



Association between vitamin D deficiency and serum lipid levels in a group of Romanian patients

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Abstract

Background and aims. Vitamin D deficiency is widespread across the globe. Numerous reports have linked vitamin D deficiency to certain non-skeletal diseases such as cardiovascular diseases. According to recent studies, there is evidence indicating a possible link between 25-hydroxyvitamin D deficiency and dyslipidemia. The main aim of this study is to investigate the relationship between vitamin D levels and lipid profile and to identify people who may benefit from vitamin D supplementation.

Methods. In this observational study, a total of 154 patients were included, 98 women and 56 men, aged between 19 and 82 years, in which serum vitamin D levels, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and blood sugar were analyzed.

Results. The serum levels of vitamin D showed some differences, being lower in patients with dyslipidemia, with a positive correlation between vitamin D levels and total cholesterol (F ratio = 7.3247, $p=0.008$), and also with LDL cholesterol (F ratio = 5.0023, $p=0.027$). The HDL-C fraction and triglycerides showed no significant correlation with the serum levels of vitamin D. Further on, we divided the patients according to the fraction that had pathological values and compared the levels of vitamin D between these categories. We observed that the lowest levels of vitamin D were present in patients with all lipid parameters modified (HIGH-TC/LOW-HDL/HIGH-LDL/HIGH-TG), and also the highest levels of low HDL-C and high LDL-C.

Conclusion. Our research provides additional evidence to the unfavorable lipid profile found in people with vitamin D deficiency.

Keywords: vitamin D deficiency, dyslipidemia, cardiovascular diseases

Background and aims

Vitamin D is part of a group of fat-soluble molecules, being synthesized mainly from 7-dehydrocholesterol in the skin, under the action of ultraviolet light [1]. Vitamin D deficiency is the most widespread nutritional deficiency in the world, estimated to affect nearly one billion people worldwide [2]. Vitamin D deficiency is multifactorial and can be caused by several factors: malabsorption, decreased fish consumption, increased fiber intake, reduced vitamin D synthesis due to decreased sun exposure, extensive

use of sun protection creams, skin pigmentation, age and reducing outdoor activities [3].

The major role of vitamin D is in calcium homeostasis [1]. In addition, the role in certain non-skeletal diseases such as cardiovascular diseases, diabetes, autoimmune diseases, neoplasias is also recognized. Vitamin D deficiency has been associated with dyslipidemia, hypertension, diabetes and obesity [4-6].

Cardiovascular diseases (CVD) are the leading cause of death worldwide [7]. Even though the number of deaths

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attributed to cardiovascular diseases has decreased in recent years in developed countries, it is estimated that approximately 23.3 million people will die from cardiovascular disease by 2030 [8]. Therefore, more investments are being made in the prevention and treatment of cardiovascular risk factors [9,10].

A key role in the occurrence of cardiovascular diseases is played by dyslipidemia, which causes the onset of atherosclerosis and thus favors the occurrence of coronary heart disease and stroke [9,10].

Dyslipidemia is a metabolic disorder, defined as increased total or low density lipoprotein cholesterol (LDL-C), decreased high density lipoprotein cholesterol (HDL-C) and disturbances in lipoprotein metabolism. This condition can result from diet, tobacco exposure, or genetic and can lead to cardiovascular disease with severe complications [11].

Dyslipidemias have traditionally been classified according to patterns of lipid and lipoprotein elevation known as Fredrickson phenotypes [12]. A more practical classification system divides dyslipidemias into primary or secondary, and describes them based on the following: elevated cholesterol levels only (isolated hypercholesterolemia), elevated tryglicerides only (isolated hypertriglyceridemia) and elevated levels of both cholesterol and triglycerides (mixed hyperlipidemias). This system ignores certain lipoprotein abnormalities, such as low HDL-C or high LDL-C, which could potentially lead to diseases even in the presence of normal cholesterol and tryglicerides levels [11].

The main aim of this study is to investigate the relationship between vitamin D levels and lipid profile, and to identify people who may benefit from vitamin D supplementation.

Methods

We conducted a study on 154 patients, 98 women and 56men, age between 19 and 82 years, who were randomly referred to the Endocrinology Department of Emergency Clinical County Hospital of Bihor, and came from a small geographical region of north west of Romania.

A blood sample was taken to determine the following parameters: 25-hydroxy vitamin D, total cholesterol (TC), high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides (TG) and blood sugar. Serum 25-hydroxyvitamin vitamin D (25(OH)D) levels and lipid panels were measured using an electrochemiluminescence assay method with the chemistry and immunology Alinity analyzer. We assessed total serum 25-hydroxyvitamin D levels because, unlike 1,25-dihydroxyvitamin D, 25-(OH) D has a biological half-life of 2-3 weeks. It also represents the quantity of vitamin D produced by the skin and dietary sources [13,14].

The study was conducted between September 2018

and March 2020.

All subjects gave their written informed consent before entering the study and all procedures were done in agreement of Declaration of Helsinki. The study was approved by the hospital's Ethics Committee (Approval No.: 29413/09.10.2019).

Data were collected regarding the demographic characteristics of the patients, age, sex, medical history (hypertension, diabetes) and the treatment followed. Anthropometric measurements such as height and weight were taken using a stadiometer and a calibrated digital scale. Body mass index (BMI) was calculated using the formula weight in kilograms divided by height measured in meters squared. Those with BMI ≥ 30 were classified as obese. The inclusion criteria were: age over 18 years and the presence of at least one cardiovascular risk factor such as: hypertension, diabetes, dyslipidemia or obesity.

Key exclusion criteria included being on vitamin D supplements and history of acute or chronic liver or renal disease.

In our study, dyslipidemia was considered present in the following cases: a level of total cholesterol above 200 mg/dl, LDL cholesterol with values higher than 100 mg/dl, HDL cholesterol with values lower than 50 mg/dl and triglycerides with values above 150 mg/dl.

Vitamin D status was divided into 4 categories: deficiency (≤ 20 ng / dl), insufficiency (21-29 ng / dl), optimal level (30-100 ng / dl) and toxicity (≥ 100 ng / dl) [15].

Statistical analysis was performed with MedCalc® version 12.5.0.0. Each continuous variable was checked for value distribution compared to the normal population using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were represented by mean and standard deviation, and those with asymmetric distribution by interquartile range. The tests used were: Student's test, analysis of variance (ANOVA test), Mann-Whitney test and Kruskal-Wallis test were used as appropriate. Also Chi-square test and Chi-square with Yates' correction were used for categorical variables which were described by their absolute values and percentages. In order to study the correlations between two continuous variables, the regression analysis was used through the formula $Y = a + bX$. In the study a value $p < 0.05$ was being considered statistically significant.

Results

We studied the correlation between lipid profile and vitamin D levels in 154 patients. The mean serum of vitamin D levels was 18.4 ng/ml (standard deviation 9.0 ng/ml). In our group 71.4% of patients have dyslipidemia. The following table (Table I) shows the general demographic and clinical characteristics for patients with and without dyslipidemia.

Table I. Demographic and general clinical characteristics in patients with and without dyslipidemia.

Characteristic	With dyslipidemia (n=110)	Without dyslipidemia (n=44)	p-value
Sex (M/F)	40/70	16/28	0.852*
Age (years) – mean (\pm SD)	58.3 (\pm 11.3)	59.6 (\pm 10.4)	0.508**
BMI (kg/m ²) – mean (\pm SD)	29.4 (\pm 7.3)	27.7 (\pm 5.7)	0.185**
SBP (mmHg) – mean (\pm SD)	132.9 (\pm 18.0)	131.1 (\pm 14.8)	0.566**
DBP (mmHg) – mean (\pm SD)	81.8 (\pm 10.4)	79.5 (\pm 8.4)	0.201**
HTA (%)	89 (80.9%)	35 (79.5%)	0.974*
Diabetes type 2 (%)	13 (11.8%)	3 (6.8%)	0.531*
Obesity (%)	45 (40.9%)	17 (38.6%)	0.937*
Blood sugar (mg/dl) – median (IQR)	92 (84-107)	89 (85.5-95)	0.098***
Vitamin D levels (ng/dl)- mean (\pm SD)	17.8 (\pm 9.1)	19.8 (\pm 8.9)	0.241**

M = male; F = female; SD = standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HTA = hypertension; IQR = interquartile range; * - chi-square test; ** - Student test; *** - Mann-Whitney test.

Table II. Lipid profile according to vitamin D levels.

Parameter	Vitamin D deficiency (n=96)	Vitamin D insufficiency (n=45)	Vitamin D sufficiency (n=13)	p-value
Total cholesterol (mg/dl) – median (IQR)	200 (178-229)	194 (177.8-226)	180 (168.3-190)	0.0279*
HDL cholesterol (mg/dl) – mean (\pm SD)	54.8 (\pm 11.8)	55.0 (\pm 9.9)	56.9 (\pm 6.5)	0.800**
LDL cholesterol (mg/dl) – median (IQR)	120 (96.5-147.8)	113 (96-134.8)	102.2 (99.2-107.3)	0.233*
Triglycerides (mg/dl) – mean (\pm SD)	111.0 (\pm 56.5)	114.4 (\pm 54.7)	94.4 (\pm 42.7)	0.391**

HDL = high density lipoprotein; LDL = low density lipoprotein; SD = standard deviation; IQR = interquartile range; * - Kruskal-Wallis test; ** - ANOVA test.

Our results do not show a positive correlation between dyslipidemia and the presence of diabetes and higher fasting blood sugar. Body mass index was higher among patients with dyslipidemia (without reaching the threshold of statistical significance), but neither obesity nor hypertension was significantly more common among them.

The serum levels of 25-OH vitamin D showed lower levels in patients with dyslipidemia, but this difference also did not reach the threshold of statistical significance.

The laboratory test results regarding the lipid profile are described in the following table (Table II) grouped according to the levels of vitamin D. The increased prevalence of vitamin D deficiency is also observed, of the 154 patients included in the study, only 8.4% patients had sufficient levels of vitamin D.

Total cholesterol was the only lipid parameter that presented differences regarding the vitamin D levels, so its level is significantly increasing as the vitamin D levels decrease.

We also proceeded to verify the positive or negative correlation between these parameters and the exact serum levels of vitamin D. The results are as follow:

- total cholesterol showed positive correlation with vitamin D levels, being able to construct by regression analysis the formula: vitamin D levels = 28.5158 – 0.04989 x total cholesterol (F ratio = 7.3247, p=0.008) – figure 1;

- also the LDL-C fraction showed a correlation: vitamin D levels = 23.8994 – 0.04672 x LDL cholesterol (F ratio = 5.0023, p=0.027) – figure 2;

- the HDL-C fraction and triglycerides showed no significant correlation with the serum levels of vitamin D.

Going into detail, we divided the patients according to the fraction that has pathological values and compared the levels of vitamin D between these categories (Table III). We observed that the lowest levels of vitamin D is present in patients with all lipid parameters modified (HIGH-TC/LOW-HDL/HIGH-LDL/HIGH-TG), and the highest levels in low HDL-C and high LDL-C category, but the difference does not reach the threshold of statistical significance.

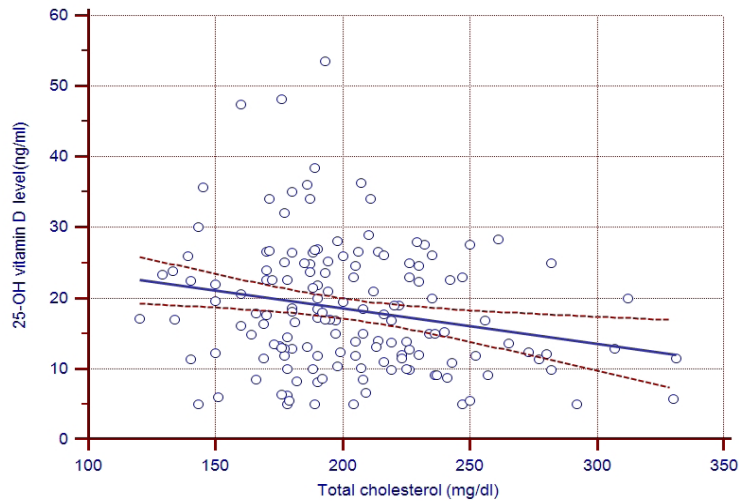


Figure 1. Correlation between vitamin D levels and total cholesterol in our study group using regression line and 95% confidence interval.

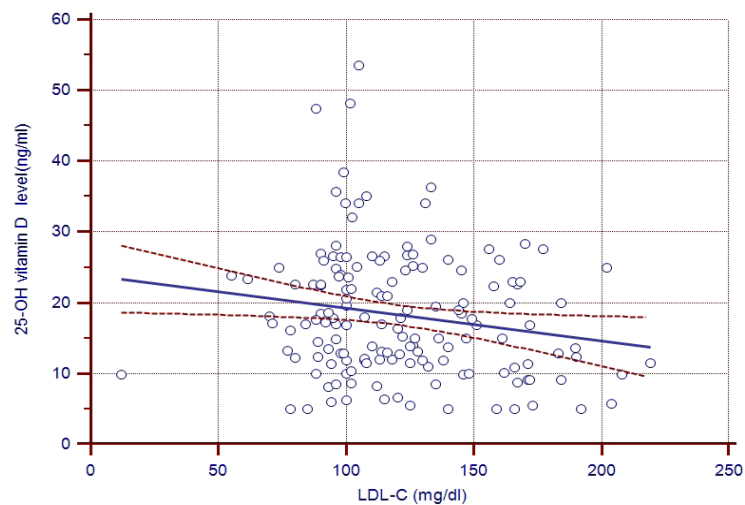


Figure 2. Correlation between serum vitamin D levels and LDL cholesterol fraction in our study group (LDL = low density lipoprotein) using regression line and 95% confidence interval.

Table III. Vitamin D levels according to different lipid profiles in patients with dyslipidemia.

Lipid profile category	Number of patients	Vitamin D levels (mean ± SD)	p - value
(1) HIGH-LDL	5	16.9 (±10.6)	
(2) HIGH-TC/HIGH-LDL	13	14.3 (±5,8)	
(3) HIGH-TC/LOW-HDL/HIGH-LDL	35	18.6 (±8.6)	0.067*
(4) HIGH-TC/LOW-HDL/HIGH-LDL/HIGH-TG	21	13.8 (±6.1)	
(5) LOW-HDL	11	18.8 (±8.9)	
(6) LOW-HDL/HIGH-LDL	25	21.9 (±11.5)	

TC= total cholesterol; TG = tryglicerides; HDL = high density lipoprotein; LDL = low density lipoprotein; SD =standard deviation; * - Kruskal-Wallis test

Discussion

Several factors contribute to the high prevalence of vitamin D deficiency even in areas with plenty of sunshine. Increased time spent indoors performing occupational activities, increased exposure to pollution, a high fiber diet with phosphates and phytates that deplete vitamin D and leads to reduced oral intake and genetic predisposition contributes to vitamin D deficiency [16]. It is estimated that around 30-50% of people are affected by vitamin D deficiency worldwide, and around 70% of European people [17].

In Romania, the current data suggest that 40-75% of people are vitamin D deficient [18]. In our study, the frequency of vitamin D deficiency is similar, at 62.33%.

The mean value of 25 hydroxyvitamin D (25(OH)D) in our study was 18.4 ng/ml, which is far below optimal levels and much lower comparable with the result from National Health and Nutrition Examination Survey (NANHES) 2001-2004, where the mean vitamin D was 24.3 ng/ml [19]. This could be explained by the fact that Romania is a country located in eastern Europe, with a latitude between 44 ° N and 48 ° N, with a window of exposure to ultraviolet radiation of several hours in the middle of the day in the cold season, so there are interseasonal variations in all age groups, with maximum values in September and minimum values in March.

Vitamin D deficiency has been linked with a number of conditions including cardiovascular diseases [20]. This study aimed to examine the correlation between vitamin D and dyslipidemia. Our findings indicate a link between low vitamin D levels and abnormal lipid levels.

The dyslipidemia which is characterized by elevations of total cholesterol, LDL cholesterol, raised tryglicerides and decreases in HDL cholesterol is widely recognized as a risk factor for cardiovascular diseases [21]. New LDL cholesterol targets across cardiovascular risk categories were published by European Society of Cardiology in 2019, with more aggressive proposed goals for LDL cholesterol levels. For very-high-risk patients LDL-C goal of below 55 mg/dl, for patients at high risk an LDL-C goal of below 70 mg/dl, for individuals at moderate risk an LDL-C goal of below 100 mg/dl and for individuals at low risk an LDL-C goal of below 116 mg/dL [22]. These categories represent a counsel of perfection, but these ideals are for guidance only and practical decision-making must be based on what is appropriate to the local situation.

Vitamin D might affect cardiovascular health by influencing serum lipids [23]. The relationship between vitamin D and serum lipids has been widely investigated in various populations. In a study conducted in Germany on the elderly female population, it was shown that 25(OH)D levels were positively associated with HDL cholesterol and there was an inverse relationship with total cholesterol and LDL cholesterol [24]. Results from a study of 909 middle-aged Finnish men (aged 45 to 75) show that serum 25(OH)

D levels are negatively associated with total cholesterol, tryglicerides and LDL cholesterol [25]. According to Sun's research on 136 Japanese men between the ages of 20 and 79, vitamin D is inversely correlated with tryglicerides and LDL-C:HDL-C fractio [26]. Results from the study conducted on 4,330 Danish adults revealed that for every 10 nmol/l increase in the level of 25(OH)D, there was a corresponding decrease in triglycerides and cholesterol in very low-density lipoprotein (VLDL) [23]. These findings indicate that there are connections between vitamin D levels and serum lipid profiles in various populations. Ensuring sufficient levels of vitamin D appears to have a positive impact on serum lipids. Moreover, observational studies have indicated that elevated levels of serum 25(OH)D are linked to a favorable lipid profile [27]. In a study conducted at the University of Tromso involving a total of 10,105 participants, strong positive correlations were observed between serum 25(OH) D levels and serum total cholesterol, HDL cholesterol and LDL cholesterol, and negative correlations between serum 25(OH)D levels and LDL-C/HDL-C ratio and triglycerides levels after adjustment for sex, BMI and month of blood sampling [28].

In our study we demonstrated an association between the levels of 25 (OH)D and the levels of total cholesterol and, to a lesser extent, with LDL cholesterol. These results are in line with similar published findings as confirmed in previous studies. Research using data from the Third National Health and Nutrition Examination Survey on non-Hispanic Black and Mexican Americans aged 60 and above revealed a correlation between high total cholesterol and 25-hydroxyvitamin D deficiency [5]. In another study, hypovitaminosis D was linked to increased total cholesterol in Belgian men [25]. Similar results were discovered in Korean adults [29].

Furthermore, the link between vitamin D deficiency and high LDL cholesterol levels is confirmed in a survey of cardiovascular risk factors in which it was discovered that elevated LDL cholesterol levels are correlated with 25-hydroxyvitamin D deficiency in Finnish people [30].

In our study we did not find a strong correlation between low levels of vitamin D and low levels of HDL cholesterol or high levels of triglycerides. Although, some of these results are consistent with those found in a observational, cross-sectional study, where changes in vitamin D levels were not associated with changes in HDL cholesterol level [31], most studies have showed that low HDL cholesterol was associated with low levels of vitamin D and significant relationship between deficiency of 25-hydroxyvitamin D and high triglycerides [20,32]. This could be explained by differences in age, lifestyle and whether the participants were using statins.

We also compared the level of vitamin D according to the category of the lipid profile, and it was observed that the lowest levels of 25 (OH)D were found in patients with all lipid parameters modified. Similar studies, in which the

association between vitamin D level and lipid fractions was evaluated, demonstrated a correlation only between vitamin D deficiency and high total cholesterol - low HDL cholesterol fraction [24,33].

The influence of vitamin D on lipid profile is still not fully understood. Earlier research has indicated that enhancing the absorption of calcium in the intestines might lead to a decrease in the production and release of triglycerides by the liver. By promoting the absorption of calcium in the intestines, vitamin D could inhibit the synthesis and secretion of triglycerides [29]. Because calcium can form insoluble calcium-fatty complexes, it has been suggested that higher levels of calcium in the intestines may result in decreased fatty acid absorption. The decreased absorption of fat, especially saturated fatty acids, would lead to lower levels of LDL cholesterol in the bloodstream [34]. Moreover, calcium could facilitate the conversion of cholesterol into bile acids, resulting in the reduction of cholesterol levels [34,35].

Several studies have demonstrated that an increased level of parathyroid hormone can lead to an increase in serum triglycerides levels, and higher concentrations of vitamin D suppress the serum levels of parathyroid hormone [36,37]. Furthermore, there is a suggestion that vitamin D plays a role in lipid metabolism, specifically the synthesis of bile acid in the liver. This implies that vitamin D might have a direct impact on the regulation of lipids [38,39].

Considering the associations found between vitamin D levels and serum lipid levels, it can be suggested that vitamin D supplementation could have a beneficial effect on cardiovascular risk factors. Vitamin D supplementation has been shown to lower total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in patient cohorts [23,40]. However, a number of randomized controlled trials have consistently found no connection between the use of vitamin D supplements and a decrease in cardiovascular incidents [41,42]. Most of the ongoing and finished studies primarily involved participants who had sufficient levels of vitamin D, with some also having low total 25 (OH) D levels [43]. Moreover, research on the possible advantages of vitamin D supplementation for CVD risk has been hindered by disagreements over the significance of race and ethnicity in establishing vitamin D cut-points. Our preliminary findings suggest a possible correlation between vitamin D status and dyslipidemia, that can be an independent predictor for progression to cardiovascular disease, therefore vitamin D levels could be used as a non invasive marker of increased risk in these patients. Also, according to the recommendation of the Romanian Ministry of Health, released in 2019, vitamin D status measurement is recommended for several risk categories of population, including adults with cardiovascular diseases [44].

Our study has some limitation. First the sample size was relatively small. Another limitation is that the study does not reflect the entire population, being conducted in only one center.

Conclusion

Our research provides additional evidence to the unfavorable lipid profile found in people with vitamin D deficiency. Considering the high prevalence of vitamin D deficiency and the association with poor lipid profile, screening and correction of vitamin D status could be beneficial in patients with high cardiovascular risk. Further research is needed to better understand the relationship between vitamin D and serum lipids, in order to prevent cardiovascular diseases.

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