

The Effect of Ezetimibe/Statin Combination and High-Dose Statin Therapy on Thyroid Autoimmunity in Women with Hashimoto's Thyroiditis and Cardiovascular Disease: A Pilot Study

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Key words

- cardiovascular disease
- ezetimibe
- statins
- thyroid autoimmunity

Abstract

Background: Intensive statin therapy was found to reduce thyroid autoimmunity in women with Hashimoto's thyroiditis. No similar data are available for other hypolipidemic agents.

Methods: The participants of the study were 16 women with Hashimoto's thyroiditis and coronary artery disease. On the basis of statin tolerance, they were divided into 2 groups. 8 patients who did not tolerate high-dose statin therapy were treated with a statin, the dose of which was reduced by half, together with ezetimibe. The remaining 8 patients tolerating the treatment continued high-dose statin therapy. Plasma lipids, serum levels of thyrotropin, free thyroxine and free triiodothyronine, as well as titers of

thyroid peroxidase and thyroglobulin antibodies were measured at the beginning of the study and 6 months later.

Results: Replacing high-dose statin therapy with ezetimibe/statin combination therapy increased serum titers of thyroid peroxidase as well as led to an insignificant increase in serum titers of thyroglobulin antibodies. At the end of the study, thyroid peroxidase and thyroglobulin antibody titers were higher in patients receiving the combination therapy than in those treated only with high-dose statin.

Conclusions: Our study shows that high-dose statin therapy produces a stronger effect on thyroid autoimmunity than ezetimibe/statin combination therapy.

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Bibliography

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Abbreviations

HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
NPC1L1	Niemann-Pick C1-Like 1
SD	standard deviation
TgAb	thyroglobulin antibodies
TPOAb	thyroid peroxidase antibodies

Introduction

Chronic lymphocytic thyroiditis, often referred to as Hashimoto's thyroiditis, is the most frequent thyroid disorder in iodine-sufficient areas, the most common autoimmune disease in the United States, as well as the most frequent cause of subclinical and overt hypothyroidism in the developed countries [1–3]. Its prevalence in women exceeds 2%, while incidence ranges between 0.3 and 1.5 cases per 1000 people [3]. The disease is characterized by the infiltration of the gland with lymphocytes and the production of autoantibodies to thyroid-specific antigens: thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) [4,5].

Autoimmune-mediated destruction of the thyroid gland and fibrotic reaction of the parenchyma may lead to thyroid hypofunction [1,4]. Recently, we have observed that intensive treatment with 3-hydroxy-3-methyl-glutaryl-CoA (HMC-CoA) reductase inhibitors (statins) reduced thyroid autoimmunity in patients with Hashimoto's thyroiditis, while less aggressive statin therapy was ineffective [6]. This effect was lipid-independent and probably resulted from the reduction of protein prenylation, which is a process involved in the regulation of many cellular processes [7]. However, pleiotropic effects are also observed in patients receiving other hypolipidemic agents, including ezetimibe, which inhibits absorption of cholesterol at the brush border of the small intestine *via* the sterol transporter, Niemann-Pick C1-Like1 (NPC1L1) [8]. Monocyte-derived macrophages have been found to express target proteins for ezetimibe: NPC1L1, aminopeptidase N, annexin-2 and caveolin-1 [9,10]. Ezetimibe reduced monocyte expression of raft-associated antigens and induced transfer of aminopeptidase N from plasma membrane to

intracellular vesicles [10]. The drug decreased the number of monocytes/macrophages in atherosclerotic lesions (particularly in patients receiving additionally atorvastatin), reduced monocyte chemoattractant protein 1 expression in atherosclerotic lesions, as well as inhibited the migratory response of monocytes in atherosclerotic rabbits [11]. Moreover, the drug decreased monocyte release of proinflammatory cytokines [12,13]. Apart from affecting monocyte, ezetimibe produced a weak suppressive effect on lymphocyte secretory function and potentiated the inhibitory effect of statin therapy on lymphocyte cytokine release and low-grade systemic inflammation [14]. Interestingly, pleiotropic effects of ezetimibe/simvastatin combination were stronger than those of simvastatin alone [15]. Monocytes/macrophages and lymphocytes are considered important cells involved in the development and progression of autoimmune disorders, and are abundantly present in inflamed tissues [16,17].

Ezetimibe does not change levothyroxine absorption and therefore both drugs may be administered simultaneously [18]. However, to the best of our knowledge, no previous study has investigated the effect of ezetimibe on the thyroid gland. Therefore, the aim of our study was to determine whether ezetimibe/statin combination therapy affects thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in women with Hashimoto's thyroiditis and coexistent cardiovascular disease.

Materials and Methods

▼ The participants of the study (n=16) were recruited among women (40–70 years old) with euthyroid Hashimoto's thyroiditis and stable coronary artery disease with a history of cardiovascular events. Hashimoto's thyroiditis was diagnosed if the patient had positive TPOAb antibodies (>100 U/mL) and reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography. In turn, normal thyroid function was defined as serum thyrotropin levels in the range between 0.4 and 4.0 mIU/L and free thyroid hormone levels within the reference range. The study included only patients who (1) had been treated with atorvastatin (40 mg daily) or rosuvastatin (10 mg daily) for more than 3 months and these doses of statins had been well tolerated; (2) at least 6 weeks before the beginning of the study, because of LDL cholesterol levels exceeding 70 mg/dL, atorvastatin or rosuvastatin dose was doubled. The subjects were excluded if they met at least one of the following criteria: positive serum antibodies against thyrotropin receptor, other autoimmune disorders, body mass index above 40 kg/m², Turner or Down syndrome, any form of coronary artery disease, stroke, moderate or severe arterial hypertension (ESC/ESH grade 2 or 3), symptomatic congestive heart failure, impaired renal or hepatic function, pregnancy or lactation, and poor patient compliance. We also excluded patients treated within 3 months preceding the study with drugs affecting hypothalamic-pituitary-thyroid axis activity (with the exception of levothyroxine), any hypolipidemic agents, as well as with drugs known to interact with levothyroxine, statins and/or ezetimibe. All participants were informed of the study aims and provided written consent before entering the study, which was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee. On the basis of high-dose statin tolerance, the participants were divided into 2 groups. In the first group (n=8), high-dose statin therapy was well tolerated and continued this

treatment throughout the study period, without any changes in dosage. In turn, the second study group (n=8) included women in whom the increase in statin dose led to an asymptomatic rise in the levels of aminotransferases (>3 times above the normal limit) and/or of creatine kinase (>5 times above the normal limit). In these patients, the daily dose of HMG-CoA reductase inhibitor was reduced by half (to the initial dose) and administered together with ezetimibe (10 mg daily). Throughout the entire study period, women who were already receiving other medications kept their pharmacologic schedule constant and were required to comply with lifestyle modifications. Compliance was assessed in all subjects at each visit by pill counts.

Venous blood samples were drawn from the antecubital vein between 8.00 and 9.00 a.m., at least 12 h after the last meal, at baseline and at the end of the treatment period, 6 months later, and assessed in duplicate. Plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) were assayed by routine laboratory techniques (Roche Diagnostics, Basel, Switzerland). LDL-cholesterol levels were measured directly. Serum levels of thyrotropin, free thyroxine and free triiodothyronine were measured using an electrochemiluminescence immunoassay method (Roche Diagnostics, Lewes, United Kingdom). Serum titers of TPOAb and TgAb were determined by enzyme-linked immunosorbent assays using reagents purchased from IBL International (Hamburg, Germany), respectively. The intra- and inter-assay coefficients of variation were below 6.1% and 8.5%, respectively.

The Shapiro-Wilk test was used to assess the distribution of variables. Variables with a skewed distribution (triglycerides, hormones and antibodies) were log-transformed. Between-group comparisons were performed by the *t* test for independent samples. Pre- and post-therapy data within the same treatment group were compared with Student's paired *t* test. The χ^2 test was employed to compare the proportional data. Correlations were calculated using Pearson's *r*-tests. Statistical significance was assumed at *p*<0.05.

Results

▼ No significant differences were observed in the age, body mass index, medical backgrounds, plasma lipids, thyrotropin, free thyroid hormones and thyroid antibody titers between the groups at the beginning of the study (◉ Table 1). Both therapies were well tolerated and all patients completed the study protocol. All safety parameters remained within normal limits.

Continuation of high-dose statin therapy insignificantly reduced TPOAb titers (*p*=0.088) did not affect plasma levels of lipids, serum levels of thyrotropin, free thyroxine and free triiodothyronine, as well as titers of TgAb (◉ Table 2). Replacing statin therapy with ezetimibe/statin combination tended to increase triglycerides (*p*=0.092), as well as insignificantly decreased HDL cholesterol (*p*=0.086). Moreover, ezetimibe/statin combination therapy increased TPOAb, tended to increase TgAb titers (*p*=0.084), but did not cause any changes in serum levels of thyrotropin and free thyroid hormones. Between-group comparisons showed differences between both groups in the strength of effects on TPOAb and TgAb titers. At the end of the study, TPOAb and TgAb titers were lower in patients treated with high-dose statin than receiving ezetimibe/statin combination therapy (◉ Table 2).

Table 1 Baseline characteristics of patients.

Variable	Ezetimibe/statin	High-dose statin
Number of patients	8	8
Age [years; mean (SD)]	60 (8)	58 (8)
Smokers [%]	25	25
Body mass index [kg/m ² ; mean (SD)]	30.5 (4.8)	29.8 (4.3)
Atorvastatin/rosuvastatin [%]	50/50	62/38
Diabetes [%]	38	25
Hypertension [%]	75	63
Levothyroxine treatment [%]	75	75
Levothyroxine dose/duration of treatment [µg daily/months; mean (SD)]	80 (15)/35 (8)	75 (18)/37 (10)
Total cholesterol [mg/dL; mean (SD)]	138 (10)	143 (12)
LDL cholesterol [mg/dL; mean (SD)]	53 (8)	55 (8)
HDL cholesterol [mg/dL; mean (SD)]	49 (7)	50 (6)
Triglycerides [mg/dL; mean (SD)]	160 (32)	173 (28)
Thyroid peroxidase antibodies [U/mL; mean (SD)]	1 255 (380)	1 305 (395)
Thyroglobulin antibodies [U/mL; mean (SD)]	1 190 (402)	1 215 (405)
Thyrotropin [mIU/L; mean (SD)]	2.1 (0.8)	2.0 (0.8)
Free thyroxine [pmol/L; mean (SD)]	15.0 (1.5)	15.5 (2.1)
Free triiodothyronine [pmol/L; mean (SD)]	5.0 (0.5)	5.1 (0.6)

SD – standard deviation

At entry, thyroid antibody titers correlated weakly with thyrotropin levels (TPOAb: $r=0.32$, $p<0.05$, TgAb: $r=0.26$, $p<0.05$), but not with total and free thyroid hormones. There were weak correlations between the effect of continuation of high-dose statin therapy on TPOAb and baseline TPOAb titers ($r=0.30$, $p<0.05$), between the effect of the combined treatment on TPOAb and baseline TPOAb titers ($r=0.28$, $p<0.05$), as well as between the effect of ezetimibe/statin combination therapy on TGAb and baseline TGAb titers ($r=0.25$, $p<0.05$). No other correlations between the investigated variables were observed in any group before and after hypolipidemic treatment.

Discussion

The most important finding of our study was that replacing high-dose statin treatment with ezetimibe/statin combination therapy was associated with an increase in thyroid antibody titers. Moreover, despite similar baseline characteristics, at the end of the study protocol there were statistical differences in TPOAb titers between both study groups. In turn, continuation of high-dose statin therapy led to a further, though slight, decrease in circulating titers of TPOAb, indicating that the strength of immunosuppressive action of statins administered at high doses on the thyroid increases with time. All these findings taken together clearly show the superiority of high-dose statin therapy over combination treatment with ezetimibe and moderate doses of HMG-CoA reductase inhibitors when it comes to their effect on thyroid autoimmunity.

Table 2 The effect of ezetimibe/statin combination and high-dose statin treatment on plasma lipids, thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in Hashimoto's thyroiditis women with cardiovascular disease.

Variable	Ezetimibe/ statin mean (SD)	High-dose statin mean (SD)
Total cholesterol [mg/dL]		
At the beginning of the study	138 (10)	143 (12)
At the end of the study	140 (14)	141 (11)
LDL cholesterol [mg/dL]		
At the beginning of the study	53 (8)	55 (8)
At the end of the study	56 (7)	53 (7)
HDL cholesterol [mg/dL]		
At the beginning of the study	49 (7)	50 (6)
At the end of the study	44 (6)	49 (7)
Triglycerides [mg/dL]		
At the beginning of the study	160 (32)	173 (28)
At the end of the study	185 (34)	169 (29)
Thyroid peroxidase antibodies [U/mL]		
At the beginning of the study	1 255 (380)	1 305 (395)
At the end of the study	1 630 (345) ^{a,b,c}	1 082 (285)
Thyroglobulin antibodies [U/mL]		
At the beginning of the study	1 190 (402)	1 215 (405)
At the end of the study	1 485 (372) ^{b,c}	1 012 (318)
Thyrotropin [mIU/L]		
At the beginning of the study	2.1 (0.8)	2.0 (0.8)
At the end of the study	2.3 (0.7)	1.8 (0.8)
Free thyroxine [pmol/L]		
At the beginning of the study	15.0 (1.5)	15.5 (2.1)
At the end of the study	14.8 (1.8)	15.7 (2.0)
Free triiodothyronine [pmol/L]		
At the beginning of the study	5.0 (0.5)	5.1 (0.6)
At the end of the study	4.8 (0.5)	5.2 (0.5)

^a $p<0.05$ vs. baseline value; ^b $p<0.01$ vs. patients treated with high-dose statin;^c $p<0.01$ – the strength of the effect of ezetimibe/statin combination different from that of high-dose statin

SD – standard deviation

Previously, we have found that euthyroid women with Hashimoto's thyroiditis are characterized by low-grade inflammation, enhanced production of proinflammatory cytokines, as well as by a prothrombotic state [19,20]. Our observations are in agreement with the results of other authors who reported that the presence of Hashimoto's thyroiditis was accompanied by increased arterial wall intima-media thickness in obese or overweight patients [21] or in adolescent girls [22], as well as by increased carotid-femoral pulse wave velocity, being a marker of arterial stiffness [23]. These findings suggest that the presence of Hashimoto's thyroiditis may make patients more prone to the earlier development and faster progression of atherosclerosis. For this reason, as well as because of the lack of sufficient data on its antiatherosclerotic action [24,25], ezetimibe/statin combination therapy should be recommended only to women with Hashimoto's thyroiditis and cardiovascular disease who do not tolerate high-dose statin therapy.

In our recent study [6], only high-dose but not moderate-dose statin therapy reduced thyroid autoimmunity. The results of the present study are in line with this finding, as well as with the results of *in vitro* studies [26,27]. However, unlike the mentioned study [6], continuation of high-dose statin therapy did not affect thyrotropin levels, probably because baseline concentrations of this hormone were within the reference range, partially as a consequence of levothyroxine treatment. To exert its

effect on lymphocytes [26] and on the aberrant thyrocyte expression of HLA-DR [27] of patients with Hashimoto's thyroiditis, cells had to be exposed to high concentrations of HMG-CoA reductase inhibitors, which may be obtained only after treatment with maximal or even supraphysiological doses of these drugs [28]. This may mean that threshold statin concentrations required to produce immunosuppressive properties at the level of target cells markedly exceed those needed to inhibit cholesterol synthesis. Interestingly, the effect of high-dose statin therapy was observed irrespective of whether patients were treated or not with levothyroxine.

Different action of both treatment option on thyroid autoimmunity contrasted with their similar effect on total and LDL cholesterol. Moreover, neither the effect of statin monotherapy on antibody titers nor that of the combination therapy correlated with their action on plasma lipids. The obtained results allow us to assume that immunosuppressive effects of high-dose statin therapy belong to pleiotropic effects of these drugs. They are probably secondary to the inhibitory action of HMG-CoA reductase inhibitors on protein prenylation, which plays a role in cellular signaling, differentiation, growth regulation and membrane transport [29]. Interestingly, lovastatin was found to increase thyroid signaling *via* stimulation of the type 2 iodothyronine deiodinase activity and this effect was similar to that of downstream inhibitors of the prenylation pathway [30]. This finding supports the role of the mevalonate pathway in mediating the effect of HMG-CoA reductase inhibitors on hypothalamic-pituitary-thyroid axis activity, being in line with our hypothesis.

More difficult is to explain why ezetimibe/statin combination therapy was clearly inferior to high-dose statin treatment. Previous studies conducted by our research team revealed a relatively weak impact of ezetimibe, but only administered alone, on monocyte and lymphocyte secretory function, on plasma levels of adipokines as well as on hemostasis in comparison with simvastatin [31–34]. However, if administered together with simvastatin the drug potentiated all its pleiotropic effects [31,32,34,35]. This discrepancy may result from differences in statin dosage, and/or, although less likely, from using various HMG-CoA reductase inhibitors or from differences in the inclusion and exclusion criteria. In the previous studies [31–35], the dose of simvastatin was the same, irrespective of whether simvastatin was administered alone or in combination. In turn, in the present one statins were administered at much lower doses when used together with ezetimibe. However, it may be explained as well by a small number of ezetimibe binding sites on thyrocytes and inflammatory cells. Although macrophages were found to express NPC1L1, the macrophage expression of this protein is only 0.3–0.5% of this observed in the cellular membrane of enterocytes [9].

Our study has some limitations. The major one is the small sample size and non-randomization of participants. For this reason, large randomized studies are required to confirm the obtained results. Moreover, because of the lack of a placebo-treated group, it remains unanswered whether the effect of the combination therapy on thyroid autoimmunity, if present, is slightly positive or unfavorable. The Upper Silesia, where the study was carried out, is a selenium-deficient area [36], whereas iodine intake is sufficient (owing to obligatory salt iodization) [37]. The study protocol does not allow us to answer whether the same results would be obtained if the study included patients inhabiting selenium-sufficient and/or iodine-deficient regions. Finally, our

study included only euthyroid women with Hashimoto's thyroiditis, most of whom had been treated with levothyroxine. It is difficult to say whether statin alone or in combination with ezetimibe affects thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in levothyroxine-naïve patients with overt or subclinical hypothyroidism.

In conclusion, our study shows for the first time that high-dose statin therapy produces a stronger effect on thyroid autoimmunity than ezetimibe/statin combination therapy, despite similar effects of both treatments on plasma lipids. The obtained results indicate that women with Hashimoto's thyroiditis and cardiovascular disease benefit more from treatment with a statin alone administered at high doses and therefore ezetimibe/statin combination therapy is justifiable mainly in patients poorly tolerating high doses of HMG-CoA reductase inhibitors.

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Institutional Approval

▼ The study was approved by the Bioethical Committee of the Medical University of Silesia.

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Conflict of interest: The authors declare no conflict of interest.

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