Short Communication

The effects of cholesterol lowering drugs on vitamin D status in familial hypercholesterolemia patients

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Abstract

Background: Familial high blood cholesterol (hypercholesterolemia) is a common disease that involves many complications for patients. The aim of this study is to investigate the effects of cholesterol-lowering drugs (Gemfibrozil and Atorvastatin) on the level of serum Vitamin D. **Materials and Methods:** In this study, the 25-hydroxy vitamin D levels were evaluated in 65 women between 30-55 years of age. After receiving drug information of patients, cholesterol-lowering medication; Gemfibrozil and Atorvastatin were prescribed by a specialist, then vitamin D and cholesterol levels were measured following 9 month treatment. Also 30 patients consumed vitamin D supplements plus medicine regularly. **Results**: In the first stage, vitamin D levels in subjects are quite normal but their cholesterol levels were higher than normal. In the second stage, vitamin D levels were measured after 9 months use of Gemfibrozil and Atorvastatin. Accordingly, cholesterol levels decreased significantly due to the use of blood cholesterol-lowering drugs (p=0.021). Also, in this stage the level of vitamin D showed a severe and significant reduction (p=0.041). However, there were no significant reductions in vitamin D in 30 women who consumed vitamin D supplements plus medicine (p=0.073). **Conclusion:** It seems that taking cholesterol-lowering medicines have reduced the amount of vitamin D. With long-term use of medications, bone diseases such as osteoporosis can be predicted in these individuals. Therefore, taking supplements and food rich in vitamin D during the use of these drugs is recommended.

Keywords: Hypercholesterolemia, Vitamin D, ELISA

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Introduction

Congenital hypercholesterolemia is characterized by high levels of LDL. Approximately 2% to 15% who suffer from a high hypercholesterolemia, have a family-defective gene. The genetic cause and pathogenicity of hypercholesterolemia is known to be about 20%-40% autosomal dominant. Hypercholesterolemia occurs by mutation in LDLR, APOB, PCSK9, and APOE genes (1, 2).

Vitamin D is a fat-soluble vitamin, which is supplied through dietary intake, vitamin D supplements and exposure to sunlight. Vitamin D has a hormonal activity that is well known in cell

differentiation, reproduction, immune system regulation, parathyroid hormone suppression, calcium and phosphorus homeostasis and bone metabolism (3, 4). The absorption of calcium in the intestine is the primary target of vitamin D and in this path indirectly enhances the intermixture of calcium in the bone. Vitamin D deficiency may result in the decline of bone quality and cause bone softness, while a sharp decrease in vitamin D, increases the risk of osteoporosis and bone fractures. In recent decades, research has also shown that there are many non-skeletal diseases associated with vitamin D (5). Vitamin D can indirectly contribute to lipid profile changes. The Increasing serum levels of vitamin D are associated with inhibition of parathormone levels in the serum, and studies have shown that parathormone can reduce lipolysis (6). Enhancing calcium levels may reduce the production or secretion of liver triglyceride (7). In general, calcium intake lead to reduction of absorption of fatty acids by creating a calcium-fatty acid complex (8). Moreover, Vitamin D is expected to reduce levels of cholesterol, triglycerides, LDL and HDL by increasing calcium absorption (9). However, the effect of intestinal calcium on the absorption of fat is very low and it has no significant effect on the serum lipid profile changes (10).

Statins reduce blood cholesterol and are involved in inflammation of cardiovascular disease (11). Atorvastatin is a statin or an inhibitor of the 3-HMG-COA (3-Hydroxymethylglutaryl Coenzyme A reductase) enzyme and a blood fat regulating agent that acts on plasma lipids. Due to the use of this drug for the treatment of hyperlipidemia, LDL, triglycerides and apolipoprotein B levels have been reduced and in opposite HDL levels have been increased (12, 13). Gemfibrozil is also a cholesterol-lowering drug and its use decreases the plasma concentration of VLDL and increases the plasma HDL. Although this drug may slightly reduce total cholesterol and LDL, but its use in patients with high triglycerides, with type IV high blood fat, often results in a significant increase in LDL (14).

In regards to the high prevalence of familial hypercholesterolemia and also the fact that familial hypercholesterolemia patients should be using cholesterol-lowering drugs such as Gemfibrozil and Atorvastatin for the long time, the aim of this study was to evaluate the effect of Gemfibrozil and Atorvastatin drugs on the levels of serum Vitamin D.

Methods

Study subjects. This study was performed on 65 women between the ages of 30-55 years, during 2014 in Bonab. The inclusion criteria were having congenital hypercholesterolemia and no consumption of cholesterol-lowering drugs (Gemfibrozil and Atorvastatin). The subjects were selected from among the referrals to Bonab Medical Laboratories. After verifying the disease by a specialist physician and completing the consent, peripheral blood sample from the venous vein was obtained from all subjects.

ELISA analysis. Sampling in fasting state (after 8 to 10 hours of fasting) was performed between 8:00 and 10:00 am. Blood tubes were centrifuged for 10 minutes at 1500 g to provide blood serum. The serum samples were stored at freezer temperature and kept at a temperature of -79 °C until tests were performed. After blood sampling, samples were taken to measure vitamin D and blood cholesterol using ELISA kit instructions and done by ELISA reader Lab System Multi Scan (Italy). The samples were then read and evaluated by optical absorption by an ELISA reader with a wavelength of 490 NM. In the following step, Gemfibrozil and Atorvastatin were prescribed by a specialist physician for patients and these drugs were used by these people for 9 months. Overall, 65 women surveyed, 30 were randomly selected as the case group and received supplements containing vitamin D along with medicine. The remaining 35 women were considered as control group and only used cholesterol-lowering drugs. After 9 months, blood samples were taken from the people studied again and blood levels of vitamin D and cholesterol were measured by ELISA method.

Statistical analysis. Finally, the results obtained from two stages of ELISA tests were analyzed by SPSS software version 23. They were expressed as a mean ±standard deviation for quantitative variables and the number and percentage of qualitative values. The level of significance was considered as $P<0.05$.

Table1. Mean on cholesterol level of serum in the case and control group in the first and second stages of the study.

Variable / Cholesterol Level (mg/dL)	First Stage	Second Stage	P value
Case Group (n=30)	251.07 ± 39.1	179.65 ± 45.5	0.011
Control Group (n=35)	243.49 ± 41.5	187 ± 39.1	0.032
P value	0.45	0.49	-

Table2. Mean of Vitamin D level of serum in the case and control group in the first and second stages of the study.

Variable / Vitamin D Level (mg/dL)	First Stage	Second Stage	P value
Case Group (n=30)	41.43 ± 8.5	36.66 ± 6.5	0.073
Control Group (n=35)	39.93 ± 6.8	17.38 ± 6.9	0.021
P value	0.81	0.003	-

Results

This study was performed in two stages. In the first stage, vitamin D and cholesterol were studied in the subjects. The results of this part of study revealed that vitamin D levels in subjects are quite normal. Also, because of high congenital cholesterol problems and not taking cholesterol-lowering drugs, their cholesterol levels were higher than normal (Table 1 and Table 2).

In the second stage, vitamin D levels were measured after 9 months use of Gemfibrozil and Atorvastatin prescribed by a specialist. Blood cholesterol measurements at this stage showed that blood cholesterol levels decreased significantly due to the use of blood cholesterol-lowering drugs (p=0.021). Also, in this stage the level of vitamin D showed a severe and significant reduction (p=0.041). However, there were no significant reductions in vitamin D in 30 women who consumed vitamin D supplements plus medicine (p=0.073) (Table 1 and Table 2).

Discussion

In the first stage, the cholesterol and vitamin D levels were evaluated in normal women. In the second stage, blood cholesterol has been significantly reduced caused by the inhabitation of the synthesis of HMG-CoA reductase that was due to the consumption of Gemfibrozil and Atorvastatin. The level of vitamin D also decreased within this group. On the other hand, women who took vitamin D supplements showed a relatively small decrease in vitamin D. The gene is continually associated with the levels of vitamin D circulation (15, 16), and in turn, the level of vitamin D is associated with lipid levels in adults (17). Interestingly, RXRG, a key gene in the pathway of vitamin D, is located in the chromosomal region 1q21-Q23, closely associated with high congenital cholesterol. The most common fatty acid metabolism disorder is atherogenic and is characterized by several hyperlipidemia phenotypes in which the level of LDL is high (18). Therefore, this evidence from studies supports that our findings on vitamin D associated with gene and lipid profiles in high congenital cholesterol.

In a prospective study by Anderson et al. In 2010, involved more than 40,000 people, the association between low levels of vitamin D and various risk factors for cardiovascular disease such as type 2 diabetes, high blood pressure and high congenital cholesterol and brain stroke have been proved. Vitamin D plays an important role on the lipid profile of genetic diversity (19). Vitamin D, whether made in the skin or taken with food, after entering the bloodstream bonds to the vitamin D binding Protein (DBP) that is responsible for transporting this vitamin in metabolic pathways and target tissues (20, 21). Vitamin D indirectly plays role in changing the lipid profile. Increasing serum levels of vitamin D is associated with parathormone

inhibition. In vitro studies have shown that parathormone can reduce lipolysis (22). On the other hand, vitamin D also plays a role in regulating calcium homeostasis. Zitterman et al. showed that vitamin D can reduce production or decrease liver secretion of triglyceride by increasing calcium levels (7). Calcium is one of the minerals that can be bonded to bile acids and cause fecal excretion of it. The production of new bile acids from cholesterol decreases its serum levels (10). Therefore, vitamin D is expected to reduce cholesterol levels by increasing calcium uptake, regarding the fact that the effect of intestinal calcium is very low in fat absorption and is less likely to have a significant effect on serum lipid profiles (23). Jorde et al., have provided 22 cross-sectional review studies on the relationship between vitamin D deficiency and lipid profiles with a minimum sample size of 500 people and 10 interferential studies with vitamin D supplements and placebo-controlled. In all cross-sectional studies, serum levels of 25-hydroxyvitamin D have a direct correlation with HDL levels and an inverse association with triglyceride, which improves the ratio of total cholesterol to LDL-C and HDL-C. On the contrary, some Interventional studies have reflected positive and negative correlations in this regard, so that the same result cannot be obtained (17). In this study, increased cholesterol levels played role in increased vitamin D levels, but Gemfibrozil and Atorvastatin consumption significantly reduced vitamin D levels.

Rejnmark et al showed that 82 healthy menopausal women treated with simvastatin 40 mg/day or placebo for one year, at the start of treatment were examined at weeks 25 and 56. The results of this study showed that Gemfibrozil and Atorvastatin, not only are regarded as cholesterol-lowering drugs, and being of the statin family, but also reduce vitamin D (22).

In addition, a cell culture study using human fibroblasts demonstrated that vitamin D is a key enzyme in the synthesis of cholesterol due to 3HMG-COA (3-hydroxymethylglutaryl coenzyme A reductase) inhibition. In the present study, with HMG-COA enzyme inhibition, the amount of vitamin D was significantly reduced (24). The limitations of this study are as follows; Due to the cross-sectional nature of the study, it is not possible to determine the cause and effect relationship between the variables of the study. Studies have shown that in obese individuals with more fat mass, the serum level of 25-hydroxylamine vitamin D decreases and so-called vitamin D in the adipose tissue is trapped. One of the limitations of this study is the lack of measurement of body composition, including body fat mass. Also, the serum level of apolipoprotein was not measured.

Conclusion

Our findings demonstrated that taking cholesterol-lowering medicines have reduced the amount of vitamin D. With long-term use of medications, bone diseases such as osteoporosis can be predicted in these individuals. Therefore, taking supplements and food rich in vitamin D during the use of these drugs is recommended.

Conflicts of Interest

There is no conflict of interest.

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