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Selenium Supplementation in Patients with Autoimmune Thyroiditis Decreases Thyroid Peroxidase Antibodies Concentrations

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In areas with severe selenium deficiency there is a higher incidence of thyroiditis due to a decreased activity of selenium-dependent glutathione peroxidase activity within thyroid cells. Selenium-dependent enzymes also have several modifying effects on the immune system. Therefore, even mild selenium deficiency may contribute to the development and maintenance of autoimmune thyroid diseases. We performed a blinded, placebo-controlled, prospective study in female patients (n = 70; mean age, 47.5 ± 0.7 yr) with autoimmune thyroiditis and thyroid peroxidase antibodies (TPOAb) and/or Tg antibodies (TgAb) above 350 IU/ml. The primary end point of the study was the change in TPOAb concentrations. Secondary end points were changes in TgAb, TSH, and free thyroid hormone levels as well as ultrasound pattern of the thyroid and quality of life estimation. Patients were randomized into 2 age- and antibody (TPOAb)-matched groups; 36 patients received 200 μg (2.53 μmol) sodium selenite/d, orally, for 3months, and 34 patients received placebo. All patients were substituted with L-T_4 to maintain TSH within the normal range. TPOAb, TgAb, TSH, and free thyroid hormones were determined by commercial assays. The echogenicity of the thyroid was monitored with high resolution ultrasound. The mean TPOAb concentration decreased significantly to 63.6% ($P = 0.013$) in the selenium group *vs.* 88% ($P = 0.95$) in the placebo group. A subgroup analysis of those patients with TPOAb greater than 1200 IU/ml revealed a mean 40% reduction in the selenium-treated patients compared with a 10% increase in TPOAb in the placebo group. TgAb concentrations were lower in the placebo group at the beginning of the study and significantly further decreased ($P = 0.018$), but were unchanged in the selenium group. Nine patients in the selenium-treated group had completely normalized antibody concentrations, in contrast to two patients in the placebo group (by χ^2 test, $P = 0.01$). Ultrasound of the thyroid showed normalized echogenicity in these patients. The mean TSH, free T_4, and free T_3 levels were unchanged in both groups.

We conclude that selenium substitution may improve the inflammatory activity in patients with autoimmune thyroiditis, especially in those with high activity. Whether this effect is specific for autoimmune thyroiditis or may also be effective in other endocrine autoimmune diseases has yet to be investigated. (*J Clin Endocrinol Metab* 87: 1687–1691, 2002)

CHRONIC AUTOIMMUNE thyroiditis with euthyroidism or hypothyroidism is a common disease, affecting more than 10% of females and 2% of males. There are several explanations for the development of this disease. There is a genetic background, as patients with human leukocyte antigens DR3 and DR5 and polymorphism of the cytotoxic T lymphocyte A4 promoter are more susceptible to the development of autoimmune thyroiditis compared with the normal population. There also are environmental factors, such as iodide intake, immunotherapeutic agents, or viral infections, that may initiate the disease (1).

In areas with combined endemic selenium and iodine deficiency, the supplementation of iodide alone leads to myxedematous cretinism (2, 3), which is defined by not only fetal hypothyroidism, but persistent hypothyroidism from early life. The thyroid of these patients is small and firm, suggesting fibrotic degeneration initiated by thyroid cell damage (4). The cause of this cell damage has been further investigated in animal studies. In severe selenium deficiency, the activity of the selenoenzyme glutathione peroxidase (GPx) is decreased, and therefore peroxide cleavage within the thyroid cells is diminished. Severe nutritional selenium deficiency therefore leads to an increased rate of thyroid cell necrosis and invasion of macrophages (5, 6). Whether this also may induce a higher incidence of autoimmune thyroiditis is unknown. It may be assumed, however, that thyroid cell damage may initiate or maintain autoimmune thyroiditis, especially in patients susceptible to the development of autoimmune diseases (7).

Furthermore, selenium has an important impact on immune function (8, 9). Selenium deficiency is accompanied by loss of immune competence. Both cell-mediated immunity and B cell function can be impaired. This might be related to the fact that the selenium-dependent enzymes, GPx and thioredoxin reductase (TxR), have antioxidative effects; they decrease free radical formation and reduce hydrogen peroxide and lipid and phospholipid hydroperoxides (9). In selenium-sufficient environment, the hydroperoxide intermediates of the cyclooxygenase and lipoxygenase pathways are therefore reduced and lead to diminished production of proinflammatory PGs and leukotrienes (10). In addition, both GPx and TxR modulate the respiratory burst and reduce superoxide production (11–13).

The possible therapeutic effect of selenium has already been shown in a double blind, randomized trial in patients with rheumatoid arthritis, in whom the supplementation of 200 μg selenium for 3 months significantly reduced pain and

Abbreviations: GPx, Glutathione peroxidase; TgAb, Tg antibodies; TPOAb, thyroid peroxidase antibodies; TxR, thioredoxin reductase.

joint involvement (14). Selenium supplementation of 500-1000 μg has also been shown to improve survival in patients with hemorrhagic pancreatitis (15) and severe sepsis (16), which may be due to the antiinflammatory effect of a higher selenium supply.

The three known deiodinases also are selenium-dependent enzymes (11, 17–19). Their activity, however, in contrast to GPx activity, is only decreased in extremely severe selenium deficiency. T_4 plasma concentrations are then elevated, and selenium supplementation lowers T_4 and increases T_3 concentrations (20).

In Germany, there is mild iodine deficiency (21) as well as mild selenium deficiency, as in most European countries (22). As selenium deficiency may influence both the immune response as well as peroxidation of thyroid cell components, it seems reasonable to investigate whether a selenium substitution may influence the natural course of chronic autoimmune thyroiditis (23). There is one small pilot study showing a significant decrease in both thyroid peroxidase antibodies (TPOAb) as well as TSH receptor antibody concentrations in patients with lymphocytic autoimmune thyroiditis (24). We therefore conducted a blinded, placebo-controlled study in patients with chronic autoimmune thyroiditis to show whether supplementation with 200 μg (2.53 μmol) sodium selenite has any effect on plasma TPOAb concentrations, free thyroid hormones, and the ultrasound pattern of the affected thyroid in patients with overt autoimmune thyroiditis.

Subjects and Methods

Patient selection and treatment

Caucasian patients with known autoimmune thyroiditis and elevated plasma TPOAb and/or Tg antibodies (TgAb) above 350 IU/ml were selected from our out-patient clinic and asked for their informed consent to participate in the study. Diagnoses had been made by elevated TPOAb, TgAb, and basal TSH levels as well as typical hypoechogenicity of the thyroid in high resolution sonography (25). From 92 patients selected, 71 agreed to participate in the study. They were randomized into 2 groups according to their initial TPOAb concentrations, age, and supposed duration of the disease. All patients were receiving L-T_4 replacement therapy in a dosage to maintain basal TSH within the normal range. Patients then received either 200 μg sodium selenite/d (verum), orally, or placebo for 90 d. The patients were asked to take the medication with water about 2 h before or after a meal. They were not given further treatment, such as over-the-counter vitamins or trace elements.

All patients were otherwise healthy, but 3 in the placebo group and 4 in the treated group suffered from vitiligo, and 3 in both groups had mild rheumatoid arthritis. Many of the patients (8 in the placebo group and 12 in the verum group) had a history of various allergies, such as hay fever, neurodermitis, nickel and mercury allergy, and asthma, but none of the patients was receiving corticoid or other antiinflammatory therapy.

The primary end point of the study was the change in TPOAb concentrations. Secondary end points were TgAb, TSH, and free thyroid hormone levels as well as ultrasound pattern of the thyroid and quality of life estimation.

Laboratory and technical investigations

Blood samples were drawn initially and at the end of the treatment. Plasma total TPOAb and TgAb concentrations were measured by a commercial enzyme luminescence assay (Byk-Sangtec, Dietzenbach, Germany). The specificity for autoimmune thyroiditis in these assays is greater than 90% when antibody concentrations are above 350 IU/ml. Free T_4 and T_3 concentrations and TSH were measured by an enzyme immunometric assay (Byk-Sangtec). Plasma selenium was determined by atomic absorption spectrometry (26).

High resolution ultrasound (7.5 MHz; SONOLINE Elegra, Siemens, Erlangen, Germany) of the thyroid gland was performed, and echogenicity as well as perfusion by Doppler sonography were documented and compared at the beginning and end of the study by an independent experienced investigator (25).

The subjective well-being was evaluated using the standardized SF 12 protocol before and after the study. The SF 12 protocol is a 12 item short-form to survey health status in medical outcome studies.

Statistics

The relative changes in antibody concentrations as well as thyroid hormone concentrations in both groups were compared using Wilcoxon's matched pairs, signed-ranks test. In addition, the differences in antibody concentrations at the beginning and end of the study were determined by *t* test for paired samples. The *P* values were corrected for the numbers of tests performed. Subgroup analyses were conducted using χ^2 testing.

Results

A total of 71 patients, all females, were enrolled in the study, one was omitted because of pregnancy during the study period. Thirty-four received placebo; the other 36 received a liquid solution of 200 μg (2.53 μmol) sodium selenite/d. The mean age in both groups was identical (verum, 41.6 ± 12.1 yr; placebo, 43.0 ± 12.1 yr).

At study entry the mean TPOAb concentrations were identical in both groups (verum, 904 ± 205 IU/ml; placebo, 1090 ± 277 IU/ml), whereas the TgAb concentrations were significantly lower in the placebo group (verum, 1507 ± 390 IU/ml; placebo, 1089 ± 255 IU/ml; $P = 0.05$). TSH, free T_4, and free T_3 were identical in both groups. All were euthyroid under L-T_4 treatment; the mean basal TSH levels were 1.2 ± 1.5 μU/ml (verum) and 1.4 ± 2.0 μU/ml (placebo). The ultrasound pattern in all patients revealed the typical hypoechoic thyroid tissue. None of the patients had thyroid nodules.

TPOAb concentrations significantly decreased in the verum group to 63.6% compared with that at study entry (100%) or in absolute values from a mean of 904 ± 205 to 575 ± 146 IU/ml ($P = 0.013$, by Wilcoxon's matched pairs test; $P = 0.016$, by paired *t* test). In contrast, in the placebo group using both statistical tests there was no change ($P = 0.95$ and $P = 0.32$, respectively); the TPOAb concentrations were 959 ± 267 IU/ml at the end of the study and 1090 ± 277 IU/ml at study entry (Fig. 1). There was no significant cor-

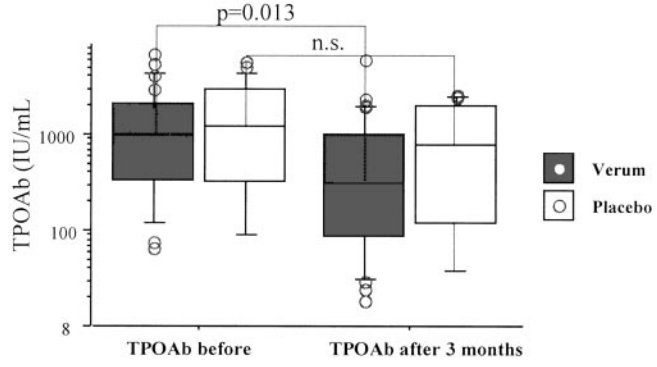

FIG. 1. TPOAb concentrations at study entry and 3 months after treatment with 200 μg (2.53 μmol) sodium selenite or placebo. *P* values are calculated by Wilcoxon's matched pairs, signed-rank test.

relation between the plasma selenium concentrations and TPOAb before and after treatment.

A subgroup analysis of patients with TPOAb greater than 1200 IU/ml (verum, n = 12; placebo, n = 8) revealed a decrease in antibody concentrations in this group to 60% in the selenium group *vs.* an increase of 10% in the placebo group.

The mean TgAb concentrations at study entry were not identical in the two groups, because patients were randomized primarily according to the TPOAb concentrations. The TgAb concentration in the selenium-treated patients decreased to 91.2% compared with that at study entry (100%) or in absolute values from a mean of 1507 ± 390 to 1375 ± 484 IU/ml, which is not significant ($P = 0.33$). In the placebo group TgAb concentrations dropped from 1089 ± 225 to 742 ± 161 IU/ml ($P = 0.014$, by Wilcoxon's paired test; $P = 0.015$, by t test for paired samples; Table 1).

A decrease in both antibody concentrations below 50 IU/ml was detected in nine patients in the selenium-treated group *vs.* two patients in the placebo group (by χ^2 test, $P = 0.015$).

Free T_4 and T_3 as well as TSH values were unchanged in both groups, and all were within the normal range.

Plasma selenium values were identical in both groups at study entry (verum, 0.87 ± 0.15 μmol/liter; placebo, 0.91 ± 0.15 μmol/liter), increased significantly to 1.09 ± 0.12 μmol/liter in the verum group ($P = 0.001$), and were unchanged in the placebo group (0.92 ± 0.23 μmol/liter) at the end of the study (Fig. 2).

Improvement of ultrasound echogenicity was observed in nine patients in the selenium-treated group *vs.* two patients in the placebo group. These were identical to those patients with a decrease in antibody concentrations below 50 IU/ml, except for one patient in the placebo group.

Evaluation of subjective well-being revealed an improvement in 25 patients in the selenium-treated group compared with 6 in the placebo group, no change in 10 patients in the verum group *vs.* 26 in the placebo group, and worsening in 1 patient in the verum group *vs.* 4 in the placebo group (Fig. 3).

Discussion

In this randomized, prospective, blinded study we could demonstrate that in patients with autoimmune thyroiditis under selenium substitution with 200 μg (2.53 μmol)/d for 3 months, thyroid-specific TPOAb concentrations significantly decreased from 100% to 63.6%. Even more important, in 9 of 36 patients, complete normalization of TPOAb concentrations as well as thyroid ultrasound echogenicity could be achieved with selenium supplementation compared with only 2 of 34 age- and TPOAb-matched controls.

TABLE 1. Thyroid-specific antibody concentrations before and after treatment with 200 μg (2.53 μmol) sodium selenite/d (verum) or placebo for 3 months

Group	Before	After	Significance	% change
TPOAb				
Verum	904 ± 205	575 ± 146	$P = 0.013^a$	−36
Placebo	1090 ± 277	959 ± 267	$P = 0.95$	−12
TgAb				
Verum	1507 ± 390	1375 ± 484	$P = 0.33$	−9
Placebo	1089 ± 255	742 ± 161	$P = 0.015^a$	−32

[a] Significant decrease (Wilcoxon's matched pairs test).

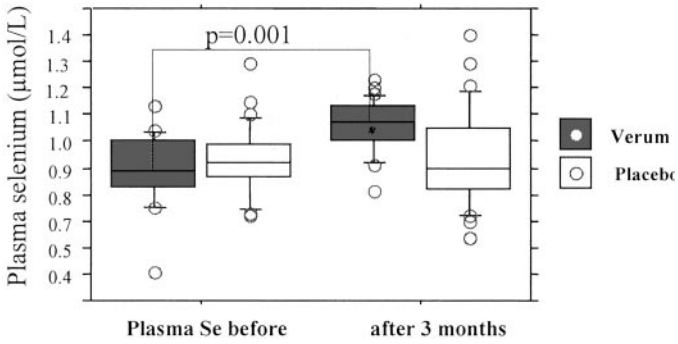

FIG. 2. Plasma selenium concentrations at study entry and 3 months after treatment with 200 μg (2.53 μmol) sodium selenite or placebo. *P* values are calculated by Wilcoxon's matched pairs, signed-rank test.

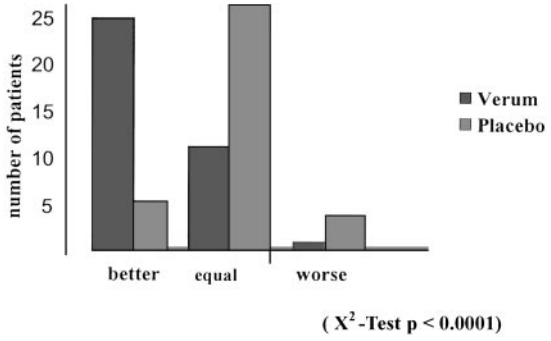

FIG. 3. Quality of life (SF 12) of patients treated with 200 μg (2.53 μmol) sodium selenite or placebo for 3 months.

In contrast to TPOAb concentrations, TgAb concentrations slightly decreased in the selenium-treated group, but significantly decreased in the placebo group. This might be due to the fact that the TgAb concentrations were already significantly lower in the placebo group at study entry compared with those in the verum group. The change in TgAb has been selected as a secondary end point of the study, because TgAb are less specific for autoimmune thyroiditis. However, plasma TPOAb concentrations are specific for autoimmune thyroiditis, thought to reflect intrathyroidal inflammation, and assumed to be cytotoxic in the presence of complement (1). Tg, in contrast to thyroid peroxidase, is a component normally secreted into the circulation and therefore is not necessarily an antigen only expressed during a thyroid-specific autoimmune response. Therefore, TgAb concentrations are less important for pathogenesis as well as diagnosis of autoimmune thyroiditis.

Selenium-dependent enzymes have diverse effects not only within the thyroid (19, 27), but also on the immune system (11, 23, 28, 29). It has been shown that during severe selenium deficiency, the lack of GPx activity may contribute to oxidative damage of the thyroid cell and initiation of thyroid damage and fibrosis (4). Selenium substitution in a rat model could prevent this oxidative damage (6). It might be supposed that even in mild selenium deficiency, this mechanism is an important environmental factor initiating or maintaining autoimmune thyroiditis in people geneti-

cally susceptible for the development of organ specific autoimmunity.

The immune modulatory effects of selenium-dependent enzymes such as GPx and TxR are involved in the organ-specific immune response (8, 10). This was demonstrated in selenium-deficient mice, where tissue damage of the lung was significantly increased after virus infection compared with selenium-adequate mice (30). The same is true for myocarditis in mice infected with coxsackie virus (31). The increased oxidative stress in all inflamed tissue leads to increased nuclear factor-κB expression, particularly in selenium deficiency, leading to enhanced chemokine mRNA expression (32, 33). In addition, it has been shown that in selenium-deficient mice, $CD8^+$ lymphocytes are significantly lower than in selenium-adequate mice, and the cytokine pattern is skewed toward a T helper cell 2-like pattern, which leads to increased inflammation in lung tissue after virus infection (30). Selenium-dependent enzymes are both antioxidative and antiinflammatory (11, 13, 22). This is because GPx can reduce hydrogen peroxides and lipid and phospholipid hydroperoxides, thereby lowering the propagation of free radicals and reactive oxygen species. Lower hydroperoxide tissue concentrations diminish the production of inflammatory PGs and leukotrienes. The respiratory burst is also dampened by selenium-dependent enzymes as well as superoxide production (10).

Although tissue damage after viral infection is not comparable to organ-specific autoimmunity, these investigations clearly demonstrates the striking effects of different nutritional selenium supply on the immune response (29). These mechanisms may also contribute to reduced inflammatory activity in the organ-specific autoimmune response (23, 34) and may explain the improvement of autoimmune thyroiditis in our study. In a nonblinded pilot study, significant decreases in TPOAb and thyroid binding inhibitory Igs, but not TgAb, concentrations were described in patients with Hashimoto's thyroiditis and Graves' disease (24), in accordance with our findings in patients with autoimmune thyroiditis.

The beneficial effect of a selenium supplementation of 200 μg (2.53 μmol)/d has also been shown clinically in double blind studies in rheumatoid arthritis (14) and asthma (34). In Crohn's disease, plasma selenium and GPx activities are inversely correlated to the activity of the disease (35).

We did not find any alterations in thyroid function after selenium supplementation. This might be due to the fact that the selenium deficiency was only moderate, and deiodinase activity decreases only in severe selenium deficiency (11). In a previous study in a small cohort of patients with reduced thyroid iodine organification after subacute thyroiditis or postpartum thyroiditis (36), supplementation with 100 μg (1.26 μmol) selenium had no effect on thyroid hormone synthesis. The thyroid is one of the organs with the highest selenium concentration (37), but during mild selenium deficiency deiodinase activities are unaltered, in contrast to GPx activities. Therefore, in tissue samples from patients with autoimmune thyroiditis and nontoxic goiter, there was no difference in selenium tissue concentration in selenium-sufficient areas (38). The selenium deficiency in our patients was mild (0.89 μmol/liter), but it is known that in individuals with such low plasma selenium concentrations GPx activity is impaired. The mean plasma selenium concentration necessary for optimal GPx activities is 1.20 μmol/liter (range, 1.12–1.44 μmol/liter) (39). This might explain the antiinflammatory activity of selenium without its affecting thyroid hormone levels.

We also determined quality of life in our study population. The change in antibody concentrations or inflammatory activity within the thyroid of course has no impact on quality of life, but there are studies showing that low selenium intake is associated with a significant greater incidence of negative mood states and depression (40, 41). Patients receiving selenium supplementation reported significantly better well-being in our trial compared with the placebo group, which supports these earlier findings (42). The cause is unknown, but there are indications that selenium is important for brain function. The turnover rate of some neurotransmitters is altered in selenium deficiency (43), and low plasma selenium concentrations are associated with senility and cognitive decline (44).

The conclusion of our study is that even in mild selenium deficiency the supplementation of this important trace element has a significant impact on inflammatory activity in thyroid-specific autoimmune disease. It would be of interest to determine whether early treatment with selenium in patients with newly developed autoimmune thyroiditis and, even more importantly, in those with Graves' disease may delay or even prevent the natural course of these diseases. It also is important to further evaluate whether selenium supplementation is effective in modulation of other organ-specific autoimmune diseases such as type I diabetes. The results of our study should encourage the initiation of further clinical trials to elucidate the beneficial effects of sufficient selenium supplementation.

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