Vitamin D Deficiency is Associated With Higher Level of High Sensitivity C-reactive Protein (Hs-crp) in Patients Undergoing Elective Coronary Stenting

farzaneh foroughinia (farzanehforoughinia@yahoo.com)
Shiraz University of Medical Sciences School of Pharmacy https://orcid.org/0000-0003-3993-2043
Shaghayegh Mottaghi
Shiraz University of Medical Sciences Medical School
Mohammad Reza Alimardani
Shiraz University of Medical Sciences

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Abstract

Background: Vitamin D deficiency, a prevalent worldwide concern, has been reported to have a pivotal role in many cardiovascular and inflammatory diseases. Percutaneous coronary intervention (PCI) is a therapeutic approach that may have several short-term and long-term cardiovascular complications, supposing to be mediated with high sensitive C-reactive protein (hs-CRP), an inflammatory marker. This study aimed to investigate the association between vitamin D status and hs-CRP level, as a prognostic marker, in patients undergoing elective PCI.

Methods: The study population comprised of 150 patients who underwent elective coronary angioplasty. In order to measure vitamin D and hs-CRP levels, venous blood samples were obtained at baseline and 24 hours after PCI.

Results: Our results showed a significant inverse relationship between post-PCI hs-CRP and also pre-post hs-CRP difference levels and vitamin D status.

Conclusion: Hs-CRP content is higher in vitamin D deficient patients. Therefore, these patients, especially severely-deficient ones (25(OH)D<10ng/ml), may benefit from supplementation with vitamin D prior to PCI.

Background

Vitamin D deficiency is a prevalent problem affecting 37-96% of adults in the general population, with higher incidences in the Middle East and the South Asia.[1, 2] In spite of some uncertainties in its definition, vitamin D deficiency is generally regarded as 25-hydroxyvitamin D (25(OH) D) levels less than 20ng/ml. Vitamin D levels ranging between 21 to 29 ng/ml and those higher than 30 ng/ml are considered as vitamin D insufficiency and sufficiency, respectively.[3]

Traditionally, vitamin D is known as a major component in regulation of calcium and phosphate hemostasis and consequently of bone mineralization. In addition, other advanced functions have been demonstrated for vitamin D in many researches.[3] The target organs of non-traditional functions of vitamin D are β-cells of pancreas, immune system, cardiovascular and vascular endothelial cells, reproductive systems, and the brain.[4, 5]

Vitamin D deficiency has been reported in patients with cardiovascular diseases. Dziedzic et. al. reported significantly higher vitamin D levels in diabetic patients with Coronary Artery Surgery Study Score (CASSS) 0, compared with those with CASSS 1, 2 or 3 that underwent cardiac catheterization.[6] Another study also showed that severe vitamin D deficiency (defined as 25(OH) D < 10ng/ml) may increase the risk of acute myocardial infarction (MI) in Indian population.[7] A prospective cohort study on 3258 patients undergoing coronary angioplasty, reported that low levels of 25(OH) D and 1, $25(OH)_2$ D could enhance cardiovascular mortality risk in these patients.[8]

High sensitive C-reactive protein (hs-CRP) is a non-specific marker for inflammation. It is produced mainly in the liver in response to pro-inflammatory cytokines (e.g. interleukin 6). Several reports associated hs-CRP level with certain cardiovascular complications, especially following coronary and carotid angioplasty. Roghani et al. described hs-CRP as a prognostic marker for identifying patients at a high risk of restenosis and recurrent cardiovascular events, after coronary stenting.[9] In addition, there are studies claimed that agents which can decrease hs-CRP may have potential to prevent cardiovascular events following percutaneous coronary intervention (PCI).[10]

Given the immunomodulatory and anti-inflammatory effects of vitamin D, this assumption was made that vitamin D deficiency may be correlated with a higher elevation of inflammatory markers after coronary angioplasty that could be translated to an increased likelihood of cardiovascular complication following PCI. Regarding evidences for aforementioned possible relationships, this study aimed to evaluate the exact association between hs-CRP levels and vitamin D status in patients undergoing elective PCI.

Methods

The study population comprised of 150 patients, undergoing coronary angioplasty at Kosar hospital, a tertiary care heart center affiliated to Shiraz University of Medical Sciences (SUMS), from January 2018 to August 2018. This prospective study conformed to the ethical principles of SUMS.

Study population

After the selection of illegible patients by the cardiologist and filling the consent form by patients, the candidates were recruited to the study. The inclusion criteria include an age range of 18-80 yrs, successful PCI and patient's consent to participate into the study.

Patients with history of vitamin D supplements, anti-seizure and glucocorticoid medications usage during the last one month, bypass surgery within the last 3 months, ST-elevated myocardial infarction (STEMI), ages above 80 or below 18 years old, and unwillingness to continue the investigation were excluded from the study.

Study protocol

Coronary angioplasty was performed for all eligible participants based on standard protocols. [10] Patients were pretreated with oral aspirin (325 mg/day), clopidogrel (600 mg loading dose at

least 12 h before the procedure) and weight-adjusted intravenous heparin with a target activated

clotting time of 250–350 seconds. Aspirin (325 mg/day for 3 months, then 80 mg/day) and clopidogrel (150 mg/day for 1 month, then 75 mg/day up to 1 year) were administered for all patients following PCI.

The demographic and clinical data such as sex, age, and risk factors for cardiac events were collected in questionnaires. Venous blood samples were obtained at baseline and 24 hours after PCI for measuring of vitamin D and hs-CRP levels, respectively.

Hs-CRP Monobind ELISA kit (INC, Lake forest, CA 92630, USA) was used to measure hs-CRP levels. According to manufacturer's instructions, the minimum measurable hs-CRP level for this kit was 0.156 ng/ml. vitamin D level was measured by High Performance Liquid Chromatography (HPLC) technique.

Patients were classified into two groups of vitamin D deficient (20ng/ml) and vitamin D insufficient/sufficient (≥20ng/ml) based on vitamin D level.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences version 21 (SPSS Inc, Chicago, USA). The Kolmogorov–Smirnov test was used to evaluate whether the variables were normally distributed. Mann–Whitney U tests was performed to examine quantitative variables in different categories of vitamin. Chi-square test was also applied to determine the correlation between vitamin D categories and qualitative variables. Pairwise comparison test was conducted for exploring the statistically significant difference regarding post-PCI hs-CRP and pre-post hs-CRP difference, using Mann-Whitney test. For all tests, $P < 0.05$ was considered significant.

Results

150 patients were enrolled in this research, of which 59.3% (n=89) were men with the mean age of 58.47±7.58 yrs and the mean vitamin D level of 15.12±7.19 ng/ml. The women's (40.7%) average age and vitamin D level were 60.86±11.91 yrs and 20.73±12.90 ng/ml, respectively. Demographic and clinical features of patients reported in table 1. No significant differences were seen in terms of mean age, history of diabetes mellitus (DM), hypertension, dyslipidemia, smoking, previous myocardial infarction (MI), previous PCI, mean glomerular filtration rate (GFR) and past drug history between two groups of vitamin D level. However, a significant difference was observed regarding sex (P=0.001) and weight (P=0.02) among study categories, revealing higher prevalence of vitamin D deficiency in males compared to females and higher weight in vitamin D deficient subjects. Vitamin D deficiency was observed in 68.66% of the patients in this study.

Table 1. Demographic and clinical features of the study patients (n=150)

p-value	Group 2 (x≥20 ng/ml) (n=49)	Group 1 (x<20 ng/ml) (n=101)	Variable
0.001	20(22.5) 29(47.5)	69(77.5) 32(52.5)	Sex, N (%) Male Female
0.05	62.57±8.38	60.13±10.63	Age, yrs, mean ± SD
0.02	66.18±9.00	72.23±14.26	Weight, Kg, mean±SD
0.81	17(34)	33(66)	Diabetes mellitus, N (%)
0.12	39(36.4)	68(63.6)	Hypertension, N (%)
0.97	21(32.8)	43(67.2)	Dyslipidemia, N (%)
0.06	6(18.7)	26(81.3)	Smoker, N (%)
0.04	7(58.3)	5(41.7)	Previous PCI, N (%)
0.18	3(60)	2(40)	Previous MI, N (%)
0.90	33(33)	67(67)	BB, N (%)
0.78	15(42.9)	20(57.1)	CCB, N (%)
0.69	25(31.3)	55(68.8)	ACEI/ARB, N (%)
0.78	36(33.3)	72(66.7)	Statin , N (%)
0.23	55.91±13.12	59.78±15.32	GFR, ml/min/1.73 $m^{2,}$ mean±SD

PCI, Percutaneous coronary intervention; MI, Myocardial infarction; BB, beta-blocker; CCB, calcium-channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/ angiotensin receptor blocker; GFR, Glomerular filtration rate.

Evaluation of the degree of coronary vessel stenosis among various vitamin D categories revealed a stepwise decrease in stent length and increase in coronary vessel stenosis as vitamin D levels decreased; however, the aforementioned differences were not statistically significant.

As mentioned in the table 2, Pre-PCI hs-CRP was not statistically different among the studied groups (P=0.15). In contrast, post-PCI hs-CRP (P=0.01) and pre-post hs-CRP difference (P=0.001), both showed a statistically significant difference between two categories of vitamin D. Pairwise comparison revealed that patients with severe vitamin D deficiency (<10 ng/ml) have significantly higher levels of post-PCI hs-CRP and pre-post hs-CRP difference compared to those with moderate vitamin D deficiency (11-19 ng/ml) and vitamin D insufficiency/sufficiency (≥20 ng/ml) (P< 0.001).

Table 2. Serum level of hs-CRP in different groups of vitamin D levels

Hs-CRP Level (mg/L)	Vitamin D_3		P-value
	Group 1 (x<20 ng/ml) (n=101)	Group 2 (x≥20 ng/ml) (n=49)	
Pre-PCI, median(IQR)	1.46(2.52)	1(2.39)	0.15
Post-PCI, median(IQR)	4.06(8.20)	1.73(3.66)	0.01
Post-pre difference, median(IQR)	2.27(5.96)	0.90(1.60)	0.001

IQR, Interquartile range

Discussion

The primary goal of this study was to investigate the association between vitamin D serum levels and hs-CRP, as a prognostic factor for post-PCI complications. The main findings of this research were as follows: 1. higher levels of post-PCI and pre-post hs-CRP difference are significantly related to lower levels of vitamin D 2. No significant differences in pre-PCI and post-PCI hs-CRP, and pre-post PCI hs-CRP difference were found between women and men 3. In terms of vitamin D status, most of vitamin D deficient patients were male.

A review of 41 observational studies demonstrated various prevalence of vitamin D deficiency in adults ranging from 44% to 96% with the mean 25(OH)D level in the range of 11-20 ng/ml.[1] Several studies have also reported the widespread prevalence of vitamin D deficiency even in sunny regions. An analysis on 12,346 patients in Abu-Dhabi, a sun-rich country, demonstrated about 83% suboptimal vitamin D level in the investigated population.[11] Another study performed on 547 patients in Qatar, another sunny country, revealed 91% vitamin D deficiency (25(OH) D level < 30 ng/ml) among studied population.[12]

In most studies, female gender was identified as a predictor for hypovitaminosis D.[1, 13] A meta-analysis of 48 investigations demonstrated a more prevalence of vitamin D deficiency in women (45% in male Vs 60% in female) among Iranian population.[14] In contrast, one study showed higher prevalence of vitamin D deficiency in obese Norwegian males compared to females.[15] Similarly, our results showed a statistically significant relation between vitamin D levels and gender (P<0.05). In other words, the majority of vitamin D deficient patients were male. In comparison to females, males who are vitamin D deficient could be at a higher risk for diseases such as diabetes mellitus, dyslipidemia, and coronary artery disease. Also, they might have a lower left ventricle ejection fraction.[12] It is believed that Matrix metalloproteinase (MMP) may be involved in the vitamin D deficiency pathophysiology. In addition, Framingham heart study mentioned that males with elevated plasma levels of MMP-9 may have a higher risk of cardiac wall thickness and large end-diastolic left ventricular size.[16] Taking all these facts into

consideration, it is conceivable that males with vitamin D deficiency might be more prone to cardiovascular complications. In addition, our results revealed that vitamin D deficient cases have significantly higher weight than patients with vitamin D levels above 20 ng/dl that is consistent with the result of studies reporting higher frequency of vitamin D deficiency in overweight and obese children and adolescents.[17]

Several mechanisms have been described for the relation between vitamin D deficiency and increment in the risk for cardiovascular diseases (CVD). Low levels of vitamin D are believed to contribute to a rise in blood pressure. The pathophysiology suggested for this indirect association, is a multifold enhancement in renin expression and plasma angiotensin II in vitamin D receptor null (VDR-null) subjects. As a result, hypertension, cardiac hypertrophy, and increased water and sodium retention may occur in vitamin D deficient subjects. This hypothesis was confirmed by injecting $1,25(OH)_2D$ to mice, followed by a suppression in renin-angiotensin system (RAS).[18] As reported in several studies, RAS has a pivotal role in cardiovascular system functions. Unregulated RAS may develop pathologic conditions including atherosclerosis, hypertension, and insulin resistance.[19]

Another explanation for the relationship between vitamin D deficiency and cardiac diseases would be the observed role of vitamin D in improving glycemic control and insulin sensitivity as demonstrated in a recent meta-analysis.[14] Overall, vitamin D deficiency is associated with multiple components of metabolic syndrome, including insulin resistance, abdominal obesity, hypertension, and even dyslipidemia.[19] As shown in our study, vitamin D deficient patients are more frequently overweight than vitamin D insufficient/sufficient ones. A study on 105 women undergoing elective coronary angiography, reported a significant negative linear correlation between 25(OH)D categories and burden of coronary artery disease (CAD). It also indicated an inverse association between vitamin D level and left circumflex (LCx) and right coronary artery (RCA) stenosis degree.[20] Even though higher degree of left anterior descending (LAD) and RCA coronary stenosis was found in vitamin D deficient patients; this difference was neither statistically nor clinically significant between groups in our study.

High hs-CRP levels have been regarded as an independent risk factor for CVDs. In addition, higher hs-CRP may increase early complications of coronary procedures such as PCI, including MI, coronary dissection, and perforation.[9, 21] Increased hs-CRP can also augment the risk of late cardiac complications, in patients undergoing coronary angioplasty, even up to 3 years after the procedure.[22] Hence, there is a concern for short term or long term cardiac complications in patients with high hs-CRP who have undergone PCI. Therefore, it is assumed that addition of agents capable of decreasing this inflammatory biomarker, to the standard drug regimen before PCI may be effective in the prevention of post-PCI complications.[23]

There are several reports demonstrating the relationship between vitamin D and inflammation. Vitamin D deficiency has been also reported to be associated with cardiovascular inflammation[24] and vascular endothelial dysfunction.[20] It has been stated that vitamin D may reduce smooth muscle cell proliferation

and pro-inflammatory cytokines secretion such as tumor necrosis factor-α (TNF-α), increase anti-inflammatory cytokines such as interleukin-10 (IL-10), and impair macrophage maturation.[24] Macrophages and dendritic cells convert vitamin D to its active form, 1, 25$(OH)_2$D that suppresses the production of inflammatory factors, namely interferon-γ (IFN-γ), interleukin-5 (IL-5), and interleukin 2 (IL-2). It is noteworthy that interleukin 6 (IL-6) synthesis, which stimulates CRP production, is inhibited by vitamin D.[25] As a result, vitamin D deficiency is theoretically expected to be associated with elevated levels of hs-CRP.

The goal of our research was to evaluate the association between serum vitamin D status and hs-CRP levels as a proposed pathway for the adverse effect of vitamin D deficiency on PCI outcome. In this study, a statistically significant inverse relationship was observed between baseline vitamin D level and post-PCI hs-CRP level. In a clinical trial, vitamin D was administered at the dose of 300 000 IU orally 12 hours before PCI. The mean difference in hs-CRP was reported to be significantly lower in the vitamin D group compared to controls. Although no clear effect of vitamin D in the prevention of cardiac injury was observed in this study, a significant lower mean difference in CK-MB was reported between 8 and 24 hours in vitamin D groups. [26] Reports of this trial in addition to ours substantiate our hypothesis about the negative impact of vitamin D deficiency on PCI outcome through masking its anti-inflammatory effect, with emphasis on hs-CRP, in these patients.

The limitation of this study was the impossibility of following the subjects up after PCI. In order to obtain more reliable clinical results, future studies should address the association between vitamin D deficiency and short-term and long-term cardiovascular complications following PCI.

Conclusion

From a practical point of view, assessing vitamin D level before the coronary artery intervention may contribute to better evaluation of the risk for post-PCI short-term and possibly long-term complications. As a result, an enhancement approach for improving survival of the post-PCI patients might involve supplementation with vitamin D in patients with vitamin D deficiency, especially severely-deficient cases, prior to PCI.

Abbreviations

hs-CRP: High sensitivity C-reactive protein

PCI: Percutaneous coronary intervention

CASSS: Coronary Artery Surgery Study Score

SUMS: Shiraz university of medical sciences

STEMI: ST-elevated myocardial infarction

DM: Diabetes Mellitus

GFR: Glomerular filtration rate

MI: Myocardial infarction

IQR: Interquartile range

VDR-null: Vitamin D receptors-null

RAS: Renin-angiotensin system

LAD: Left anterior descending

LCX: Left circumflex artery

RCA: Right coronary artery

MMP: Matrix metalloproteinase

CVD: Cardiovascular diseases

TNF-α: Tumor necrosis factor-α

IL-10: Interleukin-10

IL-5: Interleukin-5

IL-2: Interleukin-2

IL-6: Interleukin-6

IFN-γ: Interferon-γ

Declarations

Ethics approval and consent to participate

This study has been approved by the ethics committee of Shiraz University of medical sciences (SUMS) and all patients signed informed consent form.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FF: Contributed to the conception and design of the work, the analysis and interpretation of data, drafted the work and substantively revised it.

MRA: Contributed to the conception of the work, the acquisition of data and drafted the work.

ShM: Contributed to the interpretation of data, drafted the work and substantively revised it.

All authors read and approved the final manuscript.

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