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Assessment of Vitamin D Levels in Relation to Statin Therapy in Elderly Hypertensive Patients with Comorbidities

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ABSTRACT

Background: Statin therapy is commonly used on the long term in hypertensive patients with dyslipidemia and can interfere with vitamin D metabolism. Overweight/obesity and type 2 diabetes mellitus (DM) are frequently associated with hypertension. The **aim of the study** was the assessment of vitamin D status in elderly hypertensive patients with metabolic comorbidities with/without statin therapy, in relation to body mass index (BMI) and lipid profile parameters. **Material and methods:** The study group included 89 hypertensive patients (61 statin-treated) admitted to the Cardiovascular Rehabilitation Clinical Hospital in Târgu Mureş between 2019 and 2021. Vitamin D levels were measured by ELISA method, lipid profile parameters by photometric procedures. Calculated values were LDL-cholesterol and BMI. **Results:** Obesity and DM were present in association with hypertension in 51% of the subjects. A total of 89% of the enrolled hypertensive patients had hypovitaminosis D. Average serum vitamin D of the studied subjects was 14.27 ± 11.96 ng/mL. No significant difference was obtained in vitamin D levels depending on gender, the presence/absence of statin therapy, and DM as a comorbidity. A negative correlation was seen between serum HDL-cholesterol and triglyceride concentrations ($r = -0.3988$, $p = 0.0008$) and between HDL levels and BMI ($r = -0.3114$, $p = 0.0475$). **Conclusions:** Suboptimal vitamin D levels were present in the majority of the studied hypertensive patients regardless of the statin therapy, which reveals the importance of concomitant assessment of vitamin D levels, especially in elderly subjects presenting chronic metabolic comorbidities.

Keywords: statins, vitamin D, hypertension, dyslipidemia, type 2 diabetes mellitus, obesity

INTRODUCTION

Hypertension, diabetes mellitus (DM), and obesity are population-level diseases with an increasing incidence, affecting many patients worldwide. Their occurrence is greatly related to modern lifestyle.[1] Cardiovascular diseases occupy a leading position in the global death statistics, dyslipidemia and DM being major risk factors for cardiovascular pathology. Dyslipidemia is a very common laboratory finding in obesity, hypertension, and type 2 diabetes. Statin therapy is used on the long term for lowering atherogenic LDL-cholesterol values, thus reducing the cardiovascular risk by 25–35%.[2] The 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor statins have several side effects. Prolonged use of statins can increase the risk of developing DM, mainly due to downregulation of glucose transporters.[3] Statin-associated muscle symptoms (SAMS) (myalgia, stiffness, cramp, muscle weakness) are common side effects, which are likely to occur especially in case of high dose statin therapy.[4]

The mechanism of statins' effect on serum vitamin D levels is not completely understood. It is known that 25-hidroxy vitamin D and some statins are metabolized in the liver by CYP3A4, an enzyme of the cytochrome P450 system.[5]

A common precursor of vitamin D and cholesterol is 7-dehydrocholesterol. The inhibition of HMG-CoA reductase can increase the levels of 7-dehydrocholesterol, offering an appropriate substrate for 25-hydroxy vitamin D synthesis. Blocking of the active site of the CYP3A4 enzyme by statins can explain the high serum levels of 25-hydroxy vitamin D.[6] Other studies showed no significant increase of vitamin D levels in patients on statin therapy.[7] Oral vitamin D supplementation can improve insulin resistance in type 2 diabetic patients[8] and could reduce myalgia in patients on statin therapy.[9,10]

Study objectives

The aim of the study was to evaluate the vitamin D status in hypertensive patients on statin therapy compared to a control group of similar age and pathology, without statin therapy. Additionally, we assessed gender differences regarding lipid profile parameters and investigated the relationship between the aforementioned laboratory test results and body mass index (BMI).

MATERIAL AND METHODS

The study was conducted at the Cardiovascular Rehabilitation Clinical Hospital in Târgu Mureș and included 89 patients with stage 2 and 3 hypertension (overweight or obese patients with/without type 2 DM), between 2019 and 2021. The study was approved by the ethics committee of the hospital and of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș.

Serum vitamin D concentration was determined using a Dynex DS2 (Dynex Technologies, Chantilly, VA, USA) automatic ELISA equipment with Redalin kit (Brașov, Romania) at the Advanced Research Centre of the university. Serum triglyceride, total and HDL-cholesterol levels were assessed using a KonelabTM Prime 60i analyzer (Thermo Fisher Scientific Inc, Waltham, MA, USA) by photometric method using reagent kits from the Diagnosticum Zrt (Budapest, Hungary) company. LDL-cholesterol levels were calculated using the Friedewald equation (total cholesterol – HDL – triglycerides/5). BMI values were calculated based on the formula: weight/square of height of the patients, expressed in kg/m^2. Statistical data was processed using GraphPad InStat 3 software (GraphPad Software Inc., San Diego CA, USA), and the significance level was set at $p < 0.05$.

RESULTS

In total, 89 hypertensive patients were enrolled in the study, who were divided into two groups: 61 patients in the statin-treated group, and 28 patients in the control group. The average age of the enrolled patients was 70.28 ± 7.79 years. Female patients (average age 69.09 ± 6.01 years) were slightly younger than enrolled males (72.15 ± 6.69 years), although the difference was not significant ($p = 0.06$). A total of 42% of the subjects were males, and 51% of patients had type 2 DM as a comorbidity.

The average serum vitamin D level of the studied patients was 14.27 ± 11.96 ng/mL. Normal range is between 30–55.5 ng/mL, values between 20.1–29.9 ng/mL correspond to insufficiency, and values ≤20 ng/mL correspond to deficiency. In our study group, 89% of the patients had hypovitaminosis, with serum vitamin D values <30 ng/mL (Figure 1).

No significant difference could be observed when comparing serum vitamin D concentration of patients treated with statins (13.65 ± 11.32 ng/mL) with that of patients without statin therapy (15.96 ± 13.67 ng/mL) using the unpaired Student's t test ($p = 0.4$).

No significant difference was seen comparing average serum vitamin D level in hypertensive patients with DM as a comorbidity (12.07 ± 4.45 ng/mL) to those without this associated pathology (16.53 ± 2.63 ng/mL) ($p = 0.09$).

The average concentration of serum cholesterol was 176.50 ± 45.44 mg/dL, the mean triglyceridemia was

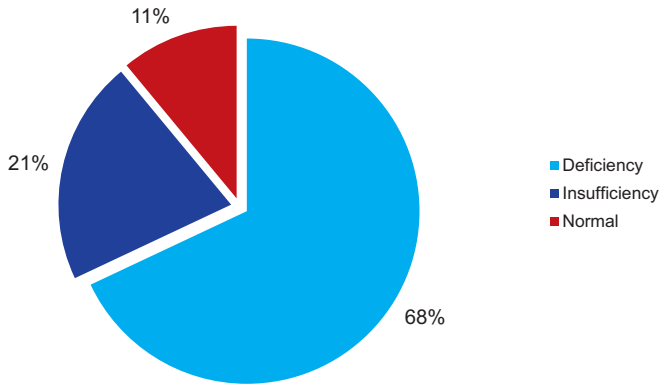

FIGURE 1. Distribution of serum vitamin D levels in the studied patients

133.76 ± 64.80 mg/dL, the average HDL-cholesterol 47.70 ± 12.84 mg/dL, and the calculated mean of LDL-cholesterol 100.58 ± 44.84 mg/dL.

There was no significant difference between genders in regards to mean serum vitamin D levels (15.65 ± 10.06 ng/mL in males and 12.18 ± 12.09 ng/mL in females, p = 0.2). No correlation was observed between serum vitamin D levels and age neither in male (r = –0.1356, p = 0.5), nor in female patients (r = –0.2000, p = 0.2).

The gender differences of lipid profile parameters are presented in Table 1.

No correlation was observed between serum vitamin D and serum total cholesterol concentration (r = 0.1253, p = 0.3). However, there was an inverse correlation between serum HDL-cholesterol and triglyceride concentrations (r = –0.3988, p = 0.0008), and a positive correlation between serum LDL- and total cholesterol (r = 0.9497, p <0.0001) levels. No correlation could be confirmed between serum total cholesterol and triglyceride concentration (r = 0.1532, p = 0.1), as well as LDL-cholesterol and triglyceride levels (r = –0.0544, p = 0.6) in the studied patients.

The average BMI of the enrolled subjects was 31.10 ± 6.83 kg/m2, 34% of the patients were overweight, and 51% had obesity as a comorbidity. BMI values ranged from 18.65 to 57 kg/m2. No correlation was found between BMI and serum vitamin D levels neither in male (r = –0.4158, p = 0.1), nor in female patients (r = –0.1743, p = 0.4).

We studied the possible correlation between BMI and lipid parameters. A negative correlation was revealed between BMI and HDL-cholesterol values (r = –0.3114, p = 0.04). There was no correlation between BMI and total cholesterol levels (r = –0.0922, p = 0.5), BMI and LDL-cholesterol (r = –0.2412, p = 0.1), and BMI and triglyceride concentration (r = –0.3082, p = 0.1).

DISCUSSION

Alterations of vitamin D and cholesterol metabolism occur frequently in elderly people, increasing the risk of age-related medical conditions. Vitamin D has an important role in the regulation of intracellular and plasmatic cholesterol homeostasis, and its supplementation reduces cardiovascular risk by exhibiting a beneficial influence on lipid profile parameters involved in atherogenesis.[7] Myalgia, as a common side effect of statin therapy, is more frequent in patients with vitamin D deficiency, and supplementation of this vitamin can improve symptoms.[11] Vitamin D deficiency was common among our study subjects, in frequent association with type 2 DM and overweight/obesity as comorbidities. The disturbance of homeostasis for this vitamin could also be related to the advanced age of the subjects enrolled. In this study, vitamin D levels were not increased by statin treatment; moreover, 68% of the subjects had vitamin D deficiency, regardless of statin treatment.

The positive correlation between total and atherogenic (LDL) cholesterol levels was an expected result. A similar inverse relationship between serum HDL-cholesterol and triglyceride concentration was obtained in another study of our research group, on a larger number of cases.[12] The inverse relationship between BMI and HDL-cholesterol is similar to the outcome of certain previous studies in the literature,[13,14] and it emphasizes the importance of weight loss to improve metabolic imbalance and protection against cardiovascular diseases.

Limitations of the study include the relatively small number of cases, the lack of direct measurement of LDL-cholesterol levels, the different types of statins (atorvastatin in the majority of cases, but rosuvastatin and simvastatin were also frequently used), combined with the

TABLE 2. Gender differences of lipid profile parameters in the studied patients

Lipid profile parameter	Unit	Female patients	Male patients	p value
Serum total cholesterol	mg/dL	171.05 ± 45.06	169.57 ± 49.69	0.9
Serum HDL-cholesterol	mg/dL	48.14 ± 13.24	44.34 ± 9.46	0.2
Serum LDL-cholesterol	mg/dL	93.65 ± 47.24	95.75 ± 41.23	0.8
Serum triglycerides	mg/dL	133.92 ± 69.07	149.83 ± 77.54	0.4

variable doses taken by patients enrolled in the study, and the differences on the duration of the treatment.

CONCLUSIONS

Vitamin D deficiency was generally present in the enrolled elderly hypertensive patients regardless of statin use, but to eliminate de limitations of this study and to validate these findings, the study should be extended to a larger number of cases. Due to frequent hypovitaminosis D in the study group, we consider that assessment of vitamin D status should be performed more frequently in elderly patients. The common association of obesity and type 2 DM with hypertension makes the management of these cases more complicated.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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