

Effect of vitamin D status on lipid profile in premenopausal women: a cross-sectional study

Gonca Tamer^a, Ozge Telci Caklili^d, Kagan Gungor^a, Ilkay Kartal^a, Hatice Gul Sagun^b, Safiye Arik^b, Irem Bozkurt Cakir^b and Hasan H. Mutlu^c

Objective High lipid levels play important roles in the pathogenesis of atherosclerosis and some authors suggest vitamin D deficiency as a risk factor for atherosclerosis. The aim of this study was to evaluate the effect of vitamin D status on lipid profile in premenopausal women.

Patients and methods A total of 315 nonsmoking premenopausal female volunteers without diabetes mellitus were included in the study. Patients were divided into four subgroups. The groups were as follows: patients with less than or equal to 12 ng/ml (group 1, $n = 126$) vitamin D levels, between 20 and 12 ng/ml (group 2, $n = 48$), between 30 and 20 ng/ml (group 3, $n = 21$), and at least 30 ng/ml (group 4, $n = 120$) vitamin D levels. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and non-HDL-C levels of the four groups were compared.

Results HDL-C levels of group 4 were the highest ($P = 0.03$), and TG and non-HDL-C levels of group 1 were the highest ($P = 0.04$, 0.016 , respectively) in all groups. There was no significant difference between serum parathormone, calcium, and phosphorus levels of the four groups ($P = 0.778$, 0.121 , 0.184 , respectively). In unadjusted analysis, 25-hydroxy vitamin D levels were found to be

correlated negatively with BMI ($P = 0.0005$), LDL-C ($P = 0.01$), and non-HDL-C ($P = 0.003$) and correlated positively with HDL-C levels ($P = 0.006$). After adjustments for age, sex, BMI, and log parathormone levels were made, no correlation was found between 25-hydroxy vitamin D and lipid (TC, LDL-C, HDL-C, and TG) levels ($P = 0.91$, 0.06 , 0.95 , 0.79 , respectively).

Conclusion There may be an association between vitamin D insufficiency and dyslipidemia. However, this association may depend on obesity. *Cardiovasc Endocrinol* 6:86–91 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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^aDepartment of Internal Medicine, Division of Endocrinology and Metabolism, ^bDepartment of Internal Medicine, ^cDepartment of Family Medicine, Goztepe Training and Research Hospital, Medeniyet University, Istanbul and ^dDepartment of Internal Medicine, Kocaeli State Hospital, Kocaeli, Turkey

Correspondence to Ozge Telci Caklili, MD, Department of Internal Medicine, Kocaeli State Hospital, Kocaeli 41433, Turkey
Tel: +90 262 309 2217; fax: +90 216 570 9191; e-mail: wattersonx@gmail.com

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Introduction

In recent years, the role of vitamin D in the autoimmunity has gained importance in terms of the effects of the vitamin beyond calcium metabolism [1–4].

Vitamin D may inhibit various aspects of inflammation, which have been established as key pathogenic mechanisms in atherosclerosis. It has been suggested that vitamin D deficiency can be a risk factor for atherosclerosis and the higher incidence of cardiovascular diseases in winter might be explained by lower vitamin D levels observed in this season [1–5]. Moreover, preliminary findings from clinical trials have suggested that vitamin D supplementation may reduce cardiovascular mortality. Wang *et al.*'s [6] meta-analysis showed that low serum 25-hydroxy vitamin D [25(OH)D] levels are associated with an increased risk of cardiovascular diseases. The dose–response curve between 25(OH)D and cardiovascular disease risk indicated that the association was generally linear across the range of 25(OH)D from 20 to 60 nmol/l with a marginally significant trend [6].

Recently, some studies reported associations between hyperlipidemia and vitamin D deficiency [1–5]. The roles of vitamin D deficiency in the pathogenesis of atherosclerosis and lipid metabolism are not exactly known. Within this context, we aimed to evaluate the effect of vitamin D status on lipid profile in premenopausal female patients.

Patients and methods

This study was approved by our institutional ethics committee (approval date and number: 21 February 2008; 44/E) and the study participants have therefore been assessed in accordance with the ethical standards established in the Declaration of Helsinki. All the participants in this study provided informed consent before their inclusion in the study. The study was carried out between October 2008 and February 2009 in winter.

A total of 315 nonsmoking, premenopausal Turkish female volunteers younger than 40 years old were

included in the study. Premenopausal status was determined by follicle-stimulating hormone, luteinizing hormone, and estradiol levels and a gynecologic examination. Patients were screened for vitamin D deficiency and were divided into four groups. The groups were as follows: patients with less than or equal to 12 ng/ml (group 1, $n=126$) vitamin D levels, between 20 and 12 ng/ml (group 2, $n=48$), between 30 and 20 ng/ml (group 3, $n=21$), and at least 30 ng/ml (group 4, $n=120$) vitamin D levels.

Because it has been suggested that the loss of estrogen at menopause causes an increase in low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL-C) levels [7], only premenopausal women were screened. Exclusion criteria included the presence of a disease that affected serum lipid levels such as diabetes mellitus, metabolic syndrome (the diagnosis of metabolic syndrome was made on the basis of the criteria of Adult Treatment Panel III guidelines), and with HbA1c of at least 5.7% [8], thyroid disorders, primary hyperparathyroidism [9] liver disorders, renal disorders, lactose or gluten intolerance (celiac disease), metabolic bone disorders, and anticonvulsant therapy. Patients on treatment with steroids, thiazides, β -blockers, oral contraceptive pills, other hormonal contraceptive methods, fibrates and/or statins or with other supplementations and medications that might alter or influence body weight, serum lipid levels, thyroid functions, serum 25(OH)D and 1,25(OH) $_2$ D $_3$ vitamin levels or metabolism, who drink alcohol, and who are currently involved in a weight loss program, and pregnant women were also excluded from the study.

BMI was calculated as body weight (kg) divided by height (m) squared and obesity was defined as BMI of 30 or higher (kg/m 2) [10].

Waist circumferences (WCs) were measured at the plane between anterior–superior iliac spines and lower costal margins at the narrowest part of the waistline while patients were standing during slight expiration [10]. Hip circumferences were measured horizontally over the farthest points of the trochanters while standing with a 20–30 cm distance between feet. For women, a measure of waist to hip ratio (WHR) more than 0.85 was considered to indicate abdominal obesity according to WHR [10].

Frequencies of obesity and abdominal obesity according to WHR were calculated.

As regular exercise causes an increase in serum levels of HDL-C and reductions in serum triglyceride (TG) and LDL-C levels [11], all the participants were questioned about their normal physical activity. If they did exercise, they were also questioned about how often they performed regular exercise. Regular exercise was defined as

minimum 45 min of walking at least 4 days a week or its calorie equivalent [12].

Laboratory investigations

As the key diagnostic test in vitamin D insufficiency is a decreased serum 25(OH)D value, we determined the serum 25(OH) level for vitamin D insufficiency. Serum levels of 25(OH)D lower than 30 ng/ml were considered to indicate vitamin D insufficiency [13,14].

Blood samples obtained following 12 h of fasting in the follicular phase were immediately centrifuged (2500 rpm) and the sera were separated. Total cholesterol (TC), HDL-C, and TG levels were determined using enzymatic methods. LDL-C was determined using the Friedewald formula and non-HDL-C was determined simply by determining the difference between TC and HDL-C [11–16].

Vitamin D levels were measured at the same time as lipid levels. To measure 25(OH)D, venous blood samples were collected into plain tubes, and serum was separated and stored at -70°C for a week until analysis. Levels of 25(OH)D were estimated using a kit 25(OH)D-Ria-CT (Biosource, Bruxelles, Belgium). The treated samples were then assayed using a competitive binding radioimmunoassay technique. Serum luteinizing hormone (reference interval for the follicular phase: 2.4–12.6 mU/ml; for the luteal phase: 1–11.4 mU/ml, for mid-cycle: 14–96 mU/ml), follicle-stimulating hormone (reference interval for the follicular phase: 3.5–12.5 mU/ml; for the luteal phase: 1.7–7.7 mU/ml, for mid-cycle: 4.7–21.5 mU/ml) and estradiol levels (reference interval for the follicular phase: 12.5–166 pg/ml; for the luteal phase: 43.8–211 pg/ml, for mid-cycle: 85.5–498 pg/ml), which are essential to determine premenopausal status and parathormone (PTH) levels (reference interval: 15–65 pg/ml) were measured by an electrochemiluminescent immunoassay (Modular Analytics E170; Roche Diagnostics, Indianapolis, USA). Other biochemical parameters included in this study were albumin (reference interval: 3.5–5.2 g/dl), calcium (reference interval: 8.8–10.6 mg/dl), phosphorus (reference interval: 2.5–4.5 mg/dl), fasting (reference interval: 70–100 mg/dl), and postprandial glucose (reference interval: <140 mg/dl). Serum levels of these biochemical parameters were determined according to standard laboratory procedures on an autoanalyzer Olympus 2700 (Center Valley, Pennsylvania, USA). Corrected calcium levels were calculated on the basis of albumin levels.

Statistical analysis

All analyses in the statistical evaluation were carried out using SPSS 13.0 software (IBM Corporation, Armonk, New York, USA). For parameters showing a normal distribution according to Shapiro–Wilk and Kolmogorov–Smirnov tests, Student's t -test was used for the comparison of variables between groups. Nonparametric tests, namely, Mann–Whitney U , Kruskal–Wallis, Wilcoxon, and McNemar tests, were used for parameters that did not show a normal distribution.

We used parametric statistics and multiple linear regressions following logarithmic transformation of data when necessary to assess relations between variables. We also used a hierarchic multiple linear regression model with preselected inclusion of serum cholesterol and anthropometric values. A *P*-value of at least 0.05 was considered to indicate statistical significance.

Results

The characteristics of the groups are shown in Table 1. HDL-C levels were the highest (*P*=0.03), and frequencies of obesity and abdominal obesity were the lowest in group 4. TG and non-HDL-C levels of group 1 were the highest (*P*=0.04, 0.016, respectively) in all groups. There was no significant difference between serum PTH, calcium, and phosphorus levels of the four groups (*P*=0.778, 0.121, 0.184, respectively (Table 1).

Table 2 presents the unadjusted and multiple adjusted relationships between 25(OH)D and participants. In the unadjusted analysis, 25(OH)D levels were found to be correlated negatively with BMI (*r*=−0.440, *P*=0.0005), WHR (*r*=−0.27, *P*=0.004), LDL-C (*r*=−0.24, *P*=0.01), and non-HDL-C levels (*r*=−0.29, *P*=0.003) and correlated positively with HDL-C levels (*r*=0.27, *P*=0.006) in women with vitamin D insufficiency. However, no correlations were found between 25(OH)D and TG levels (*r*=−0.132, *P*=0.186). After adjustment for age, sex, BMI, and PTH levels, no significant correlations were found between 25(OH)D and serum lipid (LDL-C, HDL-C, TG, non-HDL-C) levels (*r*=−0.05, *P*=0.06; *r*=0.19, *P*=0.95; *r*=−0.02, *P*=0.79; *r*=−0.09, *P*=0.36, respectively). In a multiple backward regression analysis including age, sex, BMI, WC, WHR, LDL-C, log PTH, and log HDL levels, 25(OH)D depended

(*P*<0.05) inversely on age and BMI. The equation was as follows:

$$\text{Log [25(OH)D]} = 0.116 - 0.013 \times (\text{age}) - 0.020 \times (\text{BMI}).$$

$$R^2 = 0.27.$$

Discussion

In the present study, serum HDL-C levels were lower and serum non-HDL-C, TG levels, BMI, WHR, obesity, and abdominal obesity frequency were higher in patients with less than or equal to 12 ng/ml (group 1, *n*=126) vitamin D levels compared with participants with sufficient vitamin D levels. In the unadjusted analysis, 25(OH)D levels were found to be correlated positively to HDL and inversely to LDL-C levels, BMI, and WHR. However, after adjustment for age, sex, BMI, and log PTH levels, no significant correlation was found between 25(OH)D and lipid levels, between 25(OH)D and WC, and between 25(OH)D and WHR. The association of vitamin D hypovitaminosis with dyslipidemia seemed to be dependent on obesity and age.

Vitamin D can inhibit various aspects of inflammation, which have been established as a key mechanism in atherosclerosis [17]. Recently, it has been suggested that vitamin D may inhibit various aspects of the inflammatory response to cardiovascular injury, and that in the presence of vitamin D deficiency, administration of vitamin D may reduce atherosclerotic plaque progression and plaque rupture [18].

Vitamin D decreases not only the proliferation of purified T (helper) h1 cells but also the production of their important cytokines in lipogenesis and lipolysis. Interferon-γ, a Th1 cell cytokine, has been determined to regulate fat inflammation. Other Th1 cell products such as TNF-α have been shown to promote lipogenesis and

Table 1 Comparison of the characteristics of patients with vitamin D insufficiency with those of vitamin D sufficient patients

	Group 1 (<i>n</i> =126) (mean ± SD)	Group 2 (<i>n</i> =48) (mean ± SD)	Group 3 (<i>n</i> =21) (mean ± SD)	Group 4 (<i>n</i> =120) (mean ± SD)	<i>P</i> -value
25(OH)D level (ng/ml)	6.96 ± 2.86	16.51 ± 2.24	25.9 ± 2.61	58.65 ± 22.79	–
Age (years)	35 ± 8	33 ± 6	30 ± 7	29 ± 7	0.007
Systolic blood pressure (mmHg)	113.8 ± 15	107.8 ± 9	110 ± 1	116 ± 89	0.476
Diastolic blood pressure (mmHg)	75.4 ± 9	71.1 ± 8	70.0 ± 1	74.3 ± 5	0.350
Parathormone (pg/ml)	40.86 ± 12	44.3 ± 16	48.26 ± 10	44.25 ± 15	0.521
Number of the patients who have hyperparathyroidism	9	6	0	9	0.778
Calcium (mg/dl)	9.5 ± 0.4	9.4 ± 0.3	9.5 ± 0.5	9.2 ± 0.4	0.121
Phosphorus (mg/dl)	3.7 ± 0.1	3.3 ± 0.1	3.5 ± 0.1	3.6 ± 0.1	0.184
TC (mg/dl)	187.3 ± 37	179 ± 24	175 ± 30	173 ± 34	0.38
LDL-C (mg/dl)	119 ± 7	113 ± 23	117 ± 28	103 ± 103	0.074
HDL-C (mg/dl)	53 ± 10	54 ± 13	52 ± 12	62 ± 17	0.03
TG (mg/dl)	112 ± 8	76.5 ± 6	80.7 ± 16	87 ± 11	0.04
Non-HDL-C (mg/dl)	134 ± 34	125 ± 27	124 ± 35	111 ± 30	0.016
BMI (kg/m ²)	28.4 ± 0.9	27.8 ± 1.2	28.0 ± 2	21.9 ± 0.6	0.001
WHR	0.81 ± 0.07	0.82 ± 0.07	0.80 ± 0.08	0.76 ± 0.06	0.005

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; 25(OH)D, 25-hydroxy vitamin D; TC, total cholesterol; TG, triglyceride.

Table 2 Simple linear regression and adjusted multiple regression analysis (partial correlation coefficients) of relations between 25-hydroxy vitamin D level and clinical indices of patients

Log [25(OH)D]	Simple linear regression			Adjusted for age, sex, BMI, and log PTH		
	<i>n</i>	<i>r</i>	<i>P</i>	<i>n</i>	<i>r</i>	<i>P</i>
LDL cholesterol	306	−0.24	0.01	306	−0.05	0.60
Log HDL-C	306	0.27	0.006	306	0.19	0.06
HDL-C	315	−0.37	<0.001	315	−0.04	0.81
WHR	315	−0.27	0.004	315	−0.01	0.91
Non-HDL-C	306	−0.31	<0.001	306	−0.08	0.43
Total cholesterol	306	−0.18	0.07	306	0.02	0.81
Triglyceride	306	−0.18	0.07	306	−0.03	0.72

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; 25(OH)D, 25-hydroxy vitamin D; PTH, parathormone; WHR, waist to hip ratio.

induce lipolysis in mice. Moreover 1,25(OH)₂D₃ has been reported to inhibit the expression of adipocyte uncoupling protein 2, which causes stimulation of lipogenesis and inhibition of lipolysis [19,20]. Also, vitamin D downregulates nuclear factor-κB activity, increases interleukin (IL)-10 production, and decreases IL-6, IL-12, leading to a cytokine profile that favors less inflammation [21–24]. However, the exact role of vitamin D in the pathogenesis of hyperlipidemia is not yet understood.

Recently, associations between vitamin D deficiency and hyperlipidemia were suggested in many studies. Melamed *et al.* [25] showed an association between 25(OH)D and cholesterol concentrations in the USA patients of the National Health and Examination Survey. In other studies, Lu *et al.* [26] and Lee *et al.* [27] determined associations between 25(OH)D and HDL-C levels and between 25(OH)D and TG levels in Chinese and European individuals, respectively. Jorde *et al.* [28] obtained similar findings that showed an association between low vitamin D levels and dyslipidemia. Alyami *et al.*'s [29] findings were also similar, showing that higher vitamin D status was associated with lower circulating lipid levels. The largest study evaluating the relationship between vitamin D and lipid levels in 108 711 American patients determined that patients with optimal 25(OH)D concentrations had lower LDL-C and TG and higher HDL-C levels than the patients with suboptimal 25(OH)D levels. However, they found that increasing vitamin D levels from 20 to 30 ng/ml compared with remaining 20 ng/ml was associated with an increase in TC and HDL-C, but did not alter LDL-C and TG levels [30]. However, in that study, the association between vitamin D deficiency and serum lipid levels might be misleading because (a) before the treatment, serum LDL-C and TG levels of the patients whose vitamin D levels increased to 30 ng/dl were higher than those of the patients whose vitamin D levels did not increase and (b) obesity, hyperparathyroidism, hypocalcemia, and important factors causing hyperlipidemia were not eliminated in that study. In other studies, it was reported that vitamin D hypovitaminosis was associated with atherogenic hyperlipidemia [31] and with increased TC concentrations

[32], and both reduced apolipoprotein (apo) A-I and HDL-C concentrations in men [33]. More recently, in a study of healthy men and women from several racial and ethnic groups, hypovitaminosis D was shown to be associated with not only lowered insulin secretion and sensitivity but also adverse effects on both TC and LDL-C concentrations [34]. This postulate is supported by John *et al.*'s [35] findings of correlations between serum 25(OH)D concentrations and both HDL-C concentrations and apo A-I concentrations and by data from the Coronary Artery Risk Development in Young Adults study. Because apo A-I is involved in the reverse transport system that clears tissue cholesterol, hypovitaminosis D may increase the risk of vascular damage by lowering the availability of apo A-I [16, 35]. It was also supported by Pannu *et al.*'s [36] finding, which showed that high vitamin D levels were associated with reduced odds of metabolic syndrome.

Recently, an association between vitamin D deficiency and an unfavorable lipid profile with low HDL-C and high TG levels was found in a meta-analysis of 22 cross-sectional studies [37]. Zimmerman *et al.* [38] systematically reviewed the literature and concluded that cross-sectional studies favored the finding of a lower TAG in participants with sufficient vitamin D levels, especially in studies where participants started from a higher TAG concentration. Similarly, in a very large dataset from one laboratory, Lupton *et al.* [39] observed a significant inverse relationship between higher 25(OH)D and all circulating lipid markers. However, Chaloumas [40] found no impact of vitamin D supplementation on lipid markers and Chen *et al.* [41] found no correlation between 25(OH)D and serum lipid levels after adjustment for age, sex, diabetes, and obesity.

In agreement with Chen and colleagues study, in the present study, no correlations were found between 25(OH)D and serum lipid levels after adjustment for age, sex, PTH levels, and BMI. As patients with diseases that affect serum lipid levels such as diabetes mellitus and thyroid disorders were excluded from our study and confounding factors that affect serum lipid levels such as age, sex, and obesity were examined, our study is important and different from the study by Ponda and colleagues and other studies. Obesity and diabetes mellitus, two of the most important confounding factors affecting serum lipid levels, were not eliminated in other studies except from the study of Chen and colleagues. Hypovitaminosis D was shown to be associated with decreased insulin secretion and sensitivity; therefore, vitamin D deficiency might cause hyperlipidemia because of its effects on insulin secretion and sensitivity [2,21,34,41]. Excluding patients with diabetes mellitus and with HbA_{1c} of at least 5.7% from the study population, we eliminated not only one of the reasons for hyperlipidemia, but the effect of vitamin D insufficiency on hyperlipidemia because of its effects on insulin secretion and sensitivity as well [2,11,15,34]. Our study

differs from Chen and colleagues study, in which serum lipid levels might have been affected by hyperparathyroidism and hypocalcemia. Serum lipid levels in our study were independent of hyperparathyroidism and hypocalcemia; no difference was found in calcium and PTH levels of vitamin D insufficient and sufficient individuals. Moreover, after adjustment of log PTH levels, the results did not change. Therefore, we suggest that the association of hyperlipidemia with vitamin D hypovitaminosis is also independent of hyperparathyroidism. As increased PTH levels in response to hypovitaminosis D state are believed to lead to an increase in intracellular calcium in adipocytes, which leads to increased lipogenesis and weight gain, vitamin D deficiency might cause hyperlipidemia because of secondary hyperparathyroidism in response to hypovitaminosis D [17]. We found that obesity and hyperlipidemia were more common in women with vitamin D insufficiency. In the unadjusted analysis, 25(OH)D levels were found to be correlated positively with HDL-C and correlated negatively with LDL-C levels and BMI. However, after adjustment for age and BMI, no significant correlations were found between 25(OH)D and lipid levels. Therefore, we suggest that the association of vitamin insufficiency and dyslipidemia may depend on obesity and age.

In the present study, hyperlipidemia in vitamin D hypovitaminosis may be depend on obesity, which may also be caused by vitamin D insufficiency [20]. The absence of any significant differences between serum PTH levels of patients with sufficient and insufficient vitamin D levels is also an impressive finding and can be explained by blunted parathyroid hormone response to vitamin D deficiency by hypomagnesemia, which means that parathyroid hormone levels are often normal when 25(OH)D levels decrease below 20 ng/ml [20]. We did not determine serum magnesium levels of individuals with insufficient and sufficient vitamin D levels; we consider this a limitation of our study. The other limitation of the present study is that we could not assess causations this was a cross-sectional study.

Conclusion

Although recent studies suggest that vitamin D insufficiency may play a role in atherosclerosis [1–4], the role of vitamin D in the pathogenesis of hyperlipidemia in patients with vitamin D deficiency and insufficiency is not yet clear. Our findings suggest that vitamin D insufficiency may be a risk factor for hyperlipidemia. However, the association of vitamin D insufficiency with hyperlipidemia may be dependent on obesity, which is also suggested to be caused by vitamin D insufficiency. Determination of vitamin D levels may be beneficial for the population with hyperlipidemia and obesity and thus especially for countries whose food products are not supplemented with vitamin D; administration of vitamin

D during the winter season to patients with hyperlipidemia and obesity may be a topic worth investigating.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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