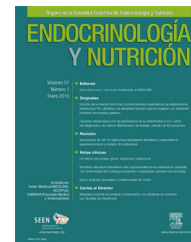




# ENDOCRINOLOGÍA Y NUTRICIÓN

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## EDITORIAL

### Selenium supplementation and autoimmune thyroid diseases

### Suplementación de selenio y enfermedad tiroidea autoinmune

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Selenium (Se) is an indispensable trace element for humans because of its antioxidant and anti-inflammatory properties. The distribution of Se in nature is widely variable in soil and geographic areas. Humans assimilate selenium through consumption of edible plants; selenium levels in food and in humans normally reflect selenium soil content, and vice versa.<sup>1</sup>

The principal form of Se in soil is selenate. By action of adenosine triphosphate (ATP) sulfurylase it is transformed to adenosine phosphoselenate, which is reduced to selenite. In mammals, selenite is directly reduced to selenide, the main metabolite of Se, by thioredoxin reductase.<sup>2</sup> Se is present in specific selenoproteins, such as selenocystein, which is essential for enzymatic activity. The thyroid gland has the highest Se concentration per unit weight among all tissues. Se is incorporated into key enzymes involved in several metabolic pathways implicated in thyroid hormone metabolism; additionally, it plays an antioxidant role in the regulation of the immune system. It has been hypothesized that these compounds activate a complex defence system that maintains normal thyroid function by protecting the gland from both hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), produced by thyrocytes, and reactive oxygen intermediates.<sup>3</sup>

To date, the interaction between Se and the thyroid gland has been investigated using laboratory experiments, clinical trials, and epidemiologic data, and the effects of selenium deficiency on iodine metabolism and thyroid function have been demonstrated. It has thus been hypothesized that Se may play a beneficial role in autoimmune thyroid diseases by blunting the autoimmune process.

Chronic autoimmune thyroiditis (Hashimoto thyroiditis, HT) is the most common thyroid disorder in iodine-sufficient areas and is characterized by the presence of anti-thyroid peroxidase complement-fixing autoantibodies (TPOAb),<sup>4</sup> which are closely associated with overt thyroid dysfunction and correlate with progressive thyroidal damage and lymphocytic inflammation.<sup>5</sup> Along with several genetic and environmental factors, Se deficiency has been implicated in its pathogenesis.<sup>5,6</sup> In animal models, impaired glutathione peroxidase together with Se deficiency may contribute to oxidative damage of thyroid cells, initiation of fibrosis, and impaired tissue repair.<sup>7,8</sup> In addition, Se deficiency may be associated with impairment in both T-cell- and B-cell-mediated immunity, which underscores its significant role in the immune system.<sup>9</sup> Nevertheless, it remains unclear whether selenium deficiency can induce HT in humans; this causal relation is difficult to demonstrate because serum Se levels do not reflect tissue concentrations.<sup>10</sup>

In view of its pivotal role in thyroid function and potential implication in HT pathogenesis, the aim of several studies has been to investigate the therapeutic effects of Se supplementation in HT patients with different baseline

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Se statuses.<sup>11</sup> In 2002, Gärtner et al. reported that in patients with HT who resided in an area in South Germany with borderline selenium intake, 200 µg 3-month supplementation, in the form of selenite, significantly reduced TPOAb concentration and improved ultrasound patterns.<sup>9</sup> In a 6-month follow-up crossover study, TPOAb concentrations continued to decrease significantly in the group that received Se, whereas TPOAb titers significantly increased in the group that stopped taking Se.<sup>12</sup> These findings were in concordance with another study conducted by Duntas et al. in patients with HT in a non-Se-deficient area in Greece, in which TPOAb concentrations also significantly decreased with a combined treatment of 200 µg of selenomethionine and levothyroxine over 6 months.<sup>13</sup> TPOAb reduction was prominent in the first 3 months of treatment, which may have been the result of elevated intrathyroidal Se levels achieved during the study with consequent enhancement of the scavenging activity of both the GPx and TRx systems. Supplemented Se protected against goiter and thyroid tissue damage in a French study by Derumeax et al. that included 792 men and 1108 women; moreover, this study demonstrated a relationship with thyroid echostructure and suggested that Se may protect against autoimmune thyroid disease.<sup>14</sup> Recently, Onal et al. evaluated the role of Se in childhood autoimmune thyroiditis and its effect on TSH, free-T4 (fT4), TPOAb, thyroglobulin autoantibodies (TgAb), and thyroid ultrasound morphology. Following the use of 50 µg of selenomethionine per day for three months, no significant changes in serum TPOAb, TgAb, and thyroid echogenicity were observed. However, a substantial decrease in thyroid volume was observed; 35% of patients demonstrated thyroid volume regression greater than or equal to 30%.<sup>15</sup> In a study published in 2005 Moncayo et al. reported a few cases of patients with autoimmune hypothyroidism who exhibited a marked recovery of thyroid function after Se treatment, with restored euthyroidism and improved ultrasound echomorphology.<sup>16</sup> Most recently, Karanikas et al. demonstrated that Se administration in a cohort of HT patients did not induce significant immunological changes, either in terms of cytokine production patterns of peripheral T lymphocytes or TPOAb levels. This suggests that AIT patients with moderate disease activity (in terms of TPOAb and cytokine production patterns) may not benefit from supplementation to the same degree as patients with high disease activity.<sup>17</sup>

Very recently, an Italian study demonstrated that a physiological dose of Se, 80 µg of sodium selenite over 12 months, prevented progression of the disease in patients with mild HT.<sup>18</sup> A significant reduction in TPOAb and TgAb serum levels, 30% and 19%, respectively, was observed after 12 months of treatment. This study demonstrated for the first time that protracted administration of a stable physiological dose of inorganic Se produces a positive effect on the course of HT. Patients who received sodium selenite also exhibited an improved thyroid ultrasound pattern after six months of treatment.<sup>19</sup> In a meta-analysis in 2010, Toulis et al. stated that selenomethionine at a dose of 200 µg once a day reduced TPOAb titer in patients with HT after a 3-month period compared to a placebo; this reduction was equal to 300 IU/mL. Patients who received Se supplementation also showed

a threefold higher chance of reporting an improvement in well-being and/or mood compared to control cases.<sup>20</sup> Taken together, these studies suggest the beneficial effects of selenium on thyroid autoimmune parameters; however, further investigation study of the efficacy of selenium supplementation in people with thyroiditis is warranted.

It has also been suggested that Se supplementation may have a protective role in pregnant women with HT who are at a higher risk of miscarriage. In fact, in women who suffered a pregnancy loss, the Se content in hair was significantly lower compared to control cases.<sup>21</sup> The study of pregnant women has been of particular interest in the field of HT, and these patients have been characterized by an increased risk of miscarriage, preterm delivery, and development of thyroid dysfunction after delivery.<sup>22</sup> In a prospective, randomized, placebo-controlled study conducted in Italy, Se supplementation (200 µg/day) during and after pregnancy in TPO-Ab positive euthyroid women resulted in a lower incidence of postpartum thyroiditis and permanent hypothyroidism compared to the placebo group.<sup>23</sup> The same study also demonstrated that women who took Se supplementation showed lower TPOAb titers during the postpartum period and better thyroid ultrasound results compared to the untreated group. These study results are the first to demonstrate the clinical benefits of selenium supplementation in pregnant women with thyroid autoimmunity.

In Graves' disease (GD), the balance between oxidants and antioxidants is disturbed, not only in the acute phase of the disease, but also in the state of euthyroidism induced by anti-thyroid medications. Several studies have underscored the correlation of GD with impaired antioxidant activity. In patients suffering from GD, the use of anti-thyroid drugs has been shown to reduce oxidant generation and improve the imbalance of antioxidant/oxidant status.<sup>24</sup> In 2007, Wertenbruch et al. compared serum Se levels in patients with remission and relapse of GD and found that the highest serum Se levels (120 µg/l) were observed in the remission group, indicating the positive effect of Se levels on the outcome of GD. In addition, the authors showed that serum Se values and TSH-receptor antibody levels were positively correlated in the relapse group, whereas a negative correlation of both parameters was observed in the remission group. This observation supports the hypothesis that there is a positive effect of Se on thyroidal autoimmune processes.<sup>25</sup> One study from Croatia, a country where nutritional selenium levels are among the lowest in Europe, evaluated the effects of supplementation with a fixed combination of antioxidants such as vitamins C and E, beta-carotene and Se on superoxide dismutase activity, copper and zinc concentrations, and total antioxidant status in erythrocytes derived from a group of patients with GD who were treated with methimazole. The results showed that patients receiving antioxidant supplementation along with methimazole therapy achieved euthyroidism at a faster rate compared to those treated with methimazole alone.<sup>26</sup> In 2013, Pedersen et al. compared serum Se values in patients with newly diagnosed autoimmune thyroid disease and control cases from the Danish population, and observed significantly lower median serum Se values in newly diagnosed GD and HT cases compared with random control cases.<sup>27</sup>

The currently on-going GRASS (GRAves' disease Selenium Supplementation) trial studies selenium supplementation versus placebo in patients with hyperthyroidism. The objective is to investigate whether adjuvant selenium supplementation may be beneficial in the standard treatment of GD. The first patient was enrolled in December 2012 and the total trial duration is expected to be approximately 4 years.

Short-term use of Se supplementation has been shown to be well tolerated, and acute intoxication is very rare and has only been caused by accidental or suicidal intake. No serious adverse effects of Se supplementation have been reported, except a number of cases with complaints of gastric discomfort.<sup>20</sup> Conflicting results from epidemiological studies on Se and diabetes have been reported. Higher serum Se concentration has been associated with higher prevalence of type-2 diabetes in several cross-sectional studies, but longitudinal studies have not supported a role.<sup>28,29</sup>

There is a level of Se above which there may be toxicity and no beneficial effects of Se supplementation.<sup>30</sup> In 2008, Negro observed that a cost/benefit evaluation of Se supplementation is warranted, considering that the final result of autoimmune chronic thyroiditis is hypothyroidism and that Se supplementation may delay Levothyroxine initiation; however, if hypothyroidism develops, substitutive treatment with Levothyroxine has no side effects and it is a very cheap drug.<sup>31</sup>

In conclusion, reports suggest that Se potentially modifies the natural history of autoimmune thyroiditis and postpartum thyroiditis by protective effects on the thyroid gland. In Graves' disease it appears to have a beneficial effect, but further studies are warranted to elucidate the role of Se in this disease.

## Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

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