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Original research article

The effect of statin therapy on thyroid autoimmunity in patients with Hashimoto's thyroiditis: A pilot study

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ABSTRACT

Background: Statins have been found to exert antiinflammatory and immunomodulatory properties. The aim of this study was to compare the effects of intensive and less aggressive statin treatment on thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in patients with Hashimoto's thyroiditis.

Methods: The study included 38 adult women with Hashimoto's thyroiditis, who required statin therapy and were allocated into one of two groups. Patients at very high cardiovascular risk ($n = 16$) received intensive statin treatment (rosuvastatin 20–40 mg daily), while patients at moderate or moderately high cardiovascular risk ($n = 22$) were treated with simvastatin (20–40 mg daily) for the following 6 months. Serum levels of thyrotropin, total and free thyroid hormones, and high-sensitivity C-reactive protein (hsCRP), as well as titers of thyroid peroxidase and thyroglobulin antibodies were measured at the beginning and at the end of the study.

Results: Thirty-six individuals completed the study and were included in the final analyses. Apart from improving plasma lipids and reducing circulating levels of hsCRP, intensive, but not less aggressive, statin therapy reduced thyroid peroxidase and thyroglobulin antibody titers, as well as tended to reduce circulating levels of thyrotropin. The effect of intensive statin therapy on thyroid antibody titers was lipid-independent but correlated with treatment-induced changes in thyrotropin and hsCRP.

Conclusions: Although 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are able to reduce thyroid autoimmunity in women with Hashimoto's thyroiditis, intensive statin therapy is required to produce this effect.

Introduction

The benefits of statin therapy in cardiovascular diseases cannot be explained exclusively by the lipid-lowering potential of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors but also by non-lipid-related mechanisms, so-called "pleiotropic effects." Apart from lowering lipids, statins were found to produce antiinflammatory, immunomodulatory, antioxidant and antithrombotic effects, to regulate the growth and migration of smooth muscle cells and to improve endothelial function [1–3]. Antiinflammatory and immunomodulatory properties of statins result from their impact on inflammatory cells including monocytes/macrophages and lymphocytes [4]. Statins were found to shift cytokine profile from Th1/Th17 to Th2 type cytokines [5], to induce T cell apoptosis [6], to inhibit T cell proliferation and activation [7], to inhibit the induction of the major histocompatibility class II expression by interferon-γ [8], as well as to inhibit natural killer-cell degranulation and cytotoxicity [9]. As a result, statins may be an interesting treatment option for patients with multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus and other autoimmune disorders [10].

Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis, is one of the most common human diseases and the most common cause of hypothyroidism in developed countries [11,12]. The incidence is estimated at 0.3–1.5 cases per 1000 people per year. In women, in whom the disorder occurs 10-fold more frequently than in men, the prevalence of clinical disease is estimated at least 2%, while the prevalence of positive thyroid antibodies is greater than 10% [13]. Hashimoto's thyroiditis is also the most common

Abbreviations: HDL, high-density lipoprotein; HLA-DR, human leukocyte antigen D-related; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SD, standard deviation; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies.

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autoimmune disorder in the United States. The thyroid gland parenchyma of patients suffering from this condition is diffusely replaced by a lymphocytic infiltrate and fibrotic reaction and in the majority of cases the disease is characterized by the presence of specific antibodies, mainly thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) [11,14]. Based on the cytokine secretion pattern, Hashimoto's thyroiditis is classified as a T-helper cell type 1-dependent disease [15].

Very few studies have investigated the effects of statins on the thyroid gland and their results are inconclusive. In patients with Hashimoto's thyroiditis and subclinical hypothyroidism, simvastatin, mevastatin, pravastatin and cerivastatin induced apoptosis of lymphocytes [16]. The effect of simvastatin was accompanied by a decrease in thyrotropin levels and an increase in free thyroid hormone levels [16]. Simvastatin and atorvastatin inhibited the human leukocyte antigen D-related (HLA-DR) expression on thyrocytes of patients with Hashimoto's thyroiditis, as well as decreased interferon-γ-induced HLA-DR expression on thyrocytes obtained from both patients with Hashimoto's thyroiditis and control subjects [17]. However, statin treatment did not protect mice from iodine- or thyroglobulin-induced autoimmune thyroiditis [18]. Finally, statin therapy reduced prevalence, number and volume of thyroid nodules in patients living in iodine-deficient [19] but not in iodine-sufficient areas [20].

Taking into account antiinflammatory and immunomodulatory effects of HMG-CoA reductase inhibitors, as well as limited data concerning statin action in patients with autoimmune thyroiditis, the aim of this study was to compare the effects of intensive and less aggressive statin treatment on thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in patients with Hashimoto's thyroiditis.

Materials and methods

The participants ($n = 38$) were selected among statin-untreated women, aged between 35 and 70 years, who had been diagnosed with Hashimoto's thyroiditis within 8 weeks before the beginning of statin therapy. To be admitted to the study, they had to meet the following inclusion criteria: thyroid peroxidase antibody (TPOAb) titers more than 100 U/mL, reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography, thyrotropin levels in the range between 0.4 and 7.5 mU/L, normal free thyroid hormone levels, as well as no thyroxine replacement therapy. The exclusion criteria were as follows: any acute and chronic inflammatory processes, other autoimmune disorders, positive antibodies against thyrotropin receptor, unstable coronary artery disease, myocardial infarction or stroke within 3 months preceding the study, symptomatic congestive heart failure, diabetes, impaired renal or hepatic function, pregnancy or lactation and poor patient compliance. We also excluded statin-intolerant patients, as well as patients treated within 6 months preceding the study with glucocorticoids or other immune suppressive agents, thyroid hormones or other drugs affecting hypothalamic-pituitary-thyroid axis activity, other hypolipidemic agents or with drugs known to interact with statins. The study protocol was approved by the local ethics committee. Informed consent was obtained from all enrolled participants.

On the basis of cardiovascular risk, the participants were allocated into one of two groups. The first group included 16 patients who because of established or recent hospitalization for coronary, carotid, and peripheral vascular disease or diabetes plus one or more additional risk factor(s) were qualified as very high-risk patients [21]. These patients needed to be treated with high-dose statin therapy to lower LDL cholesterol levels to less than 70 mg/dL and received rosuvastatin at the daily dose of 20 mg. They were compared with 22 age-, weight-, lipid-, hormone- and antibody-matched women with moderate or moderately high risk for cardiovascular disease. Target LDL cholesterol levels in this group of patients were below 130 mg/dL and they were treated with simvastatin. Both statins were administered at the daily dose of 20 mg once daily at bedtime and, if after 6 weeks LDL cholesterol levels were still abnormal, the daily doses of rosuvastatin and simvastatin were increased to 40 mg daily. During the entire study, all participants complied with the lifestyle modification and no changes in the dosage of other medications were allowed. The investigation of possible drug-induced side effects was performed fortnightly. Compliance was assessed during each visit by tablet counts and was considered satisfactory when the number of tablets taken by a patient exceeded 90%.

Venous blood samples for laboratory assays were drawn from antecubital vein, after a 12-h overnight fast, in a quiet temperature-controlled room (24–25 °C) between 8:00 and 9:00 a.m. (to avoid possible circadian fluctuations in the parameters studied) at the beginning and at the end of the study. Laboratory tests were performed by a person blinded to subject identity and clinical diagnosis. All measurements were performed in duplicate and final results were averaged. 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 C-reactive protein levels were assessed by a highly sensitive enzyme immunoassay using monoclonal antibodies (IBL International, Hamburg, Germany). Serum levels of thyrotropin, as well as total and free thyroxine and triiodothyronine were determined by chemiluminescent immunoassays (Roche Diagnostics, Basel, Switzerland). Serum titers of TPOAb and TgAb were determined by enzyme-linked immunosorbent assay using reagents purchased from IBL International (Hamburg, Germany).

The Kolmogorov–Smirnov test was used to test for data normality. Because of skewed distributions, natural logarithmic transformations were performed for triglycerides, antibody titers, thyrotropin and thyroid hormones. Comparisons between both groups were made by the *t*-test for independent samples with the multiple testing correction of Benjamini and Hochberg false discovery rate. Student's paired *t*-test was used to assess any significant differences before and after treatment for both study groups. To verify the correctness of statistical analysis for triglycerides, antibody titers, thyrotropin and thyroid hormones, their median values on the original scale were recalculated using non-parametric tests (the Mann–Whitney *U* test and the Wilcoxon matched paired test). Since the results of non-parametric statistics did not differ from the ones obtained after using non-parametric tests, they were not shown. The χ^2 test was used for categorical parameters. Correlations were calculated using Pearson's or Kendall's tau test. A probability of $p < 0.05$ was used to determine significance.

Results

Both groups were well-matched for age, weight as well as for the mean values of lipids, thyrotropin, total and free thyroxine, total and free triiodothyronine, TPOAb and TgAb (Tables 1 and 2).

Two patients, one treated with rosuvastatin and one receiving simvastatin, discontinued treatment because of myalgia and increased creatine kinase activity. Neither significant adverse effects nor any other complications were observed in the remaining 36 individuals who completed the study.

As expected, both rosuvastatin and simvastatin reduced plasma levels of total and LDL cholesterol levels (Table 2). Rosuvastatin, but not simvastatin, treatment also reduced plasma triglycerides and increased plasma HDL cholesterol levels. In both treatment groups, statin treatment reduced serum hsCRP levels. At the end of