Cross-sectional Study

ANNALS OF MEDICINE & SURGERY

OPEN

Alterations in serum levels of calcium, vitamin D, phosphorus, and parathyroid hormone in patients with clinically confirmed familial hypercholesterolemia: a cross-sectional study

Kiyan Heshmat-Ghahdarijani, MD[a], Golnaz Vaseghi, PharmD[b], Shabnam Hajian, MD[c], Marzieh Taheri, MSc[c], Shaghayegh Haghjooy-Javanmard, MD[b], Nizal Sarrafzadegan, MD[c], Danial Habibi, PhD[d], Anahita Babak, MD[d], Mehrdad Rabiee Rad, MD[c,*]

Background: Familial hypercholesterolemia (FH), an autosomal dominant disease, is associated with an increased risk of premature cardiovascular disease (CVD). This study aimed to examine the variations in serum levels of calcium, vitamin D, phosphorus, and parathyroid hormone (PTH) among FH patients, as these factors have been associated with an increased susceptibility to CVD.

Materials and methods: In this cross-sectional study, the authors used data from Isfahan FH registry. The Dutch Lipid Clinic Network (DLCN) criteria was used for diagnoses of FH patients. Control group included participants with hyperlipidemia and were unlikely FH according to DLCN criteria. All biochemical parameters were measured using standard methods.

Results: A total of 131 patients (mean age, 53.1 ± 12.2; male, 51.4%) were included in the analysis. Patients with FH had lower serum vitamin D levels compared with control groups in the unadjusted model ($P = 0.028$). The relationship between serum vitamin D and FH was not significant after adjustment for traditional risk factor ($P = 0.184$). No significant association was observed between FH and serum calcium ($P = 0.886$), phosphorus ($P = 0.463$), and PTH ($P = 0.849$). Besides, there was no significant association between LDL-C or total cholesterol and serum minerals in FH patients.

Conclusion: This study found no significant changes in serum calcium, vitamin D, phosphorus, and PTH in patients with FH.

Keywords: calcium, familial hypercholesterolemia, FH, phosphorus, vitamin D

Introduction

Familial hypercholesterolemia (FH) is a common, dominantly inherited disorder with a prevalence of ~1 per 300 in the general population. FH is characterized by severely elevated low-density lipoprotein cholesterol (LDL-C), tendon and skin xanthomas, and premature atherosclerotic events. A functional mutation in the LDL receptor is the most common cause of FH and accounts for ~85–90% of all mutations, followed by mutations in the apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes. Untreated FH can be associated with a reduction in period life expectancy and premature cardiovascular disease (CVD)[1,2].

Recent research has highlighted the potential role of vitamin D and calcium in cardiovascular health. Vitamin D plays a crucial role in maintaining bone health, but it also exhibits pleiotropic effects, such as modulation of immune system function, regulation of endothelial homeostasis, and influencing inflammation and oxidative stress[3–5]. Moreover, vitamin D deficiency has been associated with increased CV risk and arterial stiffness[6,7]. Besides, previous studies showed the association of serum calcium with cardiovascular events including myocardial infarction and coronary heart disease[8]. Some evidence showed an association between alteration in serum calcium level and worsening lipid profile. An observational study on 8610 subjects revealed

HIGHLIGHTS

- Lower serum vitamin D levels observed in familial hypercholesterolemia (FH) patients compared to control groups.
- No significant association between FH and serum vitamin D, calcium, phosphorus, and parathyroid hormone (PTH) levels.
- No significant relationship found between LDL-C or total cholesterol levels and serum minerals in FH patients.

[a]Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, [b]Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, [c]Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences and [d]Department of Biostatistics and Epidemiology, School of Public Health, Babol University of Medical Sciences, Babol, Iran

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Isfahan university of Medical Sciences, Hezar Jerib Avenue, Isfahan 8174675731, Iran. Tel.: +98 930 351 1302, +98 913 824 7938. E-mail: m.rabieerad@yahoo.com (M. Rabiee Rad).

Annals of Medicine & Surgery (2024) 86:6502–6506

Received 26 June 2024; Accepted 27 August 2024

Published online 10 September 2024

http://dx.doi.org/10.1097/MS9.0000000000002558

increasing in serum calcium levels while increasing lipids including total cholesterol (TC) and LDL-C in men and postmenopause women[9].

Calcium and phosphorus are regulated by parathyroid hormone (PTH) and calcitonin. By acting on bones, PTH increases the level of calcium in the blood[10]. Previous studies found an increase and a decrease in the level of LDL-C and high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperparathyroidism, respectively[11]. Moreover, it has been found that the elevated level of LDL results in disruption of PTH function and inhibition of its anabolic effects on bones[12].

Therefore, understanding the association between these minerals and FH could offer insights into additional strategies for managing cardiovascular risk in FH patients. To address this knowledge gap, this study aimed to compare the serum level of calcium, phosphor, vitamin D, and PTH in FH patients with non-FH participants in order to evaluate possible associations of these mineral changes and FH.

Materials and methods

Study design and population

Patients in this cross-sectional study were recruited from the Isfahan Registry of Familial Hypercholesterolemia (IRFH). A detailed protocol of the study design has been published previously in greater detail[13]. In brief, all participants aged 2–80 years with an LDL-C greater than or equal to 190 mg/dl or an LDL-C greater than or equal to 150 after use of LLT were included in the study. We used the Dutch Lipid Clinic Network Score (DLCNS), which was based on clinical symptoms of FH and family history. This involves categorizing individuals into four groups: those with scores below 3 are highly unlikely to have familial hypercholesterolemia (FH), scores above 8 indicate definite FH, scores between 6 and 8 suggest probable FH, and scores between 3 and 5 indicate possible FH. In this study, patients with a score of 6–8 points (probable) or greater than 8 points (definite) were clinically diagnosed with FH, and participants with hyperlipidemia and a DLCNS score of less than three (unlikely FH) were considered as a control group. Exclusion criteria were secondary hyperlipidemia, hypothyroidism, kidney disease, abnormal liver function, triglyceride levels greater than 400 mg/dl, and a history of calcium or vitamin D supplementation (Fig. 1). Written informed consent was obtained from all patients before biochemical measurements. Ethical approval was received our Institutional Research Ethics Committee (IR.MUI.MED.REC.1401.099).

Biochemical measurements

Patients' blood samples were collected after fasting for at least 8 h overnight, and the laboratory conducted tests on the same day. Enzymatic assays were used to measure levels of high-density lipoprotein (HDL-C), TC, triglycerides (TG), calcium, phosphorus, and HbA1C. The serum 1,25 dihydroxy vitamin D and PTH were measured using enzyme-linked immunosorbent assay (ELISA) kits. The LDL Cholesterol Assay Kit was used to measure LDL-C. An automated machine was used to perform the FBS test. We corrected serum calcium level with albumin concentration using the following formula: corrected calcium = total calcium + (0.8 × (4-serum albumin concentration)).

Endpoints

The primary endpoint of this study was to compare the changes in serum vitamin D, calcium, phosphorus, and PTH between FH and non-FH participants. The secondary endpoint was to assess the association of these changes with LDL-C and TC in these groups.

Statistical analysis

Quantitative variables are expressed as mean and standard deviation (SD), and categorical variables are expressed as numbers and percentages. The comparison of categorial and

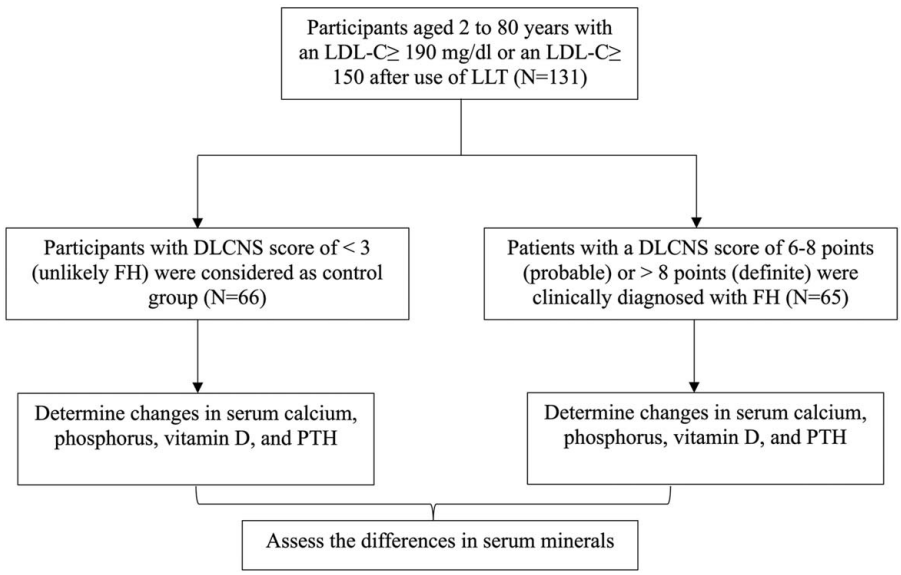

Figure 1. Flowchart of participants through the study. DLCNS, Dutch Lipid Clinic Network Score; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering drugs; PTH, parathyroid hormone.

continues variables between groups was performed using Chi-square tests and independent sample *t*-test, respectively. Multiple logistic regression analysis was performed in four models to compare the serum mineral levels between FH and non-FH groups. Model 1, crude model; Model 2, adjusted for age, sex, BMI, waist circumference (WC), hip circumference (HC), and smoking; Model 3, additionally adjusted for history of CVD, hypertension (HTN), type2-DM, and LLT use; and Model 4, additionally adjusted for TC and LDL-C. For all models, β (95% CI) was reported. Spearman's correlation was applied to analyses the correlation of serum minerals with TC and LDL-C levels. All analysis of data was performed using SPSS version 24. Statistical significance was set at *P* less than 0.05 (two-tailed).

Results

The demographic and clinical characteristics of the participants are summarized in Table 1. A total of 131 participants were included in the study, 65 (49.6%) of whom were diagnosed with FH and 82 (62.6%) of whom were female. The mean age of participants was 53.1 (12.2), 53.0 (11.6), and 53.2 (12.9) in total population, control group, and FH group, respectively. There were significant between-group differences in terms of LLT use, history of CVD, TC, and LDL-C (all *p* values <0.001).

Table 2 represents the serum mineral levels in FH and non-FH participants. Patients with FH had significantly lower levels of vitamin D compared to the control group ($P = 0.004$). However, there were no significant differences in serum calcium, PTH, and phosphorus levels between the two groups.

Unadjusted analysis showed a lower serum vitamin D level in patients with FH (B= −0.027; 95% CI= 0.950, 0.997; $P = 0.028$). After adjusting for age, sex, BMI, WC, HC, smoking status, history of CVD, HTN, type2-DM, LLT use, LDL-C, and TC, there was no significant between group difference in serum vitamin D level. Moreover, serum calcium, phosphorus, and PTH were not significantly different between FH and non-FH groups in all four models (Table 3).

Table 1

Demographics and characteristics of patients with FH and controls.

Variable	Non-FH	FH	*P*
Age (years)	53.0 (11.6)	53.2 (12.9)	0.901
Sex (female)	41 (62.1%)	41 (63.1%)	1.000
BMI (kg/m^2)	26.6 (4.3)	27.7 (3.6)	0.118
Smoking (smokers)	5 (9.5%)	7 (10.6%)	0.731
WC	95.0 (10.8)	97.4 (9.9)	0.202
HC	103.1 (9.1)	106.2 (8.4)	0.052
HTN	20 (30.3%)	26 (40.0%)	0.275
Type2-DM	4 (6.1%)	5 (7.7%)	0.744
CVD history	2 (3.0%)	24 (36.9%)	< **0.001**
LLT use	25 (38.5%)	47 (73.4%)	< **0.001**
Total cholesterol (mg/dl)	204 (50.4)	249 (75.7)	< **0.001**
LDL-C (mg/dl)	121.88 (37.4)	157.68 (63.5)	< **0.001**
HDL-C (mg/dl)	49.9 (7.2)	51.4 (10.6)	0.356
Triglyceride (mg/dl)	151.95 (61.7)	159.65 (61.5)	0.477

CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; HC, hip circumference; HDL-C, high density lipoprotein cholesterol; HTN, hypertension; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering drugs; WC, waist circumference.
Bold values are statically significant.

Table 2

Serum mineral levels in FH and non-FH groups.

Variable	Non-FH	FH	*P*
Ca (mg/dl)	9.43 (0.63)	9.44 (0.65)	0.895
Ph (mg/dl)	3.85 (0.46)	3.83 (0.42)	0.963
Vitamin D (IU)	39.72 (17.96)	32.72 (15.95)	**0.004**
PTH (pg/ml)	33.22 (19.98)	30.98 (19.83)	0.258

FH, familial hypercholesterolemia; PTH, parathyroid hormone.
Bold value is statically significant.

Our analysis revealed no significant correlations between the serum mineral levels and LDL-C and TC levels in the FH group. Besides, no significant correlations were found between serum mineral levels and these lipid parameters in the control group (Table 4).

Discussion

This study aimed to investigate the association of serum mineral changes including calcium, phosphorus, vitamin D, and PTH with FH. Our findings revealed no significant differences in serum mineral levels between FH patients and non-FH individuals. These findings suggest that alterations in mineral metabolism may not be associated with FH. The results of this study are relatively in line with some studies in subject. Awan and colleagues, a study conducted on 22 FH patients, showed that serum calcium and phosphorus are within reference limit in all included patients. Besides, their results indicated normal serum PTH and vitamin D level in almost all FH patients[14]. Another study included 65 FH patients revealed normal serum vitamin D level in

Table 3

Comparison of crude and adjusted serum minerals between FH and non-FH participants.

Variable	B (SE)	95% CI	*P*
Ca			
Model 1	0.036 (0.272)	0.608, 1.768	0.894
Model 2	0.119 (0.289)	0.639, 1.985	0.681
Model 3	0.199 (0.362)	0.599, 2.481	0.584
Model 4	0.060 (0.421)	0.466, 2.424	0.886
Ph			
Model 1	−0.115 (0.397)	0.409, 1.942	0.773
Model 2	0.118 (0.447)	0.469, 2.800	0.792
Model 3	0.003 (0.603)	0.308, 3.270	0.996
Model 4	0.208 (0.639)	0.352, 4.304	0.463
Vitamin D			
Model 1	−0.27 (0.012)	0.950, 0.997	0.028
Model 2	−0.035 (0.019)	0.930, 1.003	0.067
Model 3	−0.025 (0.014)	0.950, 1.002	0.068
Model 4	−0.031 (0.024)	0.925, 1.015	0.184
PTH			
Model 1	−0.006 (0.009)	0.977, 1.012	0.519
Model 2	−0.013 (0.010)	0.968, 1.007	0.193
Model 3	−007 (0.013)	0.968, 1.018	0.576
Model 4	0.003 (0.014)	0.976, 1.030	0.849

Model 1: crude model; Model 2: adjusted for age, sex, WC, HC, smoking; Model 3: additionally adjusted history of CVD, HTN, LLT use, and type 2-DM; Model 4: additionally adjusted for total cholesterol and LDL-C.
CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; HC, hip circumference; HTN, hypertension; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering drugs; PTH, parathyroid hormone; WC, waist circumference.

Table 4

The association of serum minerals with TC and LDL-C in FH and non-FH patients.

		TC			LDL-C		
Variable	**Group**	**Correlation coefficient**	**95% CI**	***P***	**Correlation coefficient**	**95% CI**	***P***
Ca	Non-FH	0.111	– 0.142, 0.350	0.374	0.123	– 0.129, 361	0.323
	FH	0.208	– 0.045, 0.4360	0.096	0.111	– 0.144, 0.352	0.378
Ph	Non-FH	– 0.124	– 0.362, 0.129	0.321	-0.136	– 0.373, 0.116	0.275
	FH	– 0.173	– 0.406, 0.082	0.169	-0.169	– 0.395, 0.095	0.204
Vitamin D	Non-FH	– 0.186	– 0.416, 0.066	0.135	-0.185	– 0.415, 0.067	0.136
	FH	– 0.172	– 0.405, 0.083	0.171	-0.130	– 0.369, 0.125	0.302
PTH	Non-FH	0.036	– 0.215, 0.283	0.772	0.008	– 0.241, 0.257	0.946
	FH	– 0.0270	– 0.276, 0.225	0.829	-0.081	– 0.325, 0.174	0.523

FH, familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; PTH, parathyroid hormone; TC, total cholesterol.

participants[15]. However, no previous study compared the serum mineral levels in FH patients with control subjects. To the best of our knowledge, our findings represent the first report compared serum mineral levels in patients with FH and non-FH participants with hypercholesterolemia.

Several studies have reported severe premature vascular calcification in patients with FH[16–18]. Coronary artery calcium (CAC), as a marker of subclinical atherosclerosis, was an independent associating factor of atherosclerotic cardiovascular disease (ASCVD) in FH patients who received standard LLT[19]. Besides, increased vascular calcification in patients with FH, regardless of their blood cholesterol levels, along with evidence from mouse models of aortic calcification, suggested that the LDL-R protein plays a part in the development of vascular calcification[20]. There are evidences suggested the association of serum calcium with coronary artery and aortic calcification[21,22]. Our results showed no significant alteration of serum calcium in FH patients. However, we did not evaluate the association of serum calcium with arterial calcification. Further studies are warranted to evaluate the association of serum calcium level with vascular calcification in FH patients.

In our study, no correlation was observed between serum minerals and lipid parameters including LDL-C and TC in both FH and non-FH participants. In agreement with our results, a cross-sectional study revealed no significant difference between type2-DM patients with sufficient and insufficient vitamin D level in terms of LDL and TC[23]. Besides, Yarparvar *et al.*[24] showed no significant correlation between serum vitamin D and LDL-C and TC in healthy adolescent . A recent meta-analysis of randomized controlled trials showed no significant change in serum LDL-C and TC following vitamin D supplementation among patients with type 2 diabetes mellitus[25]. In contrast, a study of three large cohorts revealed that a year-over-year decrease in in serum vitamin D level is associated with a significant increase in levels of LDL-C and TC[26]. Almesri *et al.*[27] showed a negative correlation between serum vitamin D and LDL-C among male adults . Moreover, supplementation with vitamin D showed to be associated with decreases in serum LDL-C and TC[28,29]. Hence, the association of serum vitamin D with lipid profile is still a controversial issue.

Statin therapy have been associated with a decreased risk of mortality and coronary artery disease among patients with FH[30]. However, statin therapy may also impact calcium homeostasis. A study compromised 72 participants revealed that statin treatment upregulates ryanodine 3 receptor (RYR3), the SERCA 3 pump, and calpain 3, all of which genes are responsible for calcium regulation[31]. Besides, studies showed an increase in coronary artery calcium score following treatment with statin[32]. Further studies are warranted to explore the potential long-term effects of statin therapy on calcium homeostasis in patients with FH.

This study does have some limitation. Firstly, the cross-sectional design and relatively small sample size may have limited our ability to detect subtle differences. Secondly, the study population consisted of individuals recruited one center, which may limit the generalizability of our findings to other populations. Finally, we did not perform genetic tests to confirm FH diagnosis. Future studies with larger cohorts and longitudinal designs are necessary to better understand the potential role of serum minerals in FH pathophysiology.

In conclusion, our results suggested that there are no significant differences between FH and non-FH participant in term of serum calcium, vitamin D, phosphorus, and PTH level. Moreover, we found no significant correlation between the serum minerals and TC and LDL-C in both control subjects and FH patients.

Ethical approval

Ethical approval was received our Institutional Research Ethics Committee (IR.MUI.MED.REC.1401.099).

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Source of funding

None.

Author contribution

K.H.G.: conceptualization; data curation; investigation; methodology; project administration; supervision; validation; writing—review and editing. G.V.: conceptualization; data curation; project administration; writing—review and editing. S.H.: conceptualization; data curation; writing—review and editing. M.T.: data curation; methodology; writing—review and editing. S.H.-J.: conceptualization; data curation; methodology; writing—review and editing. N.S.: conceptualization; investigation; supervision; writing—review and editing. D.H.: formal analysis; software; writing—review and editing, A.B.: formalanalysis; investigation; software; writing—review and editing. M.R. R.: investigation; methodology; software; writing—original draft; writing—review and editing.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Guarantor

Kiyan Heshmat-Ghahdarijani.

Data availability statement

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

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Bélanger AM, Akioyamen L, Alothman L, *et al*. Evidence for improved survival with treatment of homozygous familial hypercholesterolemia. Curr Opin Lipidol 2020;31:176–81.

[2] Beheshti SO, Madsen CM, Varbo A, *et al*. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. J Am Coll Cardiol 2020;75:2553–66.

[3] Martens PJ, Gysemans C, Verstuyf A, *et al*. Vitamin D's effect on immune function. Nutrients 2020;12:1248.

[4] Renke G, Starling-Soares B, Baesso T, *et al*. Effects of vitamin D on cardiovascular risk and oxidative stress. Nutrients 2023;15:769.

[5] Guillot X, Semerano L, Saidenberg-Kermanac'h N, *et al*. Vitamin D and inflammation. Joint Bone Spine 2010;77:552–7.

[6] de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, *et al*. Vitamin D and cardiovascular health. Clin Nutr 2021;40:2946–57.

[7] Rodriguez AJ, Scott D, Srikanth V, *et al*. Effect of vitamin D supplementation on measures of arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. Clin Endocrinol (Oxf) 2016;84:645–57.

[8] Reid IR, Gamble GD, Bolland MJ. Circulating calcium concentrations, vascular disease and mortality: a systematic review. J Intern Med 2016;279:524–40.

[9] Gallo L, Faniello MC, Canino G, *et al*. Serum calcium increase correlates with worsening of lipid profile: an observational study on a large cohort from South Italy. Medicine 2016;195:e2774.

[10] Shaker JL, Deftos L. Calcium and phosphate homeostasis. Endotext [Internet] 2023. Published online.

[11] Han D, Trooskin S, Wang X. Prevalence of cardiovascular risk factors in male and female patients with primary hyperparathyroidism. J Endocrinol Invest 2012;35:548–52.

[12] Huang MS, Lu J, Ivanov Y, *et al*. Hyperlipidemia impairs osteoanabolic effects of PTH. J Bone Miner Res 2008;23:1672–9.

[13] Vaseghi G, Arabi S, Haghjooy-Javanmard S, *et al*. CASCADE screening and registry of familial hypercholesterolemia in Iran: rationale and design. ARYA Atheroscler 2019;15:53.

[14] Awan Z, Alwaili K, AlShahrani A, *et al*. Calcium homeostasis and skeletal integrity in individuals with familial hypercholesterolemia and aortic calcification. Clin Chem 2010;56:1599–607.

[15] Nasirpour H, Key YA, Kazemipur N, *et al*. The effects of cholesterol lowering drugs on vitamin D status in familial hypercholesterolemia patients. Arch Med Lab Sci 2017;3.

[16] Mszar R, Nasir K, Santos RD. Coronary artery calcification in familial hypercholesterolemia: an opportunity for risk assessment and shared decision making with the power of zero? Circulation 2020;142:1405–7.

[17] Drouin-Chartier JP, Tremblay AJ, Godbout D, *et al*. Correlates of coronary artery calcification prevalence and severity in patients with heterozygous familial hypercholesterolemia. CJC Open 2021;3:62–70.

[18] Awan Z, Alrasadi K, Francis GA, *et al*. Vascular calcifications in homozygote familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2008;128:777–85.

[19] Miname MH, Bittencourt MS, Moraes SR, *et al*. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. JACC Cardiovasc Imaging 2019;12:1797–804.

[20] Fantus D, Awan Z, Seidah NG, *et al*. Aortic calcification: novel insights from familial hypercholesterolemia and potential role for the low-density lipoprotein receptor. Atherosclerosis 2013;226:9–15.

[21] Shin S, Kim KJ, Chang HJ, *et al*. Impact of serum calcium and phosphate on coronary atherosclerosis detected by cardiac computed tomography. Eur Heart J 2012;33:2873–81.

[22] Rubin MR, Rundek T, McMahon DJ, *et al*. Carotid artery plaque thickness is associated with increased serum calcium levels: the Northern Manhattan study. Atherosclerosis 2007;194:426–32.

[23] Saedisomeolia A, Taheri E, Djalali M, *et al*. Association between serum level of vitamin D and lipid profiles in type 2 diabetic patients in Iran. J Diabetes Metab Disord 2014;13:7.

[24] Yarparvar A, Elmadfa I, Djazayery A, *et al*. The association of vitamin D status with lipid profile and inflammation biomarkers in healthy adolescents. Nutrients 2020;12:590.

[25] Lu Q, Liang Q, Xi Y. The effects of vitamin D supplementation on serum lipid profiles in people with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Front Nutr 2024;11:1419747.

[26] Li Y, Tong CH, Rowland CM, *et al*. Association of changes in lipid levels with changes in vitamin D levels in a real-world setting. Sci Rep 2021;11:21536.

[27] Almesri N, Das SN, Ali EM, *et al*. Gender-dependent association of vitamin D deficiency with obesity and hypercholesterolemia (LDLC) in adults. Endocr Metab Immune Disord Drug Targets 2020;20(3):425–36.

[28] Dibaba DT. Effect of vitamin D supplementation on serum lipid profiles: a systematic review and meta-analysis. Nutr Rev 2019;77:890–902.

[29] Mirhosseini N, Rainsbury J, Kimball SM. Vitamin D supplementation, serum 25 (OH) D concentrations and cardiovascular disease risk factors: a systematic review and meta-analysis. Front Cardiovasc Med 2018;5:87.

[30] Besseling J, Hovingh GK, Huijgen R, *et al*. Statins in familial hypercholesterolemia: consequences for coronary artery disease and all-cause mortality. J Am Coll Cardiol 2016;1968:252–60.

[31] Draeger A, Sanchez-Freire V, Monastyrskaya K, *et al*. Statin therapy and the expression of genes that regulate calcium homeostasis and membrane repair in skeletal muscle. Am J Pathol 2010;177:291–9.

[32] Pang J, Chan DC, Watts GF. The knowns and unknowns of contemporary statin therapy for familial hypercholesterolemia. Curr Atheroscler Rep 2020;22:1–0.