

The Effects of Simvastatin on the Serum Concentrations of Thyroid Stimulating Hormone and Free Thyroxine in Hypothyroid Patients Treated with Levothyroxine

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Abstract

Background: Statins, such as simvastatin, are the drugs of choice for the treatment of hypercholesterolemia. On the other hand hypercholesterolemia can occur in hypothyroid patients, who receive levothyroxine. There are few clinical case reports in regards to drug interaction between levothyroxine and lovastatin or simvastatin, indicating decreased levothyroxine effects. This study aimed at determining possible interaction between simvastatin and levothyroxine in hypothyroid patients by assessing serum levels of thyroid stimulating hormone (TSH) and free thyroxine (FT4), the two important laboratory indices for levothyroxine therapy.

Methods: In a cross sectional study, 41 eligible hypothyroid patients receiving levothyroxine (50-150 µg/d) were selected. Blood samples were taken before and after three months of simultaneous treatment with simvastatin (20 mg/d) and levothyroxine to determine the serum levels of TSH and FT4.

Results: There was no significant difference between the serum levels of TSH (P=0.77) or FT4 (P=0.76) before and after three months of simultaneous treatment. Also, there was no aggravation or initiation of any sign or symptom of hypothyroidism in the patients during the study period.

Conclusion: Considering that FT₄ and TSH are the most reliable indicators for the levothyroxine treatment, the findings of the present study suggest that there may not be any significant interaction between simvastatin and levothyroxine.

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Keywords • Simvastatin • levothyroxine • drug interaction • thyroid stimulating hormone • free thyroxine

Introduction

Levothyroxine is the best drug for the treatment of hypothyroidism.¹ The clinical and laboratory tests have played an important role in the assessment of effects of levothyroxin, and the relief of signs and symptoms of hypothyroidism.¹ Among thyroid function tests (TFTs), Thyroid Stimulating Hormone (TSH) and Free Thyroxin (FT4) are the most reliable laboratory indices in the diagnosis and follow up of hypothyroid patients.^{2,3}

A number of medicines cause thyroid dysfunction by interacting with aspects of thyroid hormone synthesis and release. Some other drugs can cause changes in the functional activity of thyroid. Lithium, amiodarone and interferon are among the well-known drugs that can cause thyroid disorders.⁴⁻⁶ On the other hand some drugs have effects on the pharmacokinetic of levothyroxine in human. For example, sucralfate, calcium carbonate and ferrous sulfate can decrease the absorption of levothyroxine via gastrointestinal tract; therefore, it has been recommended that a space of at least 4 hours between the consumption of these drugs and levothyroxine is necessary.⁷⁻⁹ Moreover, carbamazepine and phenytoin could increase the metabolism of thyroxine via enzyme induction.¹⁰

There are a few clinical case reports, which have demonstrated the interaction between statin drugs and levothyroxine. The first report of interaction, performed by Demke and colleagues, was in a patient taking thyroxine (0.125 µg/d). They showed that after starting lovastatin, a statin drug, the efficacy of thyroxine, as indicated by clinical and biochemical measures, decreased significantly.¹¹

Since statin drugs and thyroxine are frequently prescribed together, it is necessary to assess the interaction between them. Therefore, the present study was designed to evaluate the effect of adding simvastatin, which is used in the treatment of hypercholesterolemia in hypothyroid patients, to thyroxine on serum levels of TSH and FT4, as two important indicators of TFTs.

Materials and Methods

This is a cross sectional study performed in a period of one year (From June 2009 to June 2010) in the Endocrine Clinic of Imam Khomeini Hospital, Tehran, Iran. Patients who were taking levothyroxine (in the range of 50-150 µg/d) and simvastatin for the treatment of hypercholesterolemia (total cholesterol more than 200 mg/dL) were included in the study.

The exclusion criteria for the study were: patients who used to take any drugs that had known effects on the metabolism of thyroxine (either inhibition or induction) such as phenytoin, carbamazepine, erythromycin or cimetidine, pregnant or breast feeding women, and patients who used to smoke. Forty one patients (38 females and three males) were included in the study. The age of participants was 55.67±9.32 years. The patients' total serum cholesterol and triglyceride were 246.63±7.09 and 153.06± 9.47 mg/dl, respectively.

The protocol of the study was in agreement

with the Declaration of Helsinki (1995), and was approved by Ethics Committee affiliated to the Deputy of Research, Pharmaceutical Sciences Unit, Islamic Azad University, Tehran, Iran.

After obtaining informed written consent from eligible hypothyroid patients, a blood sample was obtained from each patient for the assessment of baseline levels of TSH and FT4. Then, patients began to receive simvastatin (20 mg/d) for the treatment of hypercholesterolemia. The patients were instructed in regards to the correct use of the drugs. They were told to take levothyroxine in the morning before breakfast and simvastatin in the evening. Also, the patients were told to allow a space of at least four hours between levothyroxine and other drugs such as sucralfate, calcium carbonate and ferrous sulfate that may interfere with gastrointestinal absorption of levothyroxine.

If a patient did experience any problem or adverse effect that might be related to simvastatin during the study period, he/she was withdrawn from the study and the drugs were discontinued. After three months into the study the patients were called in, and a second blood sample was obtained from each patient for the determination of serum levels of TSH and FT4. The serum of samples were separated, and kept frozen until the end of the study. The levels of TSH were determined using ELISA method (Enzaplata N-TSH, Ciba Corning Japan). The intra-assay and interassay coefficients of variation for TSH assays were 1.28% and 5.64%, respectively. Serum FT4 concentration was measured by radioimmunoassay (RIA) using a kit from Kavoooshyar (Tehran, Iran). Intra-assay and interassay coefficients of variation for this assay were 2.24% and 5.65%, respectively. Data, presented as mean±SD, were analyzed using paired t test. Data were analyzed using statistical Package for Social Sciences (SPSS, version 16). A p value of <0.05 was considered as the level of statistical significance.

Results

Fifty seven patients who had fulfilled the study inclusion and exclusion criteria were enrolled. Sixteen patients did not return for follow up, and were withdrawn from the study. The remaining patients (n=41) including 38 females and three males did complete the study. The age of them was 55.67±9.32 years. Their serum total cholesterol and triglyceride were 243±7.09 and 153.06±9.47 mg/dl, respectively.

Serum levels of TSH before and after the administration of simvastatin were 3.50±2.44

and 3.62 ± 2.98 mIU/L, respectively. Also, serum levels of FT4 before and after the administration of simvastatin were 1.75 ± 1.22 and 1.81 ± 1.49 $\mu\text{g/dL}$, respectively. As the variables (TSH and FT4) were normally distributed, paired *t* test was used to compare the mean value of TSH or FT4 before and after the administration of simvastatin. There wasn't seen any significant difference in serum levels of TSH or FT4 before and after simvastatin use ($P=0.77$ and 0.76 , respectively).

Discussion

Because of efficacy and tolerability, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are well-established pharmacological agents for the treatment of hypercholesterolemia in human.¹² We found that there were some published articles that reported interactions between statins and other drugs.¹³ There are only few case reports in regards to the interaction between some statins (such as lovastatin and simvastatin) and levothyroxine.^{11,14} Demke et al reported that the addition of lovastatin to levothyroxine in a hypothyroid patient resulted in reversible decrease and increase in the serum levels of thyroxine and increase in thyroid-stimulating hormone, respectively.¹¹ Also, there were two case reports of interaction between simvastatin and thyroxine. The first one was a 75-year-old hypothyroid woman whose thyroid status was well-controlled with levothyroxine (800 $\mu\text{g/wk}$). Because of hypercholesterolemia she began taking simvastatin (10 mg/d). Afterwards, she gradually felt tired, complained of abdominal pain, and had an increased serum level of TSH and a lower than normal limit of FT4. Increasing the dose of levothyroxine to 900 $\mu\text{g/week}$ did not lead to the improvement in the patient's symptoms. After discontinuation of simvastatin, the symptoms of the case resolved slowly, and the TSH level returned to normal.¹⁴ The second case was a man (81 years old) whose TSH levels increased to 11.76 IU/L, and FT4 was lower than normal levels. Therefore, thyroxine at 50 $\mu\text{g/d}$ was prescribed for him. In addition, the patient started receiving simvastatin at 10 mg/d. After one week of treatment, serum levels of TSH continued to increase up to 23.9 IU/L. However, four weeks after simvastatin discontinuation TSH serum concentrations decreased to the normal range, with no need to make a change in the thyroxine dosage.¹⁴

Sometimes drug interactions can cause failure in the thyroxine therapy of hypothyroid patients. There are some interactions between

levothyroxine, namely interfering in the absorption of levothyroxine.⁷⁻⁹ The present study showed that serum levels of TSH and FT4 in the hypothyroid patients under treatment of levothyroxine did not change after simvastatin use. Demke et al suggested that lovastatin might have caused the gastrointestinal absorption of thyroxine.¹¹ Kisch et al suggested that excess formation of CYP 3A4 in the liver by simvastatin can be the cause of increased thyroxine catabolism.¹⁴ All patients who referred to the Clinic were asked to observe a space of at least 4 hours between administration of levothyroxine and simvastatin, so it's unlikely that simvastatin could cause a decrease in the absorption of levothyroxine. If there had been an interaction between levothyroxine and simvastatin, serum levels of FT4 should have been decreased after simvastatin administration. However, the findings did not show any significant change in FT4 after simvastatin administration.

The FT₄ test is the most reliable test for the evaluation of hormone concentrations.¹⁵ On the other hand the serum TSH is the most sensitive test for the evaluation of thyroid function.¹⁶ Thyroid stimulating hormone is elevated when thyroid hormone replacement therapy is inadequate. Thyroid stimulating hormone can be abnormal even if the FT₄ remains within the normal range, because the TSH is specific for each person's physiological set point.¹⁷ The important limitation of the study was the difficulty to find eligible patients, who could meet all of the required criteria. Also, we recommend the repeat of such a study using a control group on healthy volunteers.

Conclusion

The findings of the present study indicate that there was no significant change in the evaluated laboratory parameters. Therefore, they suggest that most likely there is no interaction between simvastatin and levothyroxine. We believe that the findings provide an additional benchmark for further studies involving more patients.

Conflict of Interest: None declared

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