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A One-Year Retrospective Study for the Evaluation of Correlation between Vitamin D and Cholesterol Levels: A Preliminary Report

D Vitamini ile Kolesterol Düzeyleri Arasındaki Korelasyonun Değerlendirilmesine Yönelik Bir Yıllık Retrospektif Çalışma: Bir Ön Rapor

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Abstract

Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. Cholesterol is the precursor of very important biochemical pathways including bile salts and other steroidogenic molecules like adrenal gland hormones, reproductive hormones, and vitamin D. In the present study, cholesterol and vitamin D test results from 13,150 patients admitted to our laboratory were analyzed over a one-year period retrospectively from the Laboratory Information System. In our study, we aimed to investigate the association between low cholesterol levels and vitamin D levels. Analyzed data revealed that low cholesterol levels (<200 mg/dl) were detected in 6,355 patients. In these patients, mean cholesterol level was 164.3 mg/dl while median vitamin D value was 20.4 ng/ml. There was a significant correlation (r=0.064, p<0.001) between low cholesterol levels and low vitamin D levels in the study group. The study group was divided into three subgroups according to age (<18, 18-35 and >35) and a significant correlation was detected between low cholesterol levels and low vitamin D (r=0.06, p<0.001) in patients >35 years of age. In this retrospective study, we determined a weak but significant correlation between vitamin D and cholesterol levels in particular >35 years of age. We think that this study data can be considered as a preliminary report for comprehensive studies that will determine the relationship between vitamin D and cholesterol levels in the general population.

Keywords: Cholesterol, Vitamin D, Statins.

Özet

D vitamini yağda çözünen bir vitamin olup, kemik metabolizmasında kritik rol oynayan, aynı zamanda antiinflamatuar ve immünmodülatör fonksiyonlara sahip bir vitamindir. Kolesterol ise safra tuzları ve adrenal hormonlar, üreme hormonları ve D vitamini gibi diğer steroidojenik molekülleri içeren çok önemli biyokimyasal yolların öncüsüdür. Bu çalışmada laboratuvarımıza başvuran 13150 hastanın kolesterol ve D vitamini test sonuçları bir yıllık süre boyunca Laboratuvar Bilgi Sisteminden retrospektif olarak analiz edildi. Çalışmamızda düşük kolesterol düzeyleri ile vitamin D düzeyleri arasındaki ilişkiyi araştırmayı hedefledik. Analiz edilen veriler 6355 hastada düşük (<200 mg/dl) kolesterol düzeylerinin varlığını gösterdi. Bu hastalarda ortalama kolesterol

düzeyi 164.3 mg/dl, medyan D vitamini değeri ise 20.4 ng/ml olarak belirlendi. Çalışma grubunda düşük kolesterol düzeyi ile düşük D vitamini düzeyi arasında anlamlı bir korelasyon (r=0.064, p<0.001) vardı. Çalışma grubu yaşa göre üç alt gruba ayrıldı (<18, 18-35 ve >35) ve 35 yaş üstü hastalarda D vitamini düşüklüğü ile kolesterol düşüklüğü arasında anlamlı bir ilişki olduğu bulundu (r=0.06, p<0.001). Bu retrospektif çalışmada D vitamini ile kolesterol düzeyleri arasında 35 yaş üstü hastalarda daha belirgin olmak üzere zayıf ancak anlamlı bir ilişki varlığını tespit ettik. Bu çalışma verilerinin genel popülasyondaki D vitamini ve kolesterol düzeyleri arasındaki ilişkiyi belirleyecek kapsamlı çalışmalar için bir ön rapor olarak kabul edilebileceğini düşünüyoruz.

Anahtar Kelimeler: Kolesterol, D Vitamini, Statinler.

Introduction

Cholesterol is a lipid classified as sterol. The molecule has a unique structure which consists of four hydrocarbon rings giving rise to a bulky steroid structure [1]. It was first discovered in gall stones in 1769 in solid form and named by the ancient Greek word chole-sterol (bile-solid alcohol) [2]. It is the key molecule for many essential biochemical processes and one of the most highly celebrated molecules in biochemical research [3]. Since the discovery of its structure in 1928; this molecule has been the subject of various scientific discoveries including 13 Nobel Prizes associated with it [3].

Cholesterol is synthesized in all animal cells and it constitutes 30% of plasma membranes in mammals [4]. Cholesterol has a tetra- cyclic ring contributes to cholesterol to the liquidity of cell membrane and it also reduces the permeability to neutral solutes, hydrogen and sodium ions [4–6]. In addition, cholesterol functions in intracellular membrane trafficking, endocytosis, nerve conduction and cell signaling [4,7].

Besides its structural functions, cholesterol is special among other lipids because it is the precursor of very important biochemical pathways including bile salts and other steroidogenic molecules like adrenal gland hormones, sex hormones and their derivatives, and vitamin D which are important metabolic and homeostatic regulators [8,9]. High cholesterol levels have been related with development of atherosclerosis and cardiovascular disease (CVD) various forms of cancer, diabetes, skeletal and neurological disorders up to date [10].

Cholesterol biosynthesis begins with the mevalonate pathway, which begins with polarity among acetyl-coA and acetoacetyl-coA to form 3-hydroxy-3-methylglutaryl-coA/HMG-CoA [11,12]. HMG-CoA is then reduced to mevalonate by the action of HMG-CoA reductase [11]. Mevalonate emergence is a rate-limiting and irreparable tread in cholesterol synthesis. Statins, a class of drugs classified as HMG-CoA reductase inhibitors, are lipid-lowering molecules that reduce morbidity and mortality in patients at high risk of CVD [12]. They are the most common cholesterol-lowering drugs used worldwide [13].

Vitamin D is a fat-soluble vitamin with important roles in bone structure and turnover and it also prevents inflammation and helps regulating immune functions [14–16]. Additionally, recent epidemiological studies have reported associations between low vitamin D levels and cardiovascular mortality, various cancers and autoimmune diseases like multiple sclerosis, and even multiple diseases such as COVID-19 [17–20]. Vitamin D deficit is a widespread health problem, and vitamin D additions are widely used in the general population of almost all ages to prevent many chronic diseases [16].

Vitamin D is a hormone pioneer that is available in two forms. Vitamin D2 or ergocalciferol is found in fish and plants [21]. Vitamin D3 or cholecalciferol on the other hand is synthesized in the skin by sunlight [22]. Vitamin D3 is synthesized from 7-dehydrocholesterol in the skin. 7-dehydrocholesterol comes from the common cholesterol pathway controlled by HMG-CoA reductase enzyme (Figure 1) [22,23].

The common usage of statins to lower cholesterol levels has led us to the question that "Is there a linkage between statin usage and low vitamin D levels" Although the PubMed search for the term "cholesterol" gives more than 250.000

articles, there only 80 articles emphasizing vitamin D and cholesterol levels. Among many causes of Vitamin D deficiency listed, statin usage is never considered. And while statins lower cholesterol level, do they also cause vitamin D deficiency? The aim of the present study is to evaluate is there a relationship between low total cholesterol and low Vitamin D levels in the general population according to age and gender, medication usage and presence of co-morbidities.

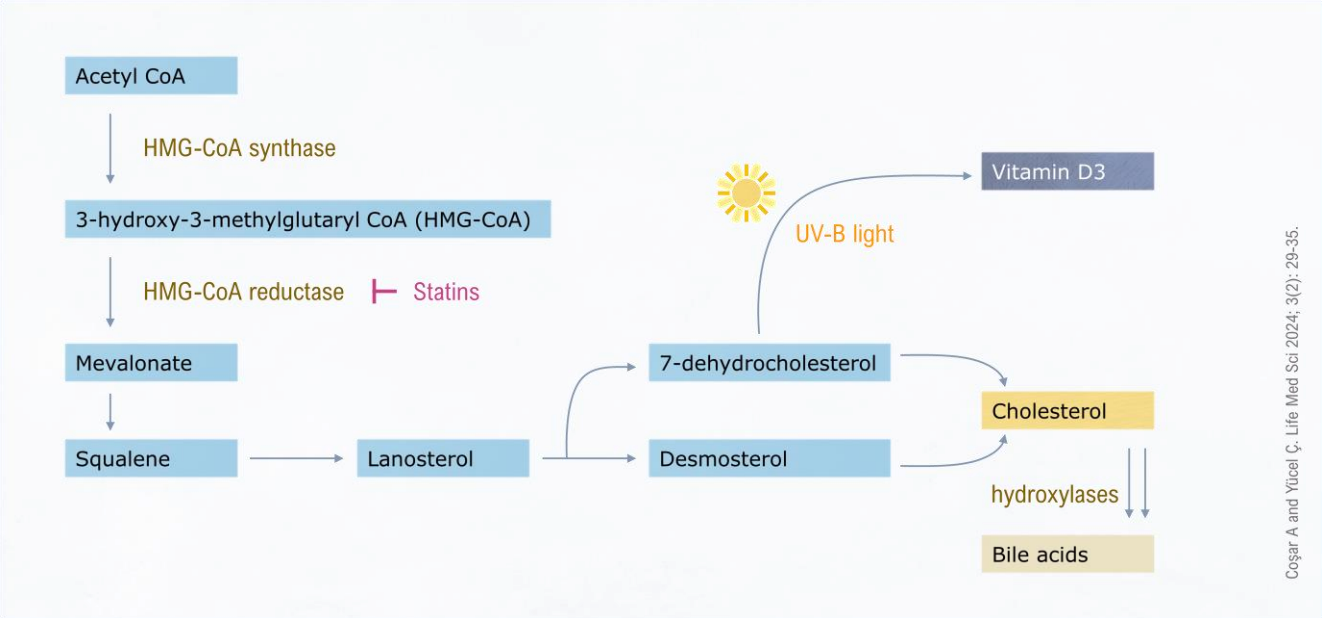

Figure 1. Biosynthesis pathway of cholesterol and Vitamin D.

Material and Method

The study was carried out in the Clinical Biochemistry Laboratory of Gulhane Training and Research Hospital. One-year retrospective data of patients having both Vitamin D and total cholesterol measurements between January 2019- January 2020 was retrieved from Laboratory Information System. Vitamin D status was measured with HPLC (Shimadzu HPLC system, Kyoto, Japan) and Total cholesterol levels were measured with enzymatic method on an immunoassay autoanalyzer (Beckman Coulter DxI 800 Unicel, Beckman Coulter, USA). Demographic features, co-morbidities and medication reports were also recorded for each participant. The study protocol was approved by the local ethics committee with the approval number 19/377.

Statistical analysis

Descriptive data were presented as percentage, standard deviation, inter quartile range (IQR), mean, and median. Normality analysis was performed with the Kolmogorov-Smirnov test. Correlation analysis was performed with Spearman's correlation analysis. Statistical significance was accepted as $p<0.05$ value within 95% confidence interval.

Results

A total of 13,150 subjects were included in the study. Among these, the cut-off of 200 mg/dL total cholesterol was selected and 6,355 subjects with total cholesterol levels <200 mg/dL were included in the study. The study population was subdivided into age subsets as <18, 18-35 and >35 years. The female/male ratio, cholesterol and vitamin D levels of the study groups are summarized in Table 1.

In the whole study group, there was a weak correlation between low cholesterol levels (<200 mg/dL) and vitamin D levels ($p<0.001$, $r=0.064$). In patients > 35 years of age, there was a weak correlation between Vitamin D and cholesterol levels ($p<0.001$) (Figure 2).

Metabolic/chronic diseases recorded in the study group and cholesterol and vitamin D levels of these patients are summarized in Table 2.

Number of patients using any kind of mediation was 989. Mean age was 55.3

(SD±13.2), median vitamin D was 23.6 ng/mL (IQR=14.1-34.9) and mean cholesterol was 164.5 (SD±23.6). No correlation was found between cholesterol and vitamin D in this group.

The number of patients using statins was 893. Mean age was 63.3 (SD±9.6); median vitamin D was 25.5 ng/mL (IQR=14.2-38) and mean cholesterol was 159.7 mg/dL (SD±26.1). No correlation was found between cholesterol and vitamin D levels in this group.

Number of patients using vitamin D supplements was 1,254. The mean age was 49.2 (SD±18.5) and median vitamin D value was 26.1 (IQR=16.7-36). Mean cholesterol values were 165.6 (SD±23.4) in this group, a weak correlation was observed between vitamin D levels.

Table 1. Demographic features and levels of study parameters in patients.

age group	female / male ratio	age (mean or median)	median vitamin D level (ng/mL)	mean total cholesterol level (mg/dL)	p/r*
<18	%60.5 (n=239) / %39.5 (n=156)	13 (IQR=9-16)	19.6 (IQR=12.2-29.1)	151.4 (SD±24.9)	p=0.33 r=0.05
18-35	%72 (n=1398) / %28 (n=543)	25.9 (SD±4.9)	17.4 (IQR= 10.1-27.6)	156.2 (SD±23.7)	p=0.52 r=0.01
>35	%67.4 (n=2710) / %32.6 (n=1309)	54.1 (SD±11.8)	21.8 (IQR=12.6-32.2)	168.6 (SD±23.1)	p<0.001 r=0.06
All subjects	%64.7 (n=4347) / %31.1 (n=2008)	42 (IQR=28.58)	20.4 (IQR=11.7-30.6)	164.3 (SD±24.1)	p<0.001 r=0.064

*Spearman's correlation coefficient. IQR; Inter quartile range. SD; Standard deviation.

Table 2. Most common chronic diseases presented in the patient group.

disease	patient (n)	age (mean or median)	median vitamin D level (ng/mL)	mean total cholesterol level (mg/dL)	p/r*
Diabetes	149	50.7	18.9 (IQR=11.5-31.4)	155.1 (SD±30.1)	p=0.002 r=0.25
Hypertension	581	59.4	22.5 (IQR=13.1-33.6)	162.6 (SD±26.3)	p=0.89 r=0.01
Thyroid dysfunction	113	27.7	16.8 (IQR=10.7-29.4)	161.3 (SD±24.3)	p=0.12 r=0.06

*Spearman's correlation coefficient. IQR; Inter quartile range. SD; Standard deviation.

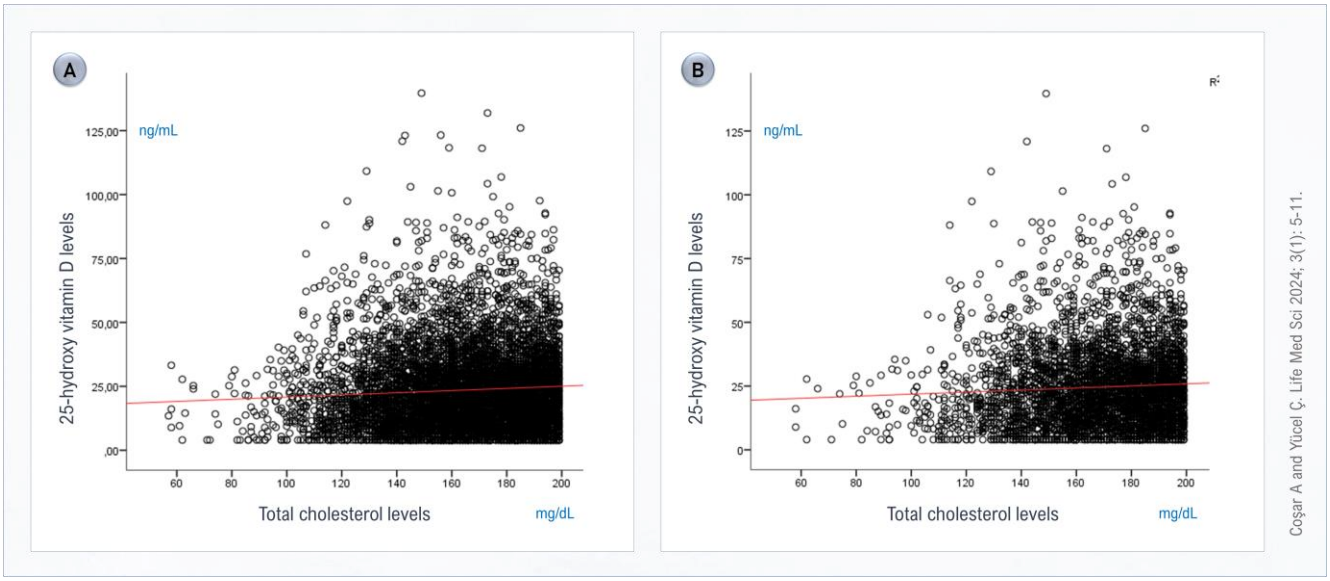

Figure 2. Correlation between Vitamin D and cholesterol. (**A**) All patients, (**B**) >35 years of age patients.

Discussion

Vitamin D is one of the 4 lipid-soluble vitamins which plays a primary role in calcium homeostasis [14]. The main source of vitamin D in humans is skin synthesis due to exposure to sunlight [22]. Besides its effects on calcium metabolism; this prohormone is known to have some anti-inflammatory and immune-modulating properties [15]. There are many vitamin D-related components in the heart and blood vessels, and vitamin D deficiency has been associated with several CVDs. As vitamin D receptors are located in the endothelium; in recent years it has been stated that vitamin D deficiency may cause some cardiovascular problems [24].

Cholesterol is a major precursor molecule for steroid hormone production, bile salts and also vitamin D [8,9]. For preventing heart disease, it is recommended to maintain cholesterol levels below 200 mg/dL [25]. Most common drugs used for this purpose are statins; which inhibit the rate limiting HMG-CoA reductase enzyme to block synthesis of cholesterol [12]. When cholesterol synthesis is diminished; synthesis of molecules driven from cholesterol can be protruded. Clinical studies have shown that plasma 25(OH) D3 levels of less than 20 ng/mL are associated with an increased risk of coronary heart disease [13,25]. Various mechanisms such as preservation of endothelial function, modulation of immune response, inhibition of vascular smooth muscle contraction, contributes to the anti-inflammatory actions of vitamin D. Invasion has been proposed to explain its atherosclerotic effects. While lowering cholesterol is protective against CV disease, what happens if vitamin D synthesis is diminished as its precursor molecule cholesterol is lowered? So, the main question of the present study is how vitamin D levels are affected by a decrease in cholesterol [26,27]. That's why we evaluated a 1-year period retrospective data of patients having both cholesterol and vitamin D test results on same admission. We divided the patient population to 3 groups according to age. Among 13,150 patients; 6,355 of them had cholesterol levels below 200 mg/dL cut-off. We focused on that group, and we carried out correlation analysis with vitamin D levels. We found a weak correlation between cholesterol and vitamin D levels in patients having cholesterol values less than 200 mg/dL. We also found a similar correlation in patients >35 years of age.

We also sub-grouped patients into groups due to most common chronic diseases. We found that median vitamin D values are lower in these subgroups when compared to general population except hypertension patients (Table 2). We think that as their mean age is higher; they were prescribed vitamin D so their median vitamin D levels are higher than the general population.

989 patients in the study were recorded to use statin group drugs. Mean age of this group was 63.3. Although the members of this group were seniors, their cholesterol mean was lower and vitamin D median values were higher than the general population. Although not recorded, we think that majority of this group were using vitamin D preparations also.

When we look at the values of all subjects; we see that female patients are in higher percentage in all age groups. Vitamin D median values in all age groups are relatively low. Vitamin D values between 20-29 ng/mL are classified as insufficient, and < 20 ng/mL are classified as deficient. According to our results, vitamin D status of our study group is classified as insufficient, with groups < 18 years of age and 18-35 years are in the deficiency range. Vitamin D status of subjects > 35 years is the highest among all groups, which can be explained by the usage of vitamin D supplements. Cholesterol levels on the other hand are below 200 mg/dL cut-off in all groups but is the highest in subjects > 35 years. This in fact is an expected result as most cardiovascular and atherosclerotic diseases are triggered over 35 years. Still, the mean cholesterol value is 168.6 in this group which brings us to the point that they use anti-cholesterol drugs.

The mean age and median vitamin D values were 49.2 and 26.1 in the group taking vitamin D supplements. But their cholesterol levels were also 165.6 mg/dL and there was a weak correlation between cholesterol and vitamin D. This correlation is not sufficient to give us an idea about the true cholesterol and vitamin D status as they take vitamin D supplementation [28].

Although we screened a quiet large group of subjects over a 1-year period; the patients with recorded chronic diseases and the ones using any kind of medication were quite low to make further statistical analyses. Vitamin D status is also affected by the weather conditions and exposure to sunlight. As our study is a single-centered one, vitamin D status is mostly reflecting the values of the citizens from the same city/region. For a better understanding of the relationship between cholesterol and vitamin D status of the population; more detailed information about diseases and all kinds of drugs and vitamin supplements used by the participants and multi-center comprehensive studies will be required.

Conclusion

The present study is a retrospective report about one year data of cholesterol and vitamin D in a training and research hospital clinical biochemistry laboratory. The study both presents a demographic summary, vitamin D and cholesterol test numbers and their correlation with each other. This can be accepted as a preliminary report between vitamin D and cholesterol levels in the general population.

Conflict of interest: The authors declare that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper. **Financial disclosure:** There is no financial support for this study.

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