk factors between the two groups could be caused by the low number of patients in our study. A good control of risk factors such as hyperlipidemia and HTN could also be considered for this similarity since in both groups any previous history of IHD was considered as an inclusion criterion. Finally, we assessed the factors that could affect the vitamin D status and we found that male gender, diabetes mellitus, and age were the factors that significantly influenced the general status of vitamin D. In accordance to our findings, a poor vitamin D status is partially associated with a higher prevalence and incidence of type II diabetes mellitus.

Vitamin D metabolites could affect insulin secretion and improve insulin sensitivity. Some interventional studies have shown that vitamin D supplementation improves glucose metabolism by reducing insulin resistance.

In conclusion, we evaluated the general status of vitamin D in a small population of patients who were referred for angiography. We did not detect remarkable differences in regard to vitamin D deficiency and could not find the correlation between serum levels of vitamin D and ischemia. One limitation of our study was the relatively low number of the subjects. The two groups of case and control in our study were not matched in terms of gender distribution. However, they presented a sex different pattern in IHD, which is generally seen in the normal population: in other words, the ischemic group had a higher percentage of male subjects than did the non-ischemic group. Further studies with larger sample sizes and well-matched groups are recommended to evaluate the role of vitamin D in ischemia and cardiovascular diseases.

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