

Selenium treatment in autoimmune thyroiditis: 9-month follow-up with variable doses

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Abstract

The aim of this study is to investigate the long-term (9 months) effects of variable doses (200/100 µg/day) of L-selenomethionine on autoimmune thyroiditis (AIT) and the parameters affecting the success rate of this therapy. The present study was designed in three steps: (1) 88 female patients with AIT (mean age = 40.1 ± 13.3 years) were randomized into two groups according to their initial serum TSH, thyroid peroxidase antibody (TPOAb) concentrations, and age. All the patients were receiving L-thyroxine to keep serum TSH ≤ 2 mIU/l. Group S2 (*n* = 48, mean TPOAb = 803.9 ± 483.8 IU/ml) received 200 µg L-selenomethionine per day, orally for 3 months, and group C (*n* = 40, mean TPOAb = 770.3 ± 406.2 IU/ml) received placebo. (2) 40 volunteers of group S2 were randomized into two age- and TPOAb-matched groups. Group S22 (*n* = 20) went on taking L-selenomethionine 200 µg/day, while others (group S21) lowered the dose to

100 µg/day. (3) 12 patients of group S22 (group S222) went on taking L-selenomethionine 200 µg/day, while 12 patients of group S21 (S212) increased the dose to 200 µg/day. Serum titers of TPOAb decreased significantly in group S2 (26.2%, *P* < 0.001), group S22 (23.7%, *P* < 0.01) and group S212 (30.3%, *P* < 0.01). There were no significant changes in group C and group S222 (*P* > 0.05). TPOAb titers increased significantly in group S21 (38.1%, *P* < 0.01). A significant decrease in thyroglobulin antibody titers was only noted in group S2 (5.2%, *P* < 0.01). L-selenomethionine substitution suppresses serum concentrations of TPOAb in patients with AIT, but suppression requires doses higher than 100 µg/day which is sufficient to maximize glutathione peroxidase activities. The suppression rate decreases with time.

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Introduction

Chronic autoimmune thyroiditis (AIT) is one of the most prevalent autoimmune diseases and affects more than 10% of females and 2% of males. Cellular destruction by CD4 cell-mediated autoimmune attacks results in permanent hypothyroidism in more than 90% of patients (Chistiakov 2005). More than one-third of the patients have other autoimmune diseases such as Sjogren syndrome, myasthenia gravis, vitamin B12 deficiency or celiac disease. AIT is also a well-known risk factor for lymphoma and is being investigated as a potent risk factor for papillary carcinoma.

There is no specific treatment modality to suppress autoimmune destruction and so replacement therapy with L-thyroxine (LT4) has been the only means of palliation. The prophylactic usage of LT4 in euthyroid patients may suppress the serum concentrations of autoantibodies mildly because of a possible decline in antigenic stimulus (due to the rest) of the thyrocytes, not by direct suppression of antibodies (Padberg *et al.* 2001). Neither corticosteroids nor nonsteroid

anti-inflammatory drugs are indicated to inhibit chronic cellular destruction.

The demonstration of a relationship between selenium deficiency and thyroid destruction in myxedematous cretinism and in rat experimental models underlined the importance of selenium (Se) in thyroiditis (Goyens *et al.* 1987, Contempre *et al.* 1992, 1993).

After a small pilot study showing a significant decrease in both thyroid peroxidase antibody (TPOAb) and in thyroid-stimulating hormone (TSH)-receptor antibody concentrations in patients with AIT (Schmidt *et al.* 1998), a significant decrease in the mean serum TPOAb levels was also noted with a daily intake of 200 µg (2.53 µmol) sodium selenite for 3 months (36.4% in the selenium group versus 12% in the control group; Gartner *et al.* 2002). Receiving the same dose of sodium selenite for an additional 6 months resulted in an additional 43% decrease and cessation of the treatment caused a 57% increase in the mean TPOAb concentrations (Gartner & Gasnier 2003). In another study, daily intake of 200 µg selenomethionine resulted in a decrease of 46 and 55.5%

in serum TPOAb levels after 3 and 6 months treatment, and of 21 and 27% in the control group respectively. In the pharmacokinetics study, the basal serum concentration of Se ($75 \pm 6 \mu\text{g/l}$) was within the reference range ($70\text{--}125 \mu\text{g/l}$); it promptly increased at 2 h, peaked at 4 h ($147 \pm 17 \mu\text{g/l}$, $P < 0.0001$) and it was abundant in serum at 24 h. Thus, selenomethionine is proven to be rapidly absorbed by the gastrointestinal tract (Duntas *et al.* 2003). No significant change in the mean thyroglobulin antibody (TgAb) levels was noted.

Se is essential for optimal endocrine and immune function and for moderating the inflammatory response. These actions are mediated in most cases through the expression of at least 30 selenoproteins. There are at least six different glutathione peroxidases (GPX); GPX1 is an antioxidant in cell cytosol and may function as a selenium store, GPX3 is an antioxidant in extracellular space and plasma, and GPX4 is a membrane antioxidant and may have a role in apoptosis. Thioredoxin reductases (TR1–3) detoxify peroxides, reduce thioredoxin control of cell growth, and maintain the redox state of transcription factors. Iodothyronine deiodinases type D1 and D2 convert thyroxine (T4) to bioactive 3,5,3'-tri-iodothyronine (T3); type D1 and D3 convert T4 to bio-inactive 3',3',5' reverse T3. Selenoprotein P is the Se transport protein and is an antioxidant on endothelium. The other types of selenoproteins are defined as H, I, K, M, N, O, R, S, T, and V, and most of their functions are still unknown (Beckett & Arthur 2005).

In Turkey, there is mild/moderate iodine deficiency as well as mild selenium deficiency, as in most European countries (Yanardag & Orak 2001, Aydın *et al.* 2002, Cinaz *et al.* 2004).

The current recommended dietary intake of Se to achieve the maximal activity of GPX in plasma or erythrocytes is between 55 and $75 \mu\text{g/day}$. Its anticancer effects become prominent with an intake of $200 \mu\text{g/day}$ (Rayman 2000). In another study (also for adults with low serum Se levels), an upper estimated requirement of $90 \mu\text{g Se/day}$ is calculated as the intake necessary for maximization of plasma GPX activity, as used in the derivation of the US recommended daily allowance (Levander 1997, Duffield *et al.* 1999). Also, a lower estimated requirement of $39 \mu\text{g Se/day}$ is the intake necessary to reach two-thirds of maximal GPX activity, as was used in calculating the World Health Organization normative requirement (Levander 1997, Duffield *et al.* 1999).

Usually authors argue that the replacement of deficient Se stores of GPX plays a major role in the suppression of TPOAb titers in AIT patients. If it is so, it could be achieved by the lower doses of Se too.

This is a critical point, not to optimize the daily dose, but to understand the effect of Se on pathogenesis. However, unfortunately, all of the older studies have been performed with a dose of $200 \mu\text{g/day}$, which is considerably higher than the limits mentioned above.

Serum Se concentrations do not reflect tissue levels (Kucharzewski *et al.* 2002, 2003). In fact, intake of a single $200 \mu\text{g}$ dose of Se can produce adequate serum levels in AIT patients, as in normal individuals (Duntas *et al.* 2003).

Furthermore, in both the studies, serum Se levels of patients were within the normal range ($70\text{--}125 \mu\text{g/l}$) or close to the lower limit, but they responded to Se therapy (Gartner *et al.* 2002, Duntas *et al.* 2003). Thus, it requires another question: is there any relationship between the deficiency state of Se and the suppression effect or does Se also have an effect on Se-sufficient patients with AIT?

Since there are limited data available to answer these questions, we conducted a blinded, prospective study. Our aims were:

- 1 To test the effect of $200 \mu\text{g}$ L-selenomethionine/day therapy in a larger group to determine the parameters that may affect the success rates.
- 2 To observe the dose–response curves by shifting doses ($200\text{--}100 \mu\text{g/day}$) after saturation of tissues with a high dose ($200 \mu\text{g/day}$) of Se for 3 months, which may exclude any doubt about the Se status of the tissue stores, instead of subjective measurements of the serum Se levels.
- 3 Finally, to follow the long-term effects of therapy.

Subjects and Methods

Eighty-eight female patients (mean age 40.1 ± 13.3 years, range 15–77) with known AIT and elevated serum TPOAb ($> 100 \text{ IU/ml}$) and/or TgAb ($> 188 \text{ IU/ml}$) were included and their informed consent to participate in the study was obtained. The present study was registered and complies with the current laws of the country in which it was performed, inclusive of ethics approval.

Patients were randomized into two groups according to their initial serum TPOAb and TSH concentrations and ages to exclude any difference in serum TPOAb and TSH levels or age. All the patients had been receiving LT4 in a titrated dose to maintain TSH within the lower half of the normal range ($\leq 2 \text{ mIU/l}$). Patients then received either $200 \mu\text{g}$ L-selenomethionine/day (group S2, $n = 48$), orally or placebo (group C, $n = 40$) for 3 months (90 days). All the patients were otherwise healthy, but one in the treated group suffered from vitiligo and another one in the same group had discoid lupus. Six in the treated group and four in the control group had serum vitamin B12 levels at the lower limit of the normal range. No patient was receiving corticosteroids, vitamins, trace elements, or antidepressive/antipsychotic drugs.

At the end of the third month, 40 patients from group S2 agreed to go on the study and were randomized into two groups according to their ages and TPOAb concentrations. Group S22 ($n = 20$) went on taking a daily dose of $200 \mu\text{g}$ L-selenomethionine, while the others (group S21, $n = 20$) lowered the daily dose of Se to $100 \mu\text{g}$. After 3 months, 12 patients of group S22 went on taking a daily dose of $200 \mu\text{g}$ (group S222) and 12 patients of group S21 increased the dose to $200 \mu\text{g}$ again (group S212). Serum TSH, free serum T3 (FT3), free serum T4, (FT4), TPOAb, and TgAb levels were measured at baseline and at the end of each 3-month period during the study.

Measurements

Serum concentrations of TPOAb, FT3, and FT4 were measured by RIA and concentrations of TgAb, and TSH were measured by IRMA (Immunotech, Prague, Czech Republic). Normal ranges, analytical sensitivities, intra-assay coefficients of variations (CV), and interassay CV are:

TSH: (0.17–4.05 mIU/l); 0.025 mIU/l; 3%; 8.6%
 FT3: (2.5–5.8 pM); 0.5 pM; 5.2%; 5.5%
 FT4: (11.5–23 pM); 0.4 pM; 6.7%; 6.5%
 TPOAb: (<100 IU/ml); 4 IU/ml; 4.26%; 8.45%
 TgAb: (<188 IU/ml); 5 IU/ml; 5.8%; 8%

Statistical analysis

All the results are presented as means \pm s.d. A multiple linear regression test was performed to investigate the difference between the ages, serum TSH, FT3, and FT4 titers, and the mean values of individual percentage changes in serum TPOAb titers for the 3-month period of the study. Abnormally distributed TPOAb titers were transformed logarithmically to achieve normal distribution values before variance analysis. Variance analysis was performed by two-way ANOVA test to find out the difference in TPOAb titers of Se-treated patients for repeated measurements.

Differences between the groups during the treatment period were analyzed by the Mann–Whitney nonparametric test. The relative changes in TPOAb, TgAb, TSH, FT3, and FT4 concentrations in subgroups were compared using Wilcoxon's matched pairs, signed-ranks test. A *P* value of 0.05 was considered significant. Instead of simple rates of mean values, percentage changes of titers were presented for every individual measurement.

Results

A significant decrease was noted in the serum TPOAb levels of the patients by two-way ANOVA compared with the basal values (*P*<0.001). There were significant decrements in the first (*P*<0.001) and the final trimesters (*P*<0.05), but the decrement in the second trimester was not significant because this group also contained increased TPOAb values in group S21 patients. So, in order to analyze subgroups independently, we used Wilcoxon's matched pairs, signed-ranks test.

Mean ages, basal TSH, FT3, FT4, TPOAb, and TgAb titers of group S2 and group C are presented in Table 1. There were no significant differences in ages and initial TSH and TPOAb titers (*P*>0.05).

TSH titers were within the normal range and unchanged in both groups. No correlation was established between the age, TSH, FT3, FT4, and percentage change in TPOAb titers in group S2 (*P*>0.05).

There was a significant decrease in mean TPOAb concentrations in group S2 (from 803.9 \pm 483.8 to 572.3 \pm 517.3 IU/ml, 26.2% decrement, *P*<0.001). However, the change was statistically insignificant in the

Table 1 Initial age, serum TSH, FT3, FT4, TPOAb, and TgAb levels (mean \pm s.d.) of group C (receiving LT4 alone) and group S2 (receiving LT4 + 200 μ g L-selenomethionine/day). There was no significant difference in age, TSH, or TPOAb levels between the groups (*P*>0.05)

	Group C	Group S2
Age (year)	39.2 \pm 14.4	40.8 \pm 12.5
TSH (mIU/l)	1.58 \pm 0.50	1.57 \pm 0.61
FT3 (pM)	3.8 \pm 0.5	3.4 \pm 0.7
FT4 (pM)	17.0 \pm 3.6	17.1 \pm 3.2
TPOAb (IU/ml)	770.3 \pm 406.2	803.9 \pm 483.8
TgAb (IU/ml)	195.9 \pm 129.9	154.2 \pm 217.3

control group (from 770.3 \pm 406.2 to 773.4 \pm 372.9 IU/ml, *P*>0.05).

At the beginning of this study, the mean TgAb concentrations were not identical in both groups, because patients were randomized primarily according to the TPOAb concentrations. The TgAb concentration in group S2 decreased from 154.2 \pm 217.3 to 138.8 \pm 205.1 IU/ml (5.2% decrement, *P*<0.01). In the control group, the change in TgAb concentration was not significant (from 195.9 \pm 129.9 to 188.5 \pm 122.2 IU/ml, *P*>0.05). FT3, FT4, as well as TSH values were unchanged in both groups, and all were within the normal range.

The mean values of TPOAb concentrations in group S22 decreased from 649.2 \pm 628.1 to 443.2 \pm 382.5 IU/ml (23.7% decrement, *P*<0.01) and mean serum TPOAb concentrations increased from 544.3 \pm 380.2 to 694.9 \pm 427.2 IU/ml (38.1% increment, *P*<0.01) in group S21. There was no statistically significant difference in serum TgAb both the S22 and S21 groups.

The mean values of serum TPOAb concentration in group S222 decreased from 451.7 \pm 381.3 to 440.2 \pm 426.7 IU/ml but the decrement was not significant (3.6% decrement, *P*>0.05). The mean values of TPOAb concentration in group S212 decreased from 666.8 \pm 383.1 to 453.2 \pm 233.8 IU/ml (30.3% decrement, *P*<0.01). There was no statistically significant difference in serum TgAb concentrations in either group (Table 2).

There was no change detected in serum vitamin B12 levels in the patients in group S2 and the control group. Unfortunately, we did not measure the antiparietal cell Ab titers concomitantly.

The frontal depigmentation in the vitiligo patient decreased by approximately 50% and the patient with discoid lupus reported a decline in the amount and frequency of lesions after 3 months, although neither of them used any other medication during this period.

One of 48 out of group S2, one of 20 of group S22 and three 12 of group S222 reached normal serum TPOAb range (<100 IU/ml) and of remained stable.

A 28-year-old female in group S22 received 200 μ g Se/day for 6 months. Her TPOAb titer decreased from 1222 to 543.6 IU/ml in this period, then she became pregnant and preferred not to continue Se therapy. Interestingly, TPOAb

Table 2 TPOAb levels (mean \pm s.d.) and the mean individual percentage changes in TPOAb levels of the subgroups. Medians and interquartile ranges are presented under mean \pm s.d. values

Group	n	TPOAb titer (IU/ml) before experiment	TPOAb titer (IU/ml) after 3 months	Percentage change	Significance
C	40	770.3 \pm 406.2 833; 441–1101	773.4 \pm 372.9 790; 414.5–1067.7	12.1	$P > 0.05$
S2	48	803.9 \pm 483.8 648.8; 390.7–116.3	572.3 \pm 517.3 340.5; 215.9–631.5	–26.2	$P < 0.001$
S21	20	544.3 \pm 380.2 563.9; 330.7–623.5	694.9 \pm 427.2 652.6; 351.4–785.5	38.1	$P < 0.01$
S22	20	649.2 \pm 628.1 290.7; 217.5–1287.9	443.2 \pm 382.5 250.9; 140.6–896.6	–23.7	$P < 0.01$
S212	12	666.8 \pm 383.1 681.6; 332.4–783.2	453.2 \pm 233.8 476; 228.7–648	–30.3	$P < 0.01$
S222	12	451.7 \pm 381.3 236; 132.7–896.6	440.2 \pm 426.7 205.7; 112.3–803.6	–3.6	$P > 0.05$

titers went on declining to 103.2 IU/ml at the end of her pregnancy.

Another 28-year-old patient with a basal TPOAb titer of 1519 IU/ml also became pregnant at the end of the third month, but she insisted on the therapy (200 μ g Se/day). At the end of 9 months, her serum TPOAb titers reached 192.8 IU/ml.

Both pregnancies ended without any problem and, according to routine tests, there was no abnormality reported in the infants.

One patient suffered from gastric discomfort during Se therapy.

Discussion

Our results confirm that oral administration of 200 μ g L-selenomethionine/day decreases serum TPOAb titers effectively. There is no relationship detected between the age and the response rate to the treatment. Thus, Se treatment seems to be effective in all age groups, but it must be kept in mind that starting treatment at an early age may save more thyrocytes. Otherwise, it may be ineffective if started later in the late, atrophic phase of the pathology.

There was a sharp decrease in serum TPOAb levels at the beginning of Se treatment, especially in patients with relatively high serum titers (Figs 1 and 2). However, response rate decreases as the serum concentration of TPOAb decreases, as Gartner *et al.* (2002) also noted (higher decrement in patients with serum TPOAb titers higher than 1200 IU/ml). This data may confirm the 'saturation theory.' However, what is the saturated component of the autoimmune process? Is it really Se store of GPX?

It is clear that 100 μ g/day is considerably higher than the amount of Se that is required for maximal GPX activity (Levander 1997, Duffield *et al.* 1999, Rayman 2000). Failure of 100 μ g L-selenomethionine/day to suppress auto-antibody titers in group S21 patients points to the fact that the therapeutic dose must be higher than the replacement dose of

Se that replenishes deficient GPX stores. For this reason, we tailored the first 3 months of therapy with a high dose of Se. A dramatic increase (38%) of mean TPOAb level in group S21 patients and reversal of increment in group S212 patients clearly proved the inefficiency of the low dose.

Lowering of serum TPOAb levels in patients whose GPX stores are saturated suggests that nondeficient AIT patients may respond to 200 μ g L-selenomethionine/day therapy too. Note that the patients whose serum Se levels were within the normal range (70–125 μ g/l) or close to the lower limit responded to Se therapy in both studies (Duntas *et al.* 2003, Gartner & Gasnier 2003). Thus, we believe that the suppressive effect of Se is not restricted by deficiency states, Se acts on Se sufficient AIT patients also.

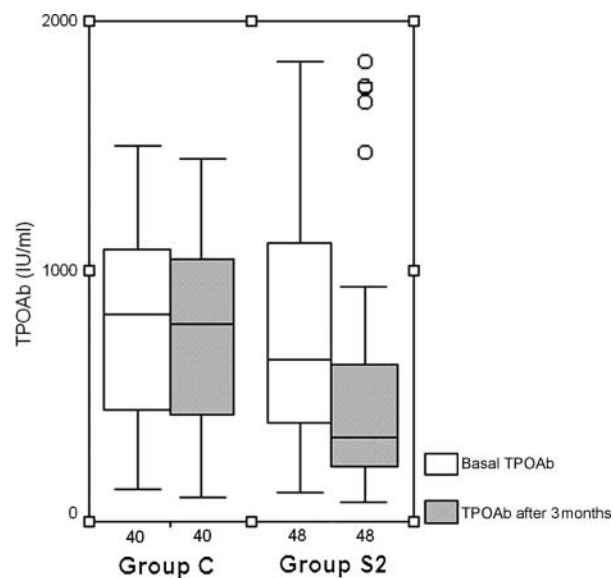


Figure 1 TPOAb concentrations at the beginning of the study and 3 months after treatment with 200 mg L-selenomethionine/day (group S2) or placebo (group C). P values were calculated by Wilcoxon's matched pairs, signed-ranks test.

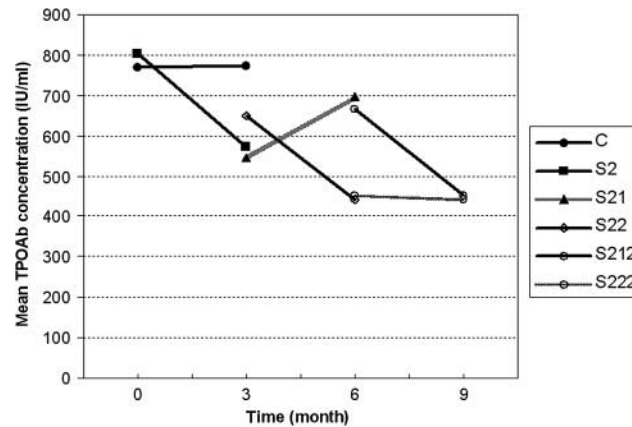


Figure 2 Dose-response curves of subgroups. Note the concordance in decrement rates in groups S2, S22 and S212, who received 200 mg L-selenomethionine/day, and the decreased response in group S222. Rising serum concentrations of TPOAb in group S21 clearly confirms the ineffectiveness of 100 mg L-selenomethionine/day.

Transient decrement of mean serum TgAb titer during the first 3 months seems to be unrelated to therapeutic effect of Se. Also, other studies did not find any decrement in the mean TgAb titers (Gartner *et al.* 2002, Duntas *et al.* 2003). Many authors attribute this to lesser specificity of TgAb because Tg is a circulating antigen and therefore is not necessarily an antigen only expressed during a thyroid-specific autoimmune response. Therefore, TgAb is less specific for pathogenesis as well as for diagnosis of AIT.

The effectiveness of Se in many other autoimmune diseases like rheumatoid arthritis (Peretz *et al.* 1992), asthma (Hasselmark *et al.* 1993, Kadrabova *et al.* 1996), and lupus erythematosus (Juhlin *et al.* 1982, Brown 2000) is well documented. It seems that the immunomodulatory effects of this element may be more prominent than the other effects. For selenium supplements augment example, the cellular immune response through increased production of interferon gamma and other cytokines, an early peak T-cell proliferation, and an increase in T helper cells (Broome *et al.* 2004). Furthermore, selenoprotein GPX4 may play an important role in apoptosis and TRs affect the control of cell growth.

Unresponsiveness of many AIT patients to Se therapy is interesting. Two hundred micrograms L-selenomethionine/day suppresses autoimmune activity, while lower doses fail. Is it possible that there is any altered Se binding capability of proteins in AIT patients?

We are quite distant from the answers of these questions and we need more data related to molecular biology of selenoproteins. We hope that the results of our study may encourage the initiation of further trials and encourage the thyroidologists to use selenium in the treatment of AIT.

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