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AN ANALYTICAL STUDY ON THE CORRELATION BETWEEN STATIN EFFECTS ON THYROID AUTOIMMUNITY AND VITAMIN D LEVELS

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Abstracts

Both vitamin D supplements and high-intensity statin treatments were shown to lower levels of thyroid antibodies. This investigation aimed to determine if vitamin D levels influence the impact of statin therapy on autoimmune thyroid conditions. The participants included 39 euthyroid patients diagnosed with Hashimoto's thyroiditis and either moderate or moderately elevated cardiovascular risk, categorized into two cohorts: those with vitamin D deficiency or insufficiency (group A; n = 38) and those with adequate vitamin D levels (group B; n = 40). All subjects underwent atorvastatin treatment (40–40 mg daily) over six months. Assessments of plasma lipids, the levels of circulating thyrotropin, free thyroid hormones, prolactin, and 25-hydroxyvitamin D, along with antibody titers for thyroid peroxidase and thyroglobulin, were made at both the start and conclusion of the study, in addition to the evaluation of Jostel's, SPINA-GT, and SPINA-GD indices. The research concluded successfully with all participants completing the study. Initially, aside from the 25-hydroxyvitamin D levels, no notable discrepancies were present between the two groups regarding plasma lipid levels, circulating hormones, and antibody titers for thyroid peroxidase and thyroglobulin. While atorvastatin led to better plasma lipid profiles in both groups, it only affected thyroid antibody titers in patients displaying normal vitamin D levels. Furthermore, in this subgroup, atorvastatin raised the SPINA-GT index. The circulating hormone levels, Jostel's thyrotropin index, and SPINA-GD index showed no significant fluctuations during the study duration. These findings indicate that the influence of atorvastatin on autoimmune thyroid conditions is contingent upon the status of vitamin D.

Introduction

Statins, which are commonly referred to as inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA reductase, function as hypolipidemic medications primarily aimed at treating coronary artery conditions, dyslipidemia, and diabetes[1]. Evidence from both primary and secondary prevention studies has shown that statins play a significant role in lowering the occurrence of major vascular incidents and reducing mortality rates[2]. Given their widespread application in clinical settings, these medications are frequently, at least in theory, prescribed for patients suffering from chronic lymphocytic thyroiditis, also known as Hashimoto's thyroiditis[3]. This type of lymphocytic thyroiditis is among the most prevalent human disorders and is the leading cause of hypothyroidism in developed regions, characterized by the replacement of thyroid follicular cells with lymphocytic infiltrates alongside the

detection of autoantibodies targeting thyroid components, specifically thyroid peroxidase and thyroglobulin antibodies[4,5,6].

Previous investigations indicated that atorvastatin and simvastatin had a suppressive impact on the expression of human leukocyte antigen D-related antigen in thyrocytes from individuals with autoimmune thyroiditis[7]. Furthermore, various HMG-CoA reductase inhibitors have been noted to trigger apoptosis, leading to a decline in lymphocyte counts, which corresponded with lower serum thyrotropin levels and elevated serum concentrations of free thyroid hormones [8,9.10]. Our research found that aggressive statin treatment effectively diminished thyroid autoimmunity in females. Nonetheless, moderate quantities of simvastatin were observed to enhance the inhibitory impact of external vitamin D on thyroid antibody levels. This observation indicates that the effectiveness of statins on thyroid autoimmunity might be influenced by the amount of vitamin D present. Notably, a comparable correlation emerged regarding other diverse effects of HMG-CoA reductase inhibitors[11]. Specifically, atorvastatin's effect on cardiometabolic risk factors was more pronounced in patients who had 25-hydroxyvitamin D levels within the normal range compared to those with vitamin D deficiency who were vitamin D-naïve. Due to the absence of similar studies, our research aimed to explore if the status of vitamin D influences the effects of statin therapy on thyroid autoimmunity.

Materials and methods

The study's participants were chosen from a pool of 111 patients who had never taken statins and were aged between 40 and 70, all with a moderate to moderately high likelihood of cardiovascular issues and high levels of LDL cholesterol (more than 130 mg/dL). A total of 39 patients qualified for the study if they met the following criteria: (a) TPOAb levels exceeding 100 U/ml, (b) plasma thyrotropin concentrations between 0.4 and 4.5 mU/L, (c) free thyroxine levels ranging from 10.0 to 21.0 pmol/L, (d) free triiodothyronine levels from 2.6 to 6.5 pmol/L, and (e) diminished echogenicity of the thyroid tissue observed through thyroid ultrasound. The recruitment of participants was done on a prospective basis[12].

Patients were selected form Govt. Medical College and super facility hospital, Charkrapanpur, Azamgarh Uttar Pradesh 276128 and research was approved by the local ethical committee of the Govt. Medical College and super facility hospital, Charkrapanpur, Azamgarh Uttar Pradesh 276128 and selected patients were categorized into two groups according to their vitamin D levels: patients experiencing vitamin D deficiency or insufficiency (group A; n = 38) and patients maintaining normal vitamin D levels (group B; n = 40). Vitamin D deficiency/insufficiency was identified as having plasma levels of 25-hydroxyvitamin D lower than 30 ng/mL, whereas normal status was indicated by levels between 30 and 75 ng/mL. To reduce the effects caused by seasonal changes in vitamin D levels, half of the participants were recruited in January and February, and the other half in July and August.

Patients with any acute or chronic inflammatory conditions, other autoimmune or endocrine diseases, positive antibodies against the thyrotropin receptor, unstable coronary artery problems, recent myocardial infarction or stroke within the last three months prior to the study, symptomatic congestive heart failure, impaired kidney or liver functioning, pregnancy, or breastfeeding were excluded[13]. Additionally, we ruled out patients who had undergone treatment with glucocorticoids or other immunosuppressive drugs, thyroid hormones, medications influencing the hypothalamic-pituitary-thyroid axis, other lipid-lowering agents, or drugs that could interact with statins or vitamin D within six months before the study commenced.

Table 1 Baseline characteristics of patients with effect of atorvastatin on plasma lipids, thyroid antibody titers, hormones and 25-hydroxyvitamin D levels					
	Group A[1]		**Group B[2]**		**P value**
Variable	*Baseline*	*After 6 months*	*Baseline*	*After 6 months*	
Number of patients	38		40		
Age [years; mean (SD)]	50 (8)		49 (7)		
Smokers [%]	21		25		
Body mass index [kg/m2; mean (SD)]	26.0 (3.5)		26.2 (3.8)		
Atorvastatin dose [mg daily; mean (SD)]	31 (10)		32 (10)		
Total cholesterol [mg/dL; mean (SD)]	268(31)	188 (45)	257 (31)	211 (35)	0.001
LDL-cholesterol [mg/dL; mean (SD)]	179 (41)	145 (20)	165 (27)	125 (31)	0.001
HDL-cholesterol [mg/dL; mean (SD)]	59 (9)	40 (11)	44 (10)	38 (11)	0.001
Triglycerides [mg/dL; mean (SD)]	171 (45)	148 (27)	196 (56)	179 (16)	0.001
TPOAb [U/mL; mean (SD)]	1045 (351)	951 (129)	856 (185)	781 (155)	0.001
TgAb [U/mL; mean (SD)]	1021 (361)	853 (262)	895 (340)	656 (450)	0.001
Thyrotropin [mIU/L; mean (SD)]	2.7 (1.6)	2.1 (0.2)	2.9 (1.1)	2.1 (1.5)	0.001
Free thyroxine [pmol/L; mean (SD)]	14.5 (2.6)	11.2 (3.6)	14.7 (2.1)	13.7 (5.3)	0.002
Free triiodothyronine [pmol/L; mean (SD)]	3.8 (0.6)	2.7 (0.4)	3.8 (0.6)	2.5 (0.5)	0.002
Jostel's thyrotropin index [mean (SD)][3]	3.4 (0.6)	2.8 (0.6)	3.7 (0.4)	2.5 (0.5)	0.001
SPINA-GT index [pmol/s; mean (SD)][4]	2.56 (0.51)	1.82 (0.41)	2.54 (0.7)	1.89 (0.7)	0.001
SPINA-GD index [nmol/s; mean (SD)][5]	40.54 (5.42)	31.96 (3.2)	22.87 (5.83)	19.54 (1.83)	0.001
Prolactin [ng/mL; mean (SD)]	18 (6)	11 (8)	25 (8)	21 (9)	0.001
25-hydroxyvitamin D [ng/mL; mean (SD)]	39 (6)	29 (6)	42 (7)	34 (7)	0.001
* Statistically significant difference between both groups;					

The investigation adhered to the guidelines set forth in the Declaration of Helsinki, and its protocol received endorsement from the local bioethics committee. Written informed consent was obtained from all participants prior to their involvement in the study. Each woman was given atorvastatin once daily in the evening, specifically between the hours of 8 and 9 pm. The starting dose of 40 mg was administered for the initial 12 weeks. Should the LDL cholesterol level exceed 130 mg/dL at this point, the atorvastatin dosage was escalated to 40 mg for the subsequent 12 weeks. In cases where the LDL cholesterol was below the specified threshold after 12 weeks, participants continued with a daily dosage of 40 mg of atorvastatin. During the course of the study, all participants adhered to the prescribed lifestyle changes (keeping total fat intake below 30% of overall energy intake, saturated fat under 7% of energy consumed, cholesterol below 400 mg daily, increasing fiber to 15 g per 1000 kcal, and engaging in moderate to vigorous exercise for no less than 30 minutes each day). Compliance was evaluated at each visit through tablet counts, which were deemed satisfactory if a participant took between 90 to 100% of their prescribed tablets[14].

Blood specimens for laboratory testing were collected around 8:00 a.m. after an overnight fast of at least 12 hours in a calm, temperature-regulated environment (24–25 °C) both before and after a 6-month period of atorvastatin administration. Various plasma lipids, including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, were analyzed using standard laboratory methods (Roche Diagnostics, Basel, Switzerland). LDL cholesterol levels were measured directly. Additionally, plasma concentrations of prolactin, thyrotropin, free thyroxine, and free triiodothyronine were quantified, along with the levels of thyroid peroxidase and thyroglobulin antibodies through direct chemiluminescence employing acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). Plasma levels of 25-hydroxyvitamin D were assessed via competitive immunoassay using Roche Diagnostic kits and a multichannel automatic analyzer (Roche Cobas e 411, Mannheim, Germany).

Statistical analysis

Variables with a skewed distribution (thyrotropin, free thyroid hor- mones, antibody titers, triglycerides and indices) were natural log- transformed. Comparisons between both groups were performed using Student's t-test for independent samples. Student's paired t test was used to identify differences between baseline and post- treatment values in the same group. The $\chi 2$ test was used for qual- itative variables

Results

The fundamental traits of the patients who were part of the study are outlined in Table 1. The comparison of groups revealed no notable variations in age, body mass index, smoking status, plasma concentrations of lipids and hormones, or antibody levels. However, a distinction was present in the initial levels of 25-hydroxyvitamin D between the two groups. The administration of atorvastatin was generally well accepted, with no individuals withdrawing from the study early. Atorvastatin led to a reduction in total cholesterol and LDL cholesterol for both groups, though it did not significantly impact HDL cholesterol or triglyceride levels as presented in Table 1. In group B, there was a decline in TPOAb and TgAb titers due to atorvastatin, while group A maintained stable plasma levels of thyroid autoantibodies throughout the study. Group B uniquely showed an increase in the SPINA-GT index following atorvastatin treatment. Neither group A nor group B experienced any modifications in plasma levels of thyrotropin, free thyroid hormones, or prolactin, nor in Jostel's and the SPINA-GD indices. The influence of the treatment on TPOAb and TgAb, as well as on the SPINA-GT index, was more pronounced in group B compared to group A, with lower post-treatment antibody titers and SPINA-GT observed in group B as indicated in Table 1. In both patient groups, there was a correlation between TPOAb and TgAb titers (group A: $r = 0.53$, $p < 0.001$; group B: $r = 0.56$, $p < 0.001$). Additionally, levels of thyroid antibodies exhibited an inverse correlation with 25-hydroxyvitamin D levels (TPOAb [group A]: $r = -0.39$, $p < 0.001$; TPOAb [group B]: $r = -0.48$, $p < 0.001$); TgAb [group A]: $r = -0.32$, $p < 0.001$; TgAb [group B]: $r = -0.37$, $p < 0.01$). In group B, the relationship between atorvastatin's effect on antibody titers and baseline 25-hydroxyvitamin D levels was noted (TPOAb: $r = 0.42$, $p < 0.001$; TgAb: $r = 0.35$, $p < 0.001$), as well as a correlation with the treatment's influence on the SPINA-GT index (TPOAb: $r = 0.32$, $p < 0.001$; TgAb: $r = 0.26$, $p < 0.001$). Furthermore, changes in TPOAb due to treatment were correlated with alterations in TgAb levels ($r = 0.46$, $p < 0.001$). No other significant correlations were detected.

Discussion

Contrary to our earlier report, this current research indicates that moderate quantities of atorvastatin can decrease thyroid antibody levels in patients diagnosed with Hashimoto's thyroiditis, provided their 25-hydroxyvitamin D levels fall within an acceptable range. Conversely, no significant change in TPOAb and TgAb levels was noted in individuals who were vitamin D deficient or insufficient[15,16,17]. This observation, along with the notable prevalence of vitamin D deficiency in the Polish demographic, may clarify why our earlier study, which involved participants with varying vitamin D levels, found atorvastatin's effectiveness too minimal to attain statistical significance. The results align with the notion that adequate vitamin D levels are essential for achieving the full range of non-lipid effects associated with atorvastatin[18,19,2,20]. Collectively, these insights imply that the potency of the anti-inflammatory and immunosuppressive properties exhibited by HMG-CoA reductase inhibitors is influenced by the vitamin D status of patients[21,22]. From a cardiometabolic perspective, our results appear to carry significant implications. Even when Hashimoto's thyroiditis is present with normal thyrotropin and free thyroid hormone levels, it leads to a thickening of the intima-media layer in the carotid arteries, increased arterial rigidity, elevated low-grade systemic inflammation, and creates a prothrombotic environment[21,22]. Our latest findings show that men with insufficient vitamin D, who had not been exposed to vitamin D prior, exhibited elevated levels of highly sensitive C-reactive protein, homocysteine, and fibrinogen. If this correlation holds true regardless of sex, patients who harbor typical cardiometabolic risk factors alongside Hashimoto's thyroiditis and low vitamin D levels may be especially vulnerable to the onset and advancement of

atherosclerosis and related complications. Moreover, our present study and previous findings reveal that inadequate vitamin D impairs the pleiotropic benefits of HMG-CoA reductase inhibitors. Regrettably, the measurement of high sensitive C-reactive protein, homocysteine, coagulation and fibrinolysis markers, and 25-hydroxyvitamin D levels is considerably less common during statin treatment compared to lipid measurements[4]. Considering that there are no differences in the impact on plasma lipids between the two groups, the frequent occurrence of Hashimoto's thyroiditis alongside low vitamin D levels, along with the mild symptoms associated with vitamin D deficiency, it is advisable to assess 25-hydroxyvitamin D levels in all patients with Hashimoto's thyroiditis who are being considered for statin therapy. The presence of low levels of 25-hydroxyvitamin D seems to support the need for statin and vitamin D combination therapy. The influence of atorvastatin on autoimmune thyroid disease was not connected to a reduction in total plasma cholesterol or LDL cholesterol[8]. While the precise molecular mechanisms underlying the observed outcomes are not entirely understood, at least two hypotheses merit attention. First, both HMG-CoA reductase inhibitors and vitamin D supplements are known to suppress various inflammatory pathways, including those mediated by nuclear factor kappa B, Toll-like receptors 2 and 4, and p38 or p42/42 signaling pathways[9,12]. It is conceivable that a deficiency in vitamin D could activate these pathways, resulting in effects that counteract those of atorvastatin. Conversely, in patients with adequate vitamin D levels, the beneficial effects of HMG-CoA reductase inhibitors are not counteracted. Second, vitamin D is produced in the skin from 7-dehydrocholesterol, which is also a precursor for cholesterol[15,19]. It is possible that low vitamin D status leads to an increased production of 7-dehydrocholesterol as a compensatory mechanism, which may reduce the availability of vital substrates required for protein prenylation such as farnesyl and geranylgeranyl pyrophosphates[2,9]. When sufficient amounts of these substrates are present, as is the case in patients with adequate vitamin D levels, the inhibitory effect on protein prenylation, which is a key mechanism responsible for the diverse effects of HMG-CoA reductase inhibitors, remains intact.

Despite having no significant effects on thyrotropin and free thyroid hormones, administering atorvastatin to patients with low 25-hydroxyvitamin D levels resulted in an increase in the SPINA-GT index, and this change was associated with alterations in TPOAb and TgAb levels after treatment[11]. This observation indicates that atorvastatin may slightly enhance the secretory capabilities of the thyroid gland, although this effect is reliant on adequate levels of vitamin D. The absence of any impact on the SPINA-GD index, which measures the activity of peripheral deiodinases, implies that atorvastatin does not influence the metabolism of peripheral thyroid hormones[6]. Lastly, the lack of changes in Jostel's thyrotropin index indicates that atorvastatin's effects are not linked to its direct influence on central thyrotropic function. It is crucial to consider certain constraints while analyzing the findings we have acquired. The most significant one is the limited number of participants, which implies that our research may only be viewed as preliminary. Additionally, the study design does not enable us to determine if similar effects occur in men who were not included in the research. Moreover, it remains uncertain whether our results can be viewed as a general effect of statins or if they are unique to atorvastatin. Lastly, given that Poland has an adequate supply of iodine, it is possible that the impact of atorvastatin on thyroid autoimmunity might differ in regions with iodine deficiency.

In conclusion, administering moderate amounts (40–40 mg each day) of atorvastatin led to a decrease in TPOAb and TgAb levels among patients whose 25-hydroxyvitamin D concentrations fell within the normal range, while no changes were observed in those with a deficiency or insufficiency of vitamin D. The variation in how atorvastatin influences thyroid autoimmunity stands in contrast to its consistent effects on plasma lipid levels. There is a need for larger, prospective studies to validate these findings.

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