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ORIGINAL ARTICLE

Effects of selenium and vitamin C on the serum level of antithyroid peroxidase antibody in patients with autoimmune thyroiditis

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Abstract

Purpose Selenium (Se), an essential trace element, has been implicated in pathogenesis of autoimmune thyroiditis (AIT). Most studies attributed the immune modulating effects of Se to its antioxidant properties. However, there is insufficient evidence to support the use of selenium supplementation or other antioxidants in patients with AIT. This clinical trial was designed to investigate the impact of Se and vitamin C supplementation on antithyroid peroxidase antibody (TPO-Ab) level in patients with AIT.

Methods One hundred and two subjects aged 15–78 years were randomized into three groups. Group one (GI) ($n=38$) was treated with 200 µg/day sodium selenite, group two (GII) ($n=36$) received 500 mg vitamin C/day, and group three (GIII) ($n=28$) received placebo over a 3-month period. Thyroid stimulating hormone (TSH), TPO-Ab, antithyroglobulin antibody (Tg-Ab) and Se concentrations were once measured before treatment and at the end of the study.

Results After 3 months, TPO-Ab concentrations decreased within Se and vitamin C-treated groups, but did not change in the placebo subjects. In this regard, there was no significant difference between the groups. We also did not find any statistically significant difference in TSH and Tg-Ab levels within and between the groups. At the end of the study, Se level was significantly higher in GI compared with GII and GIII.

Conclusion Our findings supported the hypothesis of antioxidant beneficial effects of Se in AIT. However, it was not superior to vitamin C, regarding its effects on thyroid-specific antibodies.

Keywords Selenium · Autoimmune thyroiditis · Antithyroid peroxidase antibody · Vitamin C

Introduction

Selenium is a trace element, essential for life and its deficiency has been associated with multiple health problems, such as cognitive disorder and increased risk of cancers and infections [1]. The thyroid gland has the highest Se concentrations per mass unit of tissue [2]. At the same time, thyroid-produced glutathione peroxidase (GPx) and thioredoxin reductase (TrxR) act as antioxidants and are involved in protecting cells against free radicals' induced oxidative damage. Furthermore, iodothyronine deiodinase enzymes (DIO), as another class of selenoproteins, catalyze the conversion of thyroxine (T4) to triiodothyronine (T3), the active form of thyroid hormone [3, 4]. It is interesting to know that the most prevalent thyroid disorders, such as Hashimoto's thyroiditis, Graves' disease, and postpartum thyroiditis, are specified by increased levels of hydrogen peroxide and free radicals [5, 6]. In this regard, it has recently been established that Se is required for optimal endocrine and immune function as well as anti-inflammatory effects [7]. Moreover, in areas with Se deficiency, a higher incidence of autoimmune thyroiditis has been reported, but the exact mechanisms remain to be unknown [8, 9]. There is the possibility that Se exerts its beneficial effects by maximizing the antioxidant enzymes' activity to ameliorate the inflammatory and immune responses [10, 11]. In the last decade, the potential benefits of Se supplementation and its underlying mechanisms in autoimmune thyroid disorders have been investigated extensively, but the results were inconclusive [12–14].

Furthermore, there is evidence that consumption of vitamins with antioxidant properties, such as vitamins C and E, might have some beneficial effects on thyroid-related

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pathologies [15–17]. In fact, despite the widespread usage of vitamins, few studies have addressed this issue [18–20]. Also, it has been shown that both hyper- and hypothyroidism can affect the concentrations of the vitamins involved in scavenging of free radicals [21]. At present, there is insufficient evidence to support the beneficial effect of selenium supplementation or other antioxidants in patients with AIT [22].

Objectives

The objective of the present study was to determine whether Se supplementation has any effect on the plasma TPO-Ab or Tg-Ab, and TSH concentrations in subjects with AIT. Furthermore, to better evaluate the possible antioxidant effects of Se, as the underlying mechanism for its thyroid benefits, we compared these parameters with those of two other groups, one group receiving vitamin C as a powerful antioxidant and the other receiving placebo.

Subjects and methods

Study design and outcomes

We performed this single-blind, prospective study in Kavar in the south-east of Fars province, Iran. A region with high incidence of familial marriages and Hashimoto's thyroiditis, conducted from June to September 2014. Our primary outcome measures were changes of TPO-Ab concentrations and secondary endpoints were changes of TSH and Tg-Ab levels.

Study registration and approval

The review board and local Ethics Committee of Shiraz University of Medical Sciences approved the study protocol. The article's Iranian Registry of Clinical Trials (IRCT) code is: IRCT201309201471N1.

Patients

Total of 140 participants were recruited based on their TPO-Ab concentrations, which had been obtained previously in the regional healthcare center. The inclusion criteria were age 15 years or older with antithyroid peroxidase antibody titer 250 IU/ml or more. Amongst the 120 people who accepted to participate in the study, 115 met the inclusion criteria and 102 completed the study. A baseline visit was done to collect their personal data and past medical history.

Exclusion criteria

The exclusion criteria were pregnant/lactating women, presence of non-thyroidal disorders, and consumption of drugs with effect on thyroid hormone metabolism or over the counter vitamins and supplements within the past 6 months.

Randomization

According to previous studies, at the error level of $\alpha = 0.05$ and power = 80%, our estimated sample size was determined at 27 participants in each group. They were randomized using systematic allocation into three age- and TPO-Ab matched groups. Group one received 200 µg/day sodium selenite orally, group two received 500 mg of vitamin C/day, and group three received placebo for 3 months. The intervention agents were sodium selenite (Webber Naturals, Canada) and vitamin C (Avehsina, Iran). The placebo was 250 mg starch, identical in appearance to the selenium and vitamin C tablets. Both intervention and placebo tablets were packaged by the school of Pharmacy at Shiraz University of Medical Sciences. The participants were blinded to the prescribed agents. They received the pills monthly and their compliance was checked by a healthcare provider each month. The patients who had TSH ≥ 10 mIU/l were replaced by levothyroxine. Moreover, to demonstrate the effect of Se on TPO-Ab, serum levels of Se were measured in some subjects of each group.

Collection of samples

Blood samples were obtained in the morning after an overnight fasting, at the baseline and at the end of the clinical trial. After centrifugation, the collected samples, blind identification, were sent to the Endocrinology and Metabolism research Center of Shiraz University of Medical Sciences and kept frozen at − 70 °C until assayed.

Biochemical data

Plasma TPO-Ab and Tg-Ab concentrations were measured by radioimmunoassay (Beckman Culter, Czech Republic), and TSH level was measured by immunoradiometric assay (Beckman Coulter, Czech Republic). Serum Se levels were also determined in a reference laboratory with a graphite furnace atomic absorption spectrometer (AA500, England) according to the manufacturer's instructions and the detection limit of < 0.01 µg/l.

Statistical analysis

Significant differences were assessed using *t* test and Mann–Whitney U test. Comparisons between baseline and

post-treatment levels of the studied parameters in the groups were performed by the ANOVA and Kruskal–Wallis tests, and Wilcoxon signed-rank test was used to evaluate the significance of changes in the variables in each group. Data analysis was done using SPSS statistical software (version 16) and data were expressed as mean ± SD. *P* value < 0.05 was considered to be statistically significant.

Results

Of the 115 participants, 13 dropped out of study before 3 months: 5 in Se, 4 in vitamin C, and 4 in placebo group. Reasons for withdrawal were pregnancy in 3 and other personal reasons in the remaining 10. No significant adverse events were reported by the participants. A total of 102 patients, 25 males and 77 females, with a mean age of 40.1 ± 13.5 years (age range 15–78) completed the study. Baseline features of the three groups did not differ at study entry, and they were randomized according to their TPO-Ab concentrations. Also, to demonstrate the effect of Se on the studied parameters, serum Se was measured in some patients of GI ($n = 18$), GII ($n = 15$) and GIII ($n = 13$). Basal characteristics of the three groups are presented in Table 1.

Serum TPO-Ab decreased within selenium and vitamin C groups

TPO-Ab concentrations decreased significantly only in the Se and vitamin C groups, but not in those who received placebo. Also, there were no statistically significant changes of Tg-Ab and TSH levels within the three groups after 3 months (Table 2).

Baseline serum Se concentrations were similar in the three groups. As expected, selenium level increased significantly after treatment in Se group compared with the placebo and vitamin C-treated subjects (Table 3). Also, there was no correlation between Se level and age, gender, TSH or thyroid-specific antibodies' concentrations.

Table 2 Comparison of mean TPO-Ab, Tg-Ab and TSH concentrations before and after treatment within each group

Group	Before	After	*P* value
TPO-Ab (IU/ml)			
Selenium ($n = 38$)	928.64 ± 742.16	790.28 ± 653.32	0.005*
Vitamin C ($n = 36$)	1000.04 ± 711.02	816.61 ± 625.90	0.002*
Placebo ($n = 28$)	1142.13 ± 715.09	1092.03 ± 628.09	0.09
Tg-Ab (IU/ml)			
Selenium	634.55 ± 523.65	612.79 ± 517.18	0.3
Vitamin C	744.19 ± 553.25	730.74 ± 563.88	0.2
Placebo	676.96 ± 427.38	652.35 ± 435.10	0.08
TSH (mIU/l)			
Selenium	3.72 ± 1.77	3.88 ± 1.98	0.6
Vitamin C	4.30 ± 2.96	5.30 ± 4.29	0.2
Placebo	5.22 ± 4.45	5.28 ± 2.74	0.1

All absolute values are presented as mean ± SD

TPO-Ab antithyroid peroxidase antibody, *TSH* thyroid stimulating hormone, *Tg-Ab* antithyroglobulin antibody

**P* value < 0.05

However, when the three groups were compared at the end of the study, no statistically significant differences were detected regarding their TSH, TPO-Ab and Tg-Ab levels (Table 4).

Six patients with TSH ≥ 10mIU/l, five in placebo and one in vitamin C group received levothyroxine replacement. Moreover, in further analysis, after excluding these subjects, no statistically significant changes were detected in our results regarding TSH levels.

Finally, the difference between pre- and post-intervention values of the studied parameters was calculated (Δ) and compared between the groups, which resulted in no statistically significant differences (Table 5).

Table 1 Basal characteristics of the participants in the three groups

	Selenium group ($n = 38$)	Vitamin C group ($n = 36$)	Placebo group ($n = 28$)	*P* value
Gender				
Female	30	27	20	
Male	8	9	8	
Age (year)	38.18 ± 13.29	43.27 ± 13.32	39.32 ± 12.28	0.07
BMI (kg/m^2)	24.34 ± 3.27	24.59 ± 3.20	24.20 ± 2.53	0.8

All absolute values are presented as mean ± SD

No significant relationship was detected between TPO-Ab or TSH concentrations and age of the participants

BMI body mass index

Table 3 Comparison of serum Se concentrations between the groups, at baseline and after treatment

Serum Se concentration(μg/l)	Selenium group ($n=18$)	Vitamin C group ($n=15$)	Placebo group ($n=13$)	*P* value
Before treatment	90.05 ± 24.12	97.93 ± 27.67	98 ± 20.73	0.6
After treatment	153.27 ± 29.28	127.66 ± 28.63	120.53 ± 23.34	0.007*

All absolute values are presented as mean ± SD

*P value < 0.05

Table 4 Comparison of mean TPO-Ab, TSH and Tg-Ab concentrations before and after treatment between the groups

	Selenium group ($n=38$)	Vitamin C group ($n=36$)	Placebo group ($n=28$)	*P* value
TPO-Ab (IU/ml)				
Before	928.64 ± 742.16	1000.04 ± 711.02	1142.13 ± 715.09	0.3
After	790.28 ± 653.32	816.61 ± 625.90	1092.03 ± 628.09	0.4
Tg-Ab (IU/ml)				
Before	634.55 ± 523.65	744.19 ± 553.25	676.96 ± 427.38	0.5
After	612.79 ± 517.18	730.74 ± 563.88	652.35 ± 435.10	0.8
TSH (mIU/l)				
Before	3.72 ± 1.77	4.30 ± 2.96	5.22 ± 4.45	0.8
After	3.88 ± 1.98	5.30 ± 4.29	5.28 ± 2.74	0.08

All absolute values are presented as mean ± SD

TPO-Ab antithyroid peroxidase antibody, *TSH* thyroid stimulating hormone, *Tg-Ab* antithyroglobulin antibody

Table 5 Comparison of pre- and post-treatment changes (Δ) of TPO-Ab, TSH and Tg-Ab levels in the three groups

	P value
Δ of TPO-Ab (IU/ml)	0.3
Δ of Tg-Ab (IU/ml)	0.8
Δ of TSH (mIU/l)	0.3

TPO-Ab antithyroid peroxidase antibody, *TSH* thyroid stimulating hormone, *Tg-Ab* antithyroglobulin antibody

Discussion

This clinical trial showed that after 3 months of Se, vitamin C, and placebo supplementation in patients with AIT, thyroid-specific TPO-Ab concentrations decreased significantly only within the first two groups, but not in those who received placebo. While no statistically significant difference was detected between the three groups in this regard.

Selenium by incorporation in selenoproteins, such as DIO and GPxs, is involved in both thyroid hormone synthesis and thyroid protection against oxidative damage [4]. Currently, many studies have supported the implication of Se deficiency in the pathogenesis of AIT [23, 24]. Even though the exact mechanisms are still unidentified, Se deficit appears to exert its adverse effects through multiple mechanisms not only on the thyroid itself, but also on the immune system [25].

In fact, both cell-mediated immunity and B-cell function can be impaired in the presence of Se deficiency [26, 27]. Most authors attributed the immune modulating effects of Se to its contribution in the oxidoreductive system, and it has been shown that both hyper- and hypothyroidism promote cellular oxidative stress [6, 7]. Moreover, it has been suggested that Se deficiency might lead to cell apoptosis due to aberrant iodination of certain proteins. In this regard, Lehmann et al. showed that preincubation with low doses of Se resulted in reduced cell apoptosis and increased levels of GPx activity [28]. Furthermore, the beneficial effect of Se consumption has also been shown in other autoimmune disorders, such as rheumatoid arthritis and asthma [29–31].

However, some researchers have provided evidence indicating that Se supplementation would be beneficial as an adjuvant therapy with levothyroxine in patients with AIT [32–35]. On the contrary, other studies showed no additional benefits or significant change in antibody titers after Se supplementation [36, 37].

In the current study, by prescribing vitamin C to one group of participants, we also aimed to investigate the possible role of another supplement with antioxidant properties in subjects with AIT. Indeed, there are few reports in the literature regarding the role of vitamins in the pathogenesis or treatment of thyroid disorders [38–40]. Also, it has been shown that both hyper- and hypothyroidism can affect the concentrations of the vitamins involved in clearing of free radicals [21, 41]. To the best of our knowledge, no study has simultaneously examined the effects of vitamin C and Se supplementation on autoimmune parameters in patients with AIT.

In this study, we showed the reduction of TPO-Ab within the Se and vitamin C-treated groups, but not in the placebo group. At the same time, there was no significant difference between the groups. These findings are in favor of the possible antioxidant effects of this trace element. However, in this regard, Nourbakhsh et al. found no significant difference in the GPx activity between normal subjects and hypothyroid patients or those who had Hashimoto's thyroiditis [42].

Furthermore, the contradictory results of previous studies might be due to different degrees of disease activity with resultant unequal benefit from Se supplementation. It should be noted that higher degrees of thyroid injury would reduce the absorption of Se, and the absorption of its different forms also varies, which might cause heterogeneous results [43].

In line with some previous reports, we could not detect significant difference regarding Tg-Ab levels within and between the groups [44, 45]. However, this finding might be attributed to differences in iodine intake [45]. Also, it should be noted that thyroglobulin is normally secreted into the circulation and is not necessarily expressed in response to a thyroid-specific autoimmune process. In contrast, plasma TPO-Ab levels are thought to reflect intra-thyroidal inflammation and are supposed to be cytotoxic in the presence of complement [46]. Therefore, Tg-Ab is less specific for pathogenesis and diagnosis of AIT.

Our findings also revealed no statistically significant changes of TSH at the end of the study in all groups, even after excluding the patients who received levothyroxine replacement. This finding was in agreement with most of the previous clinical trials on subjects with and without Se deficiency [44, 45, 47]. Indeed, only few investigations have reported changes in TSH levels following Se supplementation [48].

In this regard, Gartner et al. reported normalization of TPO-Ab levels and resolution of sonographic changes after Se supplementation without any significant change in the TSH levels or in the required treatment doses of levothyroxine [45]. On the contrary, Esposito et al. showed no significant difference of thyroid echogenicity, or TSH and TPO-Ab levels after 6 months of Se supplementation [47].

However, different intensities of Se deficits might be an explanation for the inconclusive results. The DIO activity decreases only in the presence of severe Se deficiency; in contrast, GPx activity will be impaired following mild to moderate deficiency of this trace element [49]. In this regard, Ericsson et al. found no significant difference in the serum Se concentrations between patients with different thyroid disorders or when they compared them with healthy controls [50]. Indeed, the normal thyroid gland is capable of retaining high Se concentrations and still expresses many of the known selenoproteins, even under inadequate Se consumption [51, 52]. Therefore, it seems necessary to have a reliable marker of intra-thyroid selenium level or thyroidal oxidative stress to identify the effective doses or durations of Se supplementation for various thyroid disorders.

In the present study, Se serum level was measured in some of the participants to demonstrate the effect of Se on TPO-Ab concentrations. As mentioned above, mean selenium levels were similar at the baseline and were within the recommended range for Se sufficiency in the three groups. As it was expected, serum selenium levels increased significantly in the selenium group.

Another possible explanation for the contradictory reports might be inadequate knowledge on the functions of all identified selenoproteins. In fact, only a few of the identified selenoproteins have been functionally characterized [51, 53].

Although several points have to be clarified around the clinical applications of Se in AIT, one of its important applications might be in pregnant women. Actually, the use of this trace element during pregnancy revealed interesting results with significantly decreased percentage of postpartum thyroiditis and subsequent hypothyroidism [54].

However, the possible useful effects of selenium on thyroid autoimmune diseases seem to be interesting. Our comparison between Se and vitamin C revealed no superiority of Se regarding the reduction of thyroid-specific antibody concentrations or thyroid function. Thus, the clinical applications of this trace element need to be investigated further, especially with respect to cost/benefit issues. Also, it would be interesting to evaluate its effect in modulation of other autoimmune disorders.

Conclusion

This study which compared selenium and vitamin C supplementation with placebo in patients with AIT showed a significant reduction of TPO-Ab titers only in the first two groups. This finding supported the hypothesis of antioxidant beneficial effects of selenium in AIT, but there was no significant difference between the groups. We also found no statistically significant difference of TSH and Tg-Ab levels within and between the groups. Currently, the available data on beneficial effects of Se on thyroid autoimmune parameters are limited. Our study also revealed no precedence of this trace element over vitamin C. However, further studies are necessary to elucidate the efficacy of Se supplement on ultrasound changes, required levothyroxine dosages, and even histologic aspects of the disease with respect to preventing or diminishing thyroid damage. Similarly, it would be interesting to determine the impact of early treatment with Se in patients with newly developed autoimmune thyroiditis to delay or prevent its progression.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

Ethical approval This study involving humans have been approved by the local Ethics Committee of Shiraz University of Medical Sciences. All procedures have been performed in accordance with the ethical standards as laid down in the 1964 declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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