Original Article

# The Effect of Levothyroxine and Selenium versus Levothyroxine Alone on Reducing the Level of Anti-thyroid Peroxidase Antibody in Autoimmune Hypothyroid Patients

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## Abstract

**Background:** Due to the prevalence of autoimmune hypothyroidism and its effects on physical and mental health it is necessary to provide a treatment which is also effective in preventing the progression of sub-clinical hypothyroidism in these patients. This study aims to investigate the effect of selenium supplementation on of anti-thyroid hormone antibodies in these patients. **Materials and Methods:** In a randomized clinical trial, 70 patients with autoimmune hypothyroidism randomly divided into two groups of 35 each, the first group was treated with oral selenium treatment with levothyroxine (LT4) and to the second group along with LT4, placebo was also prescribed. Serum selenium level, thyroid hormones and anti-thyroid hormone antibodies before and after 3 months of treatment in both groups, were determined, and the results were analyzed using SPSS software. **Results:** The mean of the serum anti-thyroid peroxidase serum level in the intervention group before and after treatment was 682.18 ± 87.25 and 522.96 ± 47.21 and the difference before and after treatment was statistically significant ($P$ = 0.021). The level of this antibody before and after treatment in the control group was 441 ± 53.54 and 501.18 ± 77.68, and no significant differences between two groups were observed before and after treatment ($P$ = 0.42). **Conclusion:** Selenium supplementation may help to reduce the levels of antibodies in patients with autoimmune hypothyroidism.

**Keywords:** *Anti-thyroid hormone antibodies, autoimmune hypothyroidism, selenium*

## Introduction

Autoimmune thyroiditis (lymphocytic thyroiditis) is a common autoimmune disorder characterized by lymphocytic infiltration of the thyroid, fibrosis, parenchymal atrophy, and eosinophilic changes of some acinar cells.[1] This chronic thyroiditis is characterized by autoantibodies against anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG).[2] There is often a sub-clinical hypothyroidism, which eventually progresses to the permanent hypothyroidism with typical clinical protests and requires hormonal replacement with levothyroxine (LT4). Ultrasonography of the thyroid shows a hyperechogenic and nonhomogenized parenchyma.[2,3] TPO, the first enzyme involved in thyroid hormonogenesis, first identified in 1959. Anti-TPO-antibody (Ab) is the hallmark of the autoimmune thyroid disease and can be found almost in all of these patients.[4] Selenium (Se) is an essential micronutrient in the selenocysteine-containing selenoprotein biosynthesis. Many of known selenoprotein such as enzymes involved in the metabolism and regulation of thyroid hormones are in the thyroid gland.[5] Synthesis, metabolism, and thyroid hormone activity requires access to iodine and selenium.[6,7] The human thyroid gland has the highest content of selenium per gram of tissue among all organs.[6,8,9] All three deiodinase enzymes that convert T4 to T3 include selenocysteine which shows the dependence of active thyroid hormone production on selenium status.[8,10,11] Selenium has a systemic anti-inflammatory effect[12] and lack of it affects free radical production, conversion of T4 to T3 and autoimmune process and accelerates autoimmune thyroid disease protests.[8,11] In areas with severe deficiency of selenium, the high incidence of thyroiditis may be associated with reduced activity of glutathione peroxidase associated with selenium in thyroid cells. Selenium-dependent enzymes have



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multiple effects on immune modulators. So, even mild selenium deficiency may lead to progression and survival of autoimmune thyroid diseases.[13] In various studies, the effect of selenium on reducing inflammatory activities of thyroid and reducing the titer of anti-TPO Ab,[3,12,14-18] as well as its potential impact on improving echostructure thyroid ultrasound,[8,19] is shown. It seems that selenium as an adjunctive treatment with LT4 is effective in autoimmune thyroiditis. But still evidences to support the efficacy of selenium supplementation in patients with autoimmune hypothyroidism is insufficient[3] and also the exact impact of basic TPO-Ab and duration of the disease is not clear on the effects of selenium.[8,13,20]

Since selenium deficiency may affect the immune response, thyroid peroxidation of the cell, selenium supplements, and the natural course of chronic thyroiditis, the aim of this study is to compare the effect of LT4 and selenium versus LT4 alone on reducing the level of anti-TPO-Ab in autoimmune hypothyroid patients in EMRI center of Isfahan University of Medical Sciences in the year 2014.

## Materials and Methods

This study was a double-blind controlled clinical trial which was conducted at EMRI center of Isfahan University of Medical Sciences in the year 2014. The statistical population of the study was patients with autoimmune hypothyroidism who were under treatment at this center.

Inclusion criteria included age range 18–70 years, the case of autoimmune hypothyroidism, not consuming selenium containing commercial supplements, not taking over-the-counter or trace element vitamins, not taking corticosteroids or anti-inflammatory medications, consent to participate in the study and not taking anti-depressants or antipsychotics.

Exclusion criteria severe medical complications, unwillingness to continue participating in the study, and a lock of need testing.

Sample size formula was used to estimate sample size, 35 patients in each group and in order to compare two portions of decrease in the level of anti-TPO-Ab, $P_1 = 0.99$ and $P_2 = 0.56$, the level of assurance was considered 95%, and the test power was considered 80%.

After the adoption of the proposal and getting Medical Ethics Committee approval and written consent of the patient, the subjects were randomly divided into two groups [Figure 1]. All patients received $LT_4$ replacement treatment with a dose which was able to keep thyroid stimulating hormone (TSH) at the lower level of the normal range (TSH = 0.3–2 mIU/L). Then, patient of first group were received a daily dose of 200 μg oral sodium selenite tablets (manufactured by 21st century company) and the second group was given placebo for 3 months (which was prepared collaboratively by one of the Pharmacies of Isfahan and School of Pharmacy of Isfahan university). Drug or placebo was given to each patient for 45 days and after re-visit, the exact consumption of selenium was surveyed in patients and for other 45 days drug or placebo was given to them. The main executor of the research was unaware about the division of patients to selenium and placebo groups, and the drug was administered by a nurse as a research collaborator. All patients were asked to take the medication with water, about 2 h before or after their meal. They also explained not to take any anti-inflammatory drugs, corticosteroids, anti-depressants, anti-psychotics, products containing vitamins, or trace element during the treatment without informing the project manager. At the beginning of the study, the serum levels of selenium (through atomic absorption method), antiTPO-Ab, antiTg Ab, FT3, FT4, and TSH were measured at the end of the 3rd month, the experiment was repeated.

The data of each patient along with his/her demographic characteristics were recorded in the data collection form and SPSS software version 22; SPSS Inc., Chicago, IL, USA. The *t*-test (for comparison of quantitative data between the two groups), *t*-paired (for comparison of quantitative data in the before and after intervention in the each group) and repeated measures ANOVA (for comparison of changes between the two groups) were used to analyze them.

## Results

Seventy patients were randomly distributed in the two groups of 35. The mean age of patients was 45.4 ± 11.4, and its range was 18–60 years old, 25 patients (35.7%) were males and 45 (64.3%) female. The mean age of the intervention and control groups was respectively, 45.3 ± 10.8 and 45.6 ± 12.1 years and there was no significant difference between the two groups ($P = 0.89$). The sex ratio (male/female) in both intervention and control groups were 12/23 and 13/22, respectively, and no there isn't significant difference between the two groups ($P = 0.8$). Also, investigating parameters revealed that there was a significant difference in selenium level after treatment between both groups. On the other hand, based on *t*-paired, in the treatment group, the levels of all the parameters had significant differences but in the control group only the levels of TSH, FT4, and FT3 had significant differences and other parameters before and after treatment, in the control group showed no significant differences. In Table 1, the mean and standard deviation level of anti-TPO, anti TG, TSH, FT4, FT3, and serum levels of selenium has been shown in treatment and control groups. Data comparison before and after treatment between two treatment and control groups by using *t*-test analysis revealed that serum levels of anti-TPO before treatment had a significant difference between two groups, but other parameters had no significant differences in both groups. The mean duration of illness of all studied

**Table 1: Mean and SD of studied markers before and after intervention in both groups**

| Marker | Time | Groups | | *P** |
|---|---|---|---|---|
| | | Intervention | Control | |
| Anti-TPO (U/L) | Before treatment | 682.18±87.25 | 441±53.54 | 0.81 |
| | After treatment | 522.96±47.21 | 501.18±77.68 | 0.021 |
| | *P*** | 0.021 | 0.42 | |
| Anti-TG (U/L) | Before treatment | 226.01±32.51 | 200.92±28.55 | 0.56 |
| | After treatment | 155.12±22.18 | 175.61±21.53 | 0.51 |
| | *P* (within groups) | 0.003 | 0.2 | |
| TSH (mU/L) | Before treatment | 11.41±1.23 | 11.06±0.86 | 0.82 |
| | After treatment | 3.3±0.3 | 3.44±0.28 | 0.74 |
| | *P* (within groups) | <0.001 | <0.001 | |
| FT4 (ng/dL) | Before treatment | 0.85±0.13 | 0.86±0.17 | 0.91 |
| | After treatment | 1.18±0.13 | 1.38±0.23 | 0.39 |
| | *P* (within groups) | <0.001 | 0.03 | |
| FT3 (pg/mL) | Before treatment | 2.86±0.59 | 2.92±0.48 | 0.64 |
| | After treatment | 3.9±0.4 | 4.21±1.48 | 0.23 |
| | *P* (within groups) | <0.001 | <0.001 | |
| Selenium level (µg/l) | Before treatment | 86.52±26.36 | 90.7±31.47 | 0.55 |
| | After treatment | 123.06±24.03 | 82.75±31.17 | <0.001*** |
| | *P* (within groups) | <0.001 | 0.17 | |

*Statistical level between the two group base Student's *t*-test, **Statistical level between before and after time in the each group base Student's *t*-test, ***Significance level. Anti-TPO: Anti- thyroid peroxidase, Anti-TG: Anto-thyroglobulin, SD: Standard deviation, TSH: Thyroid stimulating hormone

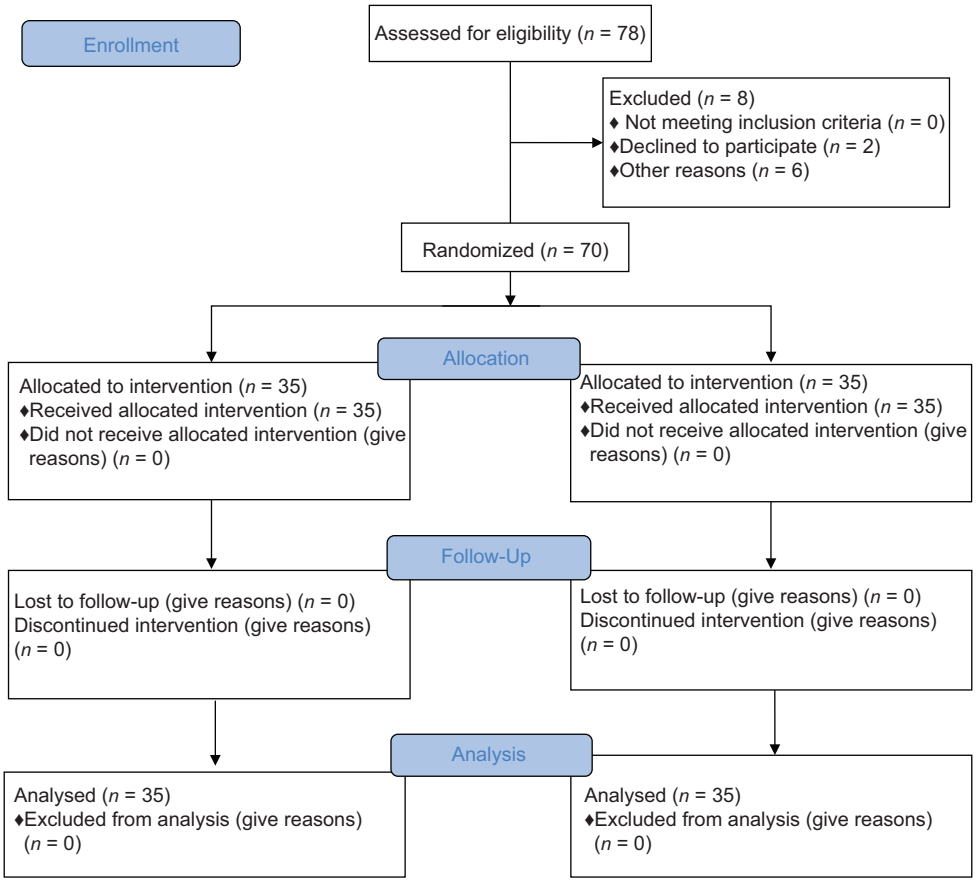


**Figure 1: Consort flow diagram**

patients was 2.93 ± 2.88 with a range of 6–12 months years. This mean in both treatment and control groups was respectively, 2.66 ± 2.68 and 3.2 ± 3.08 years. According to the *t*-test, there was no significant difference between two

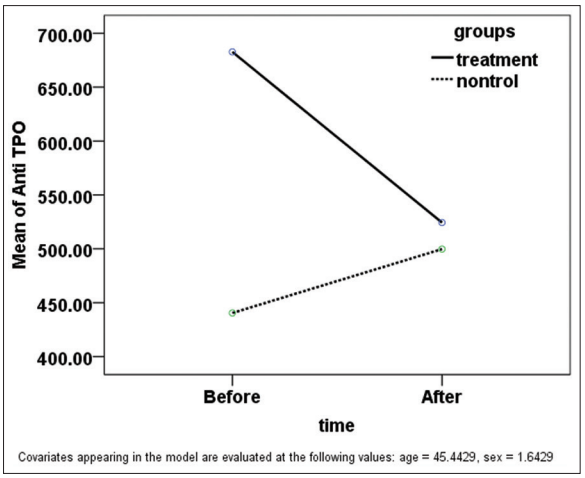


**Figure 2: Mean changes of anti-thyroid peroxidase between the two groups (*P* = 0.12)**

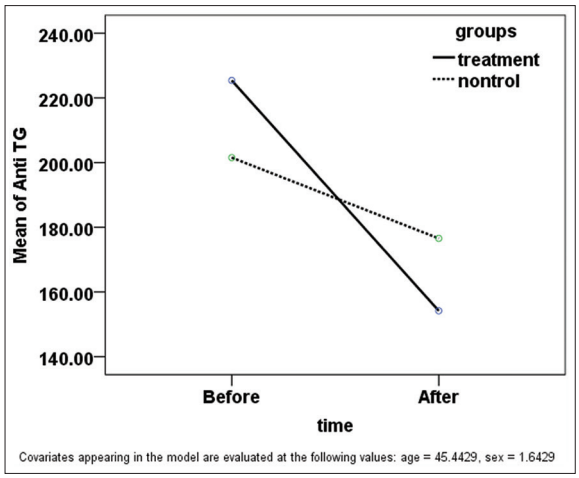


**Figure 3: Mean changes of anti-thyroglobulin between the two groups (*P* = 0.98)**

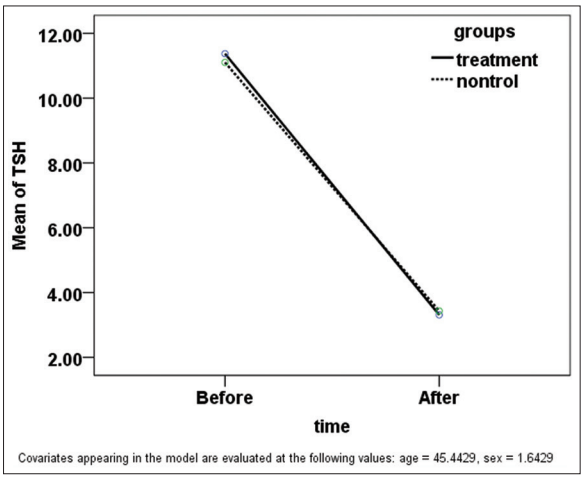


**Figure 4: Mean changes of thyroid stimulating hormone between the two groups (*P* = 0.93)**

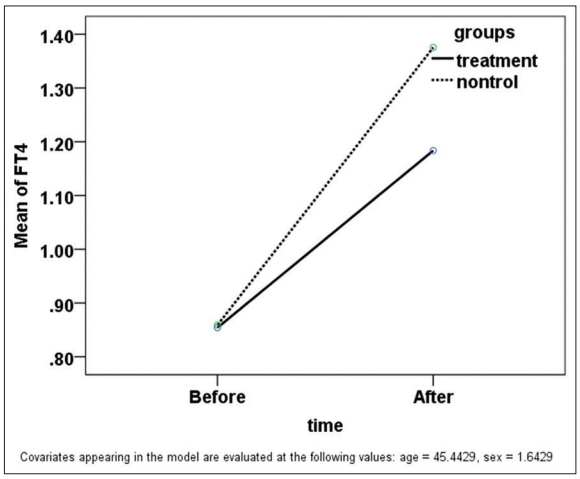


**Figure 5: Mean changes of FT4 between the two groups (*P* = 0.41)**

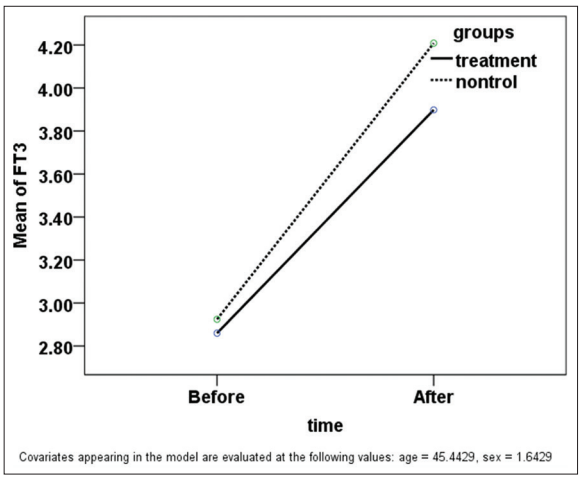


**Figure 6: Mean changes of FT3 between the two groups (*P* = 0.21)**

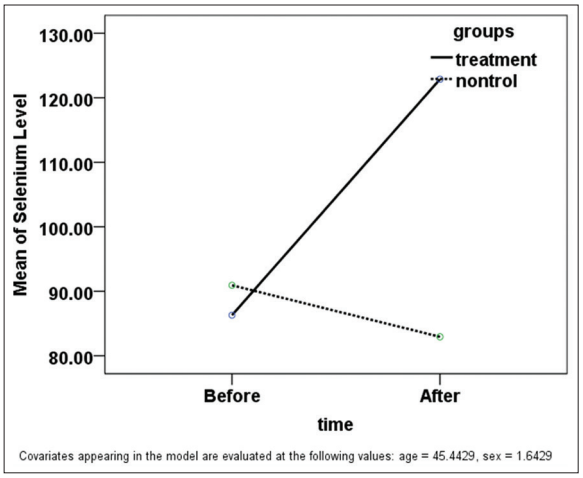


**Figure 7: Mean changes of selenium level between the two groups (*P* = 0.003)**

groups ($P$ = 0.43). Based on the obtained results, before starting the intervention out of 70 studied patients, 25 of them (35.7%) had low selenium levels that 13 patients were in the treatment group and 12 patients in the control group (37.1% vs. 34.3%) and there was no significant difference between the two groups ($P$ = 0.8) but at the end

of the intervention, the number of patients with selenium deficiency in the treatment group was 1 and in the control group were 9 patients (2.9% vs. 25.7%) and difference between the two groups was significant ($P$ = 0.006). Figures 2-7 show the average level of changes in the studied markers of both two groups before and after treatment. ANOVA with repeated tests showed that selenium level changes of both two groups before and after the intervention had a significant difference ($P$ = 0.003) but the rest of the markers had not significant difference after treatment. In addition, according to the mentioned test, the variables of age, sex, disease duration had no significant effect on the parameter changes.

## Discussion

The overall aim of this study was to compare the effect of LT4 and selenium versus LT4 alone on reducing the level of anti-TPO-Ab in autoimmune hypothyroid patients. The study was based on this assumption that selenium as a micronutrient has an essential role in the biosynthesis of selenocysteine-containing selenoprotein and many of known selenoprotein such as enzymes involved in the metabolism and regulation of thyroid hormones in the thyroid gland.[5] According to the results of this study, before starting treatment, 37.1% of the treatment group and 34.3% of the control group had lower levels of selenium but at the end of the intervention, the prevalence of low levels of selenium in the two groups were 2.9% and 25.7% respectively. On the other hand, thyroid hormone levels before and after the intervention showed a significant reduction at the levels of anti-TPO and anti-TG in selenium receiving group but in the control group no significant difference before and after treatment was observed. On the other hand, FT3 and FT4 levels in both groups fell to the same level. In other words, it can be concluded that the increase in serum levels of selenium have significantly reduced the levels of anti-thyroid hormone antibodies and our study confirms the hypothesis that selenium has inhibitory effect on the activity of anti-thyroid hormone antibodies although studies conducted by van Zuuren *et al*., Krysiak and Okopien and Negro *et al*., also revealed the effect of selenium on reducing inflammatory activity of the thyroid and anti-TPO titer,[3,12,14-18] and the potential impact of increased serum levels of selenium on the improvement of thyroid echostructure has been demonstrated in studies of Onal *et al*., and Duntas during ultrasound.[8,19] It has been shown that selenium as an adjunctive treatment with LT4 is effective in autoimmune thyroiditis.[19] Leonidas in his study concluded that the use of selenium containing supplements is efficient in the prevention of thyroid diseases.[8] The study of Toulis *et al*., indicated that a significant reduction can occur in the level of anti-TPO due to the selenium prescription for 3 months in patients with Hashimoto's thyroiditis[15] in the study of Anastasilakis *et al*., the selenium prescription for 3 months in patients with hypothyroidism autoimmune had no significant effect on anti-TPO level but anti-TG level significantly reduced 3 months after treatment.[21] Considering the results of this study and other studies, the overall conclusion is that selenium supplementation in patients with autoimmune hypothyroidism may be helpful in reducing the levels of antibodies however, due to limitations of the present study, including the number of samples and the follow-up time still evidences are inadequate to support the efficacy of selenium supplementation in patients with autoimmune hypothyroidism[3] and also the exact impact of TPO-Ab and duration of the disease is not clear on the effect of selenium.[8,13,20] Therefore, further studies are required with a larger sample size and longer follow-up period and other factors affecting the level of anti-thyroid hormone antibodies.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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