The Effect of Vitamin D Deficiency Treatment on Lipid Profile and C-reactive Protein in Patients with Ischemic Heart Disease: Double-blind Randomized Clinical Trial

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Abstract

Background: Atherosclerosis is the main process in coronary artery stenosis, which is exacerbated by vitamin D deficiency. This study aims to investigate the relationship between vitamin D deficiency treatment, lipid profile, and C-reactive protein (CRP) in ischemic heart disease (IHD).

Materials and Methods: This is a double-blind, randomized clinical trial involving 44 IHD patients with hypovitaminosis, aged 40–65 years, who were referred to Chamran Specialty Heart Hospital, Isfahan, Iran. Participants were randomly divided into two groups: The intervention group received weekly doses of 50,000 units of vitamin D_3 for 5 weeks, while the placebo group received a control substance. CRP and serum lipid profiles, including total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were assessed before and after the intervention. Trial registration number: IRCT20200905048622N1.

Results: The mean age of the IHD patients was 57.84 ± 9.66 years, and among all 44 patients, 40 patients (91%) were male In the intervention group receiving vitamin D_3, serum levels of HDL ($P = 0.048$) and 25-hydroxyvitamin D (25(OH)D) ($P < 0.001$) increased, while serum level of TG ($P = 0.008$) decreased significantly. In the placebo group, HDL level ($P = 0.007$) was increased and alanine transaminase (ALT) ($P = 0.05$) was significantly decreased. The results showed that the correlation between serum 25(OH)D treatment and CRP level was not significant.

Conclusion: Vitamin D supplementation in IHD patients led to notable improvements in lipid profiles, including increased HDL-C levels and decreased TG levels. These findings hold potential clinical implications for healthcare professionals in managing risk factors in IHD patients.

Keywords: Cholesterol, C-reactive protein, ischemic heart disease, triglyceride, vitamin D

INTRODUCTION

Cardiovascular disease is a multifactorial process influenced by various lifestyle behaviors and genetic factors. With shifts in people's lifestyles, there has been an increase in the risk factors for ischemic heart disease (IHD) such as diabetes mellitus, hypertension, dyslipidemia, and obesity.[1] IHD imposes a significant burden of mortality and morbidity on healthcare systems worldwide, stemming from inadequate blood flow and oxygen supply to the myocardium. Atherosclerosis, characterized by coronary artery stenosis, is identified as an inflammatory process wherein various factors, including

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vitamin D, C-reactive protein (CRP) levels, and lipid profile, play pivotal roles in this cascade.[2–4]

Vitamin D, an essential fat-soluble vitamin, exhibits a common worldwide deficiency, which is defined by a serum threshold of 25-hydroxyvitamin D (25(OH)D) below 25-30 nmol/l, with reported rates ranging from 20% to 80% in the general population and even higher in severely ill patients.[5,6] While sunlight stimulates the major natural source of vitamin D through chemical reactions in the skin, dermal synthesis can be hindered by various factors. Moreover, natural dietary sources of vitamin D are limited and rarely consumed. Consequently, there is a growing trend towards vitamin D supplementation to mitigate diseases such as cardiovascular disease, cancer, and infections.[7]

Dyslipidemia has consistently been identified as a primary risk factor for atherosclerosis and subsequently cardiovascular disease, which is characterized by the accumulation of lipid plaques within arteries. Dyslipidemia manifests as an imbalance of one or more lipoproteins in the blood, including elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or diminished levels of high-density lipoprotein cholesterol (HDL-C).[8] Vitamin D deficiency is associated not only with cardiovascular disease but also with its risk factors, including dyslipidemia. Jiang *et al.*,[9] in a cohort study of 3788 adults, reported an inverse correlation between serum 25(OH)D and LDL-C, as well as triglyceride (TG), and a positive correlation with HDL-C levels. While most studies have demonstrated the positive impact of vitamin D on improving lipid profiles, some have yielded contrasting results.[10,11]

CRP is an annular pentameric protein primarily synthesized by the liver and serves as an acute inflammatory marker that elevates rapidly in response to tissue injury, infection, and inflammation. Higher levels of CRP indicate more severe inflammation.[12,13] Recent research suggests that individuals with elevated CRP levels face an increased risk of developing diabetes, hypertension, and cardiovascular diseases, underscoring the significance of this marker in IHD patients. Elevated CRP levels may be indicative of ischemic necrosis in coronary arteries, and the inhibition of CRP could potentially serve as an effective therapeutic approach for IHD, warranting further investigation in future studies.[14] Additionally, low vitamin D status is often associated with inflammation, leading to elevated CRP levels. Thus, rectifying vitamin D deficiency may contribute to the reduction of this biomarker.[15]

Despite numerous studies examining the effect of vitamin D on lipid profiles and CRP, limited studies have specifically assessed this relationship in patients with IHD. Therefore, our objective is to investigate and evaluate the effectiveness of vitamin D treatments on lipid profiles and CRP levels in IHD patients.

In this era of specialized research, various studies were conducted, leading to different results. Considering the central role of dyslipidemia in the development of myocardial infarction (MI) in conjunction with the current knowledge of the influence of vitamin D on blood lipids, it is plausible that correcting vitamin D deficiency could attenuate the influencing factors in the inflammatory process and dyslipidemia. This, in turn, could attenuate the atherosclerotic process in the coronary arteries and contribute to the improvement of symptoms after MI. Consequently, this intervention could bring positive results for the patients.

This study is aimed to evaluate the effect of vitamin D supplementation on serum levels of TG, LDL-C, HDL-C, TC, and CRP in patients with IHD.

MATERIALS AND METHODS

This study is a double-blind, randomized clinical trial conducted on 44 IHD patients who were referred to Chamran Specialty Heart Hospital in 2019. The study protocol received approval from the Research Committee of Isfahan University of Medical Sciences and was confirmed by the ethics committee.

All IHD patients who were referred to Chamran Hospital in 2019 and then referred to a cardiac rehabilitation center, including those who met the inclusion criteria, were enrolled in this study. The inclusion criteria for this study were IHD patients aged between 40 and 65 years with hypovitaminosis (serum level of 25(OH)D <25 ng/ml), and a willingness to participate in this clinical trial. Patients with severe vitamin D deficiency (below 10 ng/ml), those with normal or higher than normal pre-study vitamin D levels, individuals with hyperparathyroidism, liver failure, kidney failure, kidney stones, or any life-threatening underlying diseases, as well as those taking vitamin supplements on their own, did not meet the inclusion criteria. Exclusion criteria encompassed patients who refused to adhere to our instructions, became unavailable, passed away, or took vitamin D supplements outside the study's protocol.

Patients with MI are considered as IHD patients. It was defined as the presence of at least two out of the three following criteria: Typical chest pain lasting more than 30 min, suggestive electrocardiographic change, and an increase in the serum level of cardiac biomarkers.

Participants were randomized using computer-generated random numbers into two groups: The placebo group and the vitamin D group. Numbered, sealed, and opaque envelopes were employed to ensure the concealment of group allocation. Random allocation sequence generation, allocation concealment, and participant enrollment were overseen by the primary investigator who was not involved in the final analysis. Neither the patients nor the researchers involved in conducting the research were aware of which patients received the drug or placebo. The drugs and placebo were produced similarly in shape (round yellow pearls) according to the Zahravi pharmaceutical company's specifications and differed only in the presence of the active ingredient.

All included patients signed a personal consent form. Before the intervention, the serum levels of TG, TC, HDL, LDL, fasting blood sugar (FBS), alanine transaminase (ALT), aspartate aminotransferase (AST), 25(OH) vitamin D, and CRP were measured. Blood samples were collected from the patient's left cubital vein and assessed using high-performance liquid chromatography (HPLC) and enzyme-linked immunosorbent assay (ELISA) methods.

The treatment for serum vitamin D deficiency involved administering 50,000 units of one pearl of vitamin D_3 per week for up to 5 weeks, while the placebo was administered to the control group concurrently. The control group received medication for vitamin D deficiency after the project.

After 5 weeks, blood samples were obtained from the patients once again, and the serum levels of TGs and cholesterol were measured and compared between the intervention and control groups. Throughout the study, patients received all necessary cardiac drugs for IHD, including statins and both groups were equivalent in this regard.

Statistical analysis

Descriptive data were presented as mean, standard deviation, absolute numbers, and percentages. Response variables included lipid profile status and high sensitivity CRP (hs-CRP) levels of IHD patients in the two groups (intervention/placebo) over the 5-week follow-up period. Independent variables encompassed demographic factors (age and sex), measurement factors (BMI (body mass index) and waist circumference), and laboratory parameters, including TC, HDL, LDL, TG, FBS, AST, ALT, and CRP levels. For parameters demonstrating a normal distribution, Student's *t*-test was utilized to compare groups, while paired *t*-tests were employed to compare variables before and after the study within each group. Chi-square tests (or Fisher's test) were used for the comparison of qualitative variables between the two groups. A *P* value of at least 0.05 was considered indicative of statistical significance. All statistical analyses were conducted using SPSS 22 software (IBM Corporation, Armonk, New York, USA).

Trial registration: Iranian Registry of Clinical Trials, Iran. IRCT20200905048622N1.

RESULTS

The mean age of the IHD patients was 57.84 ± 9.64 years old, and among all 44 patients, 40 (91%) were males. The basic characteristics of both groups are presented in Table 1. At the outset of the study, the two groups exhibited homogeneity in terms of baseline characteristics ($P > 0.05$).

Within the intervention group (receiving vitamin D_3), notable changes were observed in serum levels of HDL ($P = 0.048$), TG ($P = 0.008$), and 25(OH)D ($P < 0.001$), all of which were statistically significant. This signifies a significant decrease in TG levels and a remarkable increase in HDL levels. Moreover, 25(OH)D levels exhibited a substantial

Table 1: Comparison of baseline characteristics in intervention and placebo groups

Baseline characteristics	Group		*P*
	Vitamin D	**Placebo**	
Demographic factors			
Sex (male)	20 (90.91%)	20 (90.91%)	
Age (years)	58.09±9.91	57.59±9.62	0.866
Measurements factors			
BMI	27.73±3.08	26.79±2.86	0.299
Waist (cm)	100.57±6.76	98.66±8.01	0.398
Laboratory factors			
TC (mg/dl)	140.67±34.92	152.67±44.57	0.337
TG (mg/dl)	167.188±71.84	167.667±95.89	0.393
HDL (mg/dl)	37.14±9.12	36.14±10.36	0.742
LDL (mg/dl)	71.67±19.81	80.86±28.89	0.236
25(OH) Vitamin D (ng/ml)	17.41±6.89	18.70±6.97	0.545
FBS (mg/dl)	101.81±18.24	111.67±30.82	0.214
AST	25.94±13.31	22.19±6.61	0.861
ALT	32.19±14.93	39.14±25.58	0.288
CRP (Mean±SD)	2.36±2.99	2.32±2.47	0.781

increase after the intervention in this group. Conversely, in the placebo group, HDL levels demonstrated a significant increase ($P = 0.007$), while ALT levels showed a significant decrease ($P = 0.05$) [Table 2].

The comparison of the two groups and their respective changes is displayed in Table 3. The results indicated a significant disparity between the two groups in terms of the 25(OH)D variable. Specifically, the intervention group exhibited a significantly higher level, with notable changes also observed. On average, ALT decreased by 29 IU/l in the placebo group, signifying a more substantial change in comparison to the intervention group [Table 3].

DISCUSSION

Our study demonstrated that treatment of vitamin D deficiency in IHD patients had a significant impact on lipid profiles. Specifically, levels of 25(OH)D and HDL increased, while serum TG levels decreased in the intervention group. Additionally, the placebo group exhibited an increase in HDL levels and a decrease in ALT levels, likely attributable to various treatments administered during follow-up. Notably, our study did not find a significant correlation between serum 25(OH)D treatment and CRP levels.

Previous research has established a close relationship between vitamin D supplementation and favorable lipid profiles, suggesting that vitamin D deficiency may elevate the risk of dyslipidemia.[16] For example, a cohort study involving 637 patients undergoing coronary catheterization reported an inverse correlation between 25(OH)D levels and TC, LDL-C, and TG levels, as well as the stage of coronary atherosclerosis.[17] Another study by Lupton *et al*.[18] found that deficient serum 25(OH)D was associated with lower

Table 2: Comparison of 5 weeks' intervention before and after in vitamin D3 and placebo groups

Variables	Vitamin D3			Placebo		
	Before	**After**	*P*	**Before**	**After**	*P*
Measurements factors						
BMI	27.13±3.33	27.31±3.06	0.377	26.41±2.78	26.69±2.67	0.216
Waist (cm)	99.81±7.73	99.84±7.17	0.941	98.06±7.98	98.32±7.63	0.492
Laboratory factors						
TC (mg/dl)	143.31±39.04	138.12±41.20	0.298	153.28±46.25	146.94±37.66	0.378
TG (mg/dl)	167.19±71.84	135.81±59.45	0.008**	167.67±95.90	136.78±86.33	0.110
HDL (mg/dl)	36.25±10.11	39.44±10.0	0.048**	36.22±10.81	40.61±8.89	0.007**
LDL (mg/dl)	72.13±22.31	70.56±23.27	0.718	82.39±30.28	78.94±28.41	0.445
25(OH) Vitamin D (ng/ml)	16.82±6.35	35.49±12.80	<0.001**	19.15±7.16	21.91±7.43	0.183
FBS (mg/dl)	100.19±16.19	103.69±15.93	0.510	112.94±32.94	107.72±29.48	0.363
AST	22.19±6.61	21.47±4.98	0.585	25.94±13.31	22.50±12.48	0.102
ALT	28.19±11.99	23.99±8.55	0.272	41.94±26.47	27.11±18.08	0.05**
CRP	2.36±2.99	2.60±4.33	0.859	2.32±2.47	2.36±1.44	0.949

**P<0.05 considered as statistically significant

Table 3: Comparison of characteristics after intervention (5 weeks) in both groups

Variables	After intervention			Change		
	Vitamin D	**Placebo**	*P*	**Vitamin D**	**Placebo**	*P*
Measurements factors						
BMI	27.32±3.06	26.69±2.67	0.535	0.86±3.27	1.17±3.34	0.791
Waist (cm)	99.84±7.17	98.32±7.63	0.560	0.09±1.71	0.31±1.48	0.696
Laboratory factors						
TC (mg/dl)	140.71±41.28	151.68	0.436	−3.49±12.16	−1.56±18.07	0.720
TG (mg/dl)	135.81±59.44	136.78±86.33	0.810	−17.91±18.44	−12.68±29.82	0.549
HDL (mg/dl)	39.18±9.74	40.37±8.71	0.701	10.57±19.32	15.41±20.90	0.490
LDL (mg/dl)	61.95±34.89	71.50±41.71	0.428	−0.96±19.20	−1.42±20.85	0.947
25(OH) Vitamin D (ng/ml)	35.00±12.55	21.91±7.43	<0.001**	18.67±12.20	2.76±8.69	<0.001**
FBS (mg/dl)	105.41±16.99	107.79±28.65	0.767	5.96±25.21	−2.92±17.72	0.240
AST	20.91±5.34	22.79±12.20	0.562	−8.57±28.48	−0.12±20.69	0.335
ALT	23.05±9.14	28.16±18.15	0.302	−4.20±14.72	−14.83±19.52	0.085
CRP	2.42±4.10	3.73±5.97	0.450	0.24±5.27	0.041±2.60	0.892

**P<0.05 considered as statistically significant

HDL-C levels and increased levels of directly measured LDL-C, as well as various types of lipid panels in over 20,000 adults.

A 2015 meta-analysis by Manousopoulou *et al*.[19] encompassing eight randomized controlled trials (RCTs) evaluated the correlation between vitamin D supplementation and lipid profile, revealing a lowering effect on TG and an elevating effect on HDL-C, while the impact on LDL-C was less consistent. Caution is warranted with these results, given the limitations of the meta-analysis including a small number of studies and high heterogeneity in interventions. There are also other studies that have demonstrated the positive effect of vitamin D on improving lipid profiles,[20–22] although few studies have not found this relationship.[23,24]

The effect of vitamin D on lipid profile can be caused by the sterol regulatory element-binding proteins (SREBPs). SREBPs are transcription factors that modulate lipid metabolism by upregulating the expression of lipogenic genes. Finally,

25(OH)D has been demonstrated to impair SREBP activation by inducing its proteolytic degradation.[25]

Previous studies have also suggested that the correlation between vitamin D levels and cardiovascular disease may be significant only in patients with elevated CRP levels, with no association found in the absence of high CRP.[26] Our findings on CRP levels align with Bahrami *et al*.,[24] who reported no significant difference between the vitamin D group and the control group in CAD patients. Conversely, Jiang *et al*.[27] found that vitamin D supplementation was associated with a significant decrease in CRP levels in their pooled results from seven RCTs. Rodriguez *et al*.[28] also supported our findings, reporting no effects of vitamin D supplementation on lowering CRP concentrations in heart failure patients.

Finally, due to vitamin D's various biological effects, including antioxidative, anti-inflammatory, antimicrobial, lipid-lowering, and cardiovascular protective effects,[29–31] it may play a significant role in reducing IHD complications. It could

potentially be used as a secondary preventive medication. Future studies may provide further insights into this area.

The main limitation of this study is its small sample size and the short duration of the intervention. Additionally, our study population consisted of patients undergoing cardiac rehabilitation, which itself could impact the lipid profile, although this condition is the same in both study groups. Future studies, by altering the study population, may yield more effective results. Also, further research with larger sample sizes and diverse doses of vitamin D is warranted to provide a more comprehensive understanding of the effects of vitamin D supplementation on lipid profiles and CRP levels. This study serves as a valuable starting point for future investigations. The strength of our study lies in its use of a clinical randomized trial, which is considered the gold standard with a low risk of bias. To build upon this, larger studies with extended follow-up times, consideration of comorbidities, and adherence assessments are recommended for a more comprehensive analysis.

CONCLUSION

The results of our study highlight the potential benefits of vitamin D supplementation for patients with IHD, particularly in decreasing serum levels of TG. This finding carries significant implications for healthcare practitioners and policymakers in the healthcare sector, offering a potential avenue to enhance life expectancy in individuals with IHD through more effective management of risk factors.

Conflicts of interest

There are no conflicts of interest.

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