

# The Role of Selenium in Thyroid Autoimmunity: A Review

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## ABSTRACT

Autoimmune thyroid diseases, including Graves' disease and Hashimoto's thyroiditis, are the most common autoimmune conditions in humans. There is significant morbidity associated with thyroid autoimmunity, and typically ongoing management is required to control disease presentation and reduce sequelae. Thyroid tissues contain the highest concentration of selenium in the body, owing to selenium's crucial role in glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases. Selenium deficiency is associated with sub-optimal thyroid function, and has been shown to be a risk factor for both Hashimoto's thyroiditis and Graves' disease. As a therapeutic intervention, selenium has been shown in a number of studies to reduce thyroid antibodies, although there remains limited information regarding its impact on clinical outcomes. In Graves' disease, and specifically in Graves' ophthalmopathy, selenium appears to play a beneficial role in altering disease progression and improving ophthalmic symptoms. The various functions of selenium in thyroid autoimmunity are reviewed.

**Keywords:** Graves' disease; Hashimoto's thyroiditis; Hypothyroidism; Selenium; Autoimmune thyroid disease

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## INTRODUCTION

Thyroid tissues contain high amounts of selenium in the form of selenocysteine, an amino acid incorporated into selenoproteins including glutathione peroxidases (GPx), thioredoxin reductases (TRx), and iodothyronine deiodinases (IDD).<sup>1-3</sup> These proteins play a role in oxidative damage prevention and thyroid hormone metabolism (Figure 1). Through its integration in GPx, selenium protects thyrocytes from oxidative damage incurred by exposure to hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>).<sup>4</sup> H<sub>2</sub>O<sub>2</sub> is required for thyroid hormone production, but must be rapidly degraded by selenium-containing enzymes in order to preserve thyroid tissues.<sup>5</sup> Selenium also seems to be linked to T cell functioning, T-helper 1 (TH1) to T-helper 2 (TH2) balance, and macrophage function, suggesting a complex, multifaceted role in immune regulation.<sup>1,5-10</sup> Selenium's crucial role in thyroid function, and thus in metabolism, is demonstrated by its physiological priority in thyroid tissues. In transient deficiency

due to critical illness or decreased intake, selenium is preferentially preserved for thyroid function.<sup>11,12</sup>

The high concentration of selenium in thyroid tissues, coupled with a well-elucidated role in thyroid metabolism through selenoprotein functioning, have lead to interest in selenium supplementation in thyroid dysfunction.

## SELENIUM DEFICIENCY AND THE ENVIRONMENT

Soil and water levels of selenium are dependent on surrounding geological features.<sup>13</sup> Areas with low selenium levels geologically have corresponding low levels of selenium present in the local food chain.<sup>14</sup> In areas where food consumption consists mainly of regionally produced foodstuffs, low soil

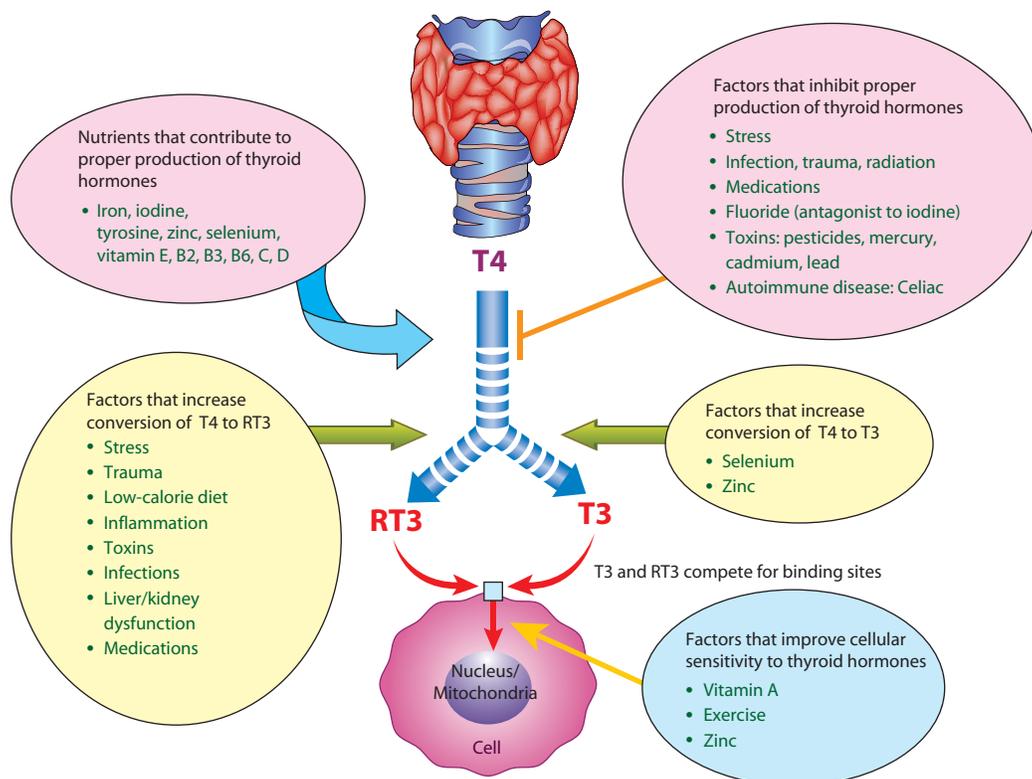


Figure 1: Factors that affect thyroid function. T4, thyroxine; T3, triiodothyronine; RT3, reverse triiodothyronine.

levels of selenium can lead to selenium deficiency. In extreme cases, such as central Asia, conditions such as Keshan disease (KD) and Kashin-Beck disease (KBD) are associated with significant selenium deficiency.<sup>10,15</sup>

KD, named for a county in China where a significant outbreak occurred in the 1930s, is a dilated cardiomyopathy associated with low selenium levels.<sup>16</sup> The condition is characterized by enlarged mitochondria, reduction in oxidative phosphorylation, low selenium levels and decreased GPx levels.<sup>16</sup> Although supplementation with selenium has been shown to reduce incidence of KD, it is likely that the etiology of KD is more complex, and involves genetic predisposition and viral infection.<sup>17,18</sup>

KBD is a form of chondrodystrophy occurring in areas of rural China, that is associated with reduced selenium and iodine status, mycotoxin exposure, coxsackie virus infection, and environmental toxin exposure. Supplementation with selenium in some areas with endemic KBD has demonstrated improvements in disease progression as well as prevention.<sup>19</sup> Although in other areas, correcting iodine deficiency was effective at disease reduction while selenium conferred no benefit.<sup>20</sup> Iodine deficiency, also common in areas with low selenium, has been implicated as a risk factor for KBD and if not corrected before selenium supplementation, hypothyroidism may persist.<sup>16</sup>

At less severe levels, deficiency of selenium is linked to depressed mood, with improved mood following repletion.<sup>21</sup> Observational data suggests an association between selenium intake and risk of hypothyroidism.<sup>22</sup> Assessment of selenium intake in an Austrian cohort through interview-based dietary data collection suggested that hypothyroid patients had, on average, lower intake of selenium.<sup>22</sup> At a physiological level, serum selenium has been shown to be inversely associated with thyroid-stimulating hormone (TSH) levels.<sup>23</sup>

Some evidence suggests there is a two-way relationship between selenium status and thyroid hormones, with animal models suggesting that thyroid hormones themselves regulate selenoprotein expression and selenium status.<sup>24</sup> Even in euthyroid individuals, reduced selenium status has been shown to be associated with decreased

conversion of triiodothyronine (T3) to thyroxine (T4),<sup>25</sup> Selenium's regulatory role on autoimmunity is apparent in both hypo- and hyperthyroid forms of autoimmune disease. Indeed, a population-based study has demonstrated an association between low selenium levels and newly diagnosed Grave's disease.<sup>26</sup>

## SELENIUM AND HEAVY METALS

Several heavy metals have been investigated for their role in thyroid autoimmunity and thyroid dysfunction. In particular, mercury and cadmium have demonstrated an ability to negatively impact thyroid health.<sup>27</sup> Cadmium has a complex array of effects on thyroid function, including decreased secretion of T4 by thyroid follicular cells, and altered peripheral conversion of T4 to T3 by deiodinase enzymes.<sup>28,29</sup> Selenium plays an important role in reducing cadmium levels by binding to cadmium and facilitating its excretion through bile.<sup>27</sup> Elevated mercury levels have been linked to increased Tg levels, with mechanistic data demonstrating that inorganic mercury affects thyroid peroxidase (TPO) and both inorganic as well as organic mercury inhibit thyroglobulin iodination.<sup>30,31</sup> Selenium has an antagonistic relationship with mercury, demonstrating a protective effect when mercury levels are elevated.<sup>32</sup>

## SELENIUM AND IODINE

Selenium is not the only micronutrient essential to optimal thyroid function. Zinc, vitamin D, vitamin A, and most importantly iodine, play crucial roles in thyroid hormone production and subsequent thyroid health.<sup>27,33</sup> The roles of zinc, vitamin D, and vitamin A in thyroid function are beyond the scope of this review, but the complex interaction and co-dependence between iodine and selenium warrants discussion (Figure 1).

In animal models, selenium has been shown to exert protective effects in cases of excessive iodine ingestion.<sup>34</sup> Similarly, human studies have demonstrated that when addressing iodine deficiency through

supplementation, co-administration of selenium is important to maintain adequate GPx function.<sup>35</sup> Population-based studies have demonstrated increases in thyroperoxidase antibody (anti-TPO) prevalence in areas practicing iodine fortification,<sup>36</sup> with possible protective effect with selenium adequacy.<sup>37,38</sup> It is hypothesized that iodine excess induces thyroid damage via selenoprotein inactivation, subsequently increasing the relative need for selenium to maintain adequate function of thyroprotective enzymes.<sup>34</sup>

While adequate selenium status may be protective in iodine excess, selenium deficiency has been shown to be protective in iodine deficiency. In cases of combined selenium and iodine deficiency, normalizing selenium levels without iodine supplementation is shown to aggravate hypothyroidism.<sup>39</sup> In a selenium and iodine deficient population in northern Zaire, both euthyroid and hypothyroid patients with iodine deficiency saw decreased thyroid function following selenium supplementation.<sup>40</sup>

It is postulated that the aggravation of hypothyroidism in an iodine and selenium deficient individual by selenium supplementation may occur through an increase in thyroxine metabolism via selenium containing IDD<sub>s</sub>.<sup>39</sup> The resulting decrease in T4 in individuals with iodine-depleted thyroid leads to an aggravation of hypothyroxinemia and hypothyroidism.<sup>39</sup> Selenium deficiency in a developing fetus may decrease thyroxine metabolism, decrease T4 utilization in less important peripheral tissues, thereby preserving and prioritizing T4 utilization in nervous tissue.<sup>39,40</sup>

## THYROID AUTOIMMUNITY

Autoimmune thyroid disease incidence is on the rise and is now estimated to affect from 5% to 10% of the population.<sup>7,41–43</sup> The thyroid gland is particularly susceptible to autoimmunity, likely the result of a complex additive effect involving environmental sensitivity, genetic predisposition, the oligoelement requirement of thyroid tissues, and the unique qualities of the thyroid cell defense system.<sup>43,44</sup> Attributed to its integral role in thyroid tissue, selenium deficiency confers increased risk of autoimmune thyroid disease, and will increase

both duration and severity of disease.<sup>43</sup> A number of studies have demonstrated selenium's ability to decrease markers of autoimmune thyroid conditions, specifically anti-TPO and thyroglobulin levels.<sup>45–47</sup>

## HASHIMOTO'S THYROIDITIS

Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism and the most prevalent autoimmune disease.<sup>48</sup> The infiltration of lymphocytes into thyroid tissue, characteristic of HT, can lead to thyrocyte destruction and ultimately hypothyroidism.<sup>41</sup> Diagnostically, HT is characterized by elevated antibodies to thyroperoxidases and thyroglobulin.<sup>48</sup> A finding of antibody positivity confirms HT, but does not indicate current hypothyroidism or that development of hypothyroidism is a certainty. Observational studies and mouse models have linked thyroglobulin antibody elevations to the initial or innate immune response early in HT, and elevated anti-TPO to later adaptive immune response.<sup>49,50</sup> TSH is the routine screening test to assess thyroid function. An elevated TSH occurs later in the immune response in HT, leading to a finding of elevated anti-TPO, which is the most common indicator of HT as the cause of hypothyroidism.<sup>51</sup>

Treatment of hypothyroidism due to HT involves the normalization of elevated TSH levels through supplementation with L-thyroxine, with a goal of restoring the patient to a euthyroid state.<sup>4</sup> This may decrease auto-antibodies due to a decrease in TSH and thyroid tissue stimulation.<sup>52</sup> Selenium supplementation in individuals with HT reduces oxidative stress through GPx and TRx function, and lowers H<sub>2</sub>O<sub>2</sub> levels.<sup>4</sup> Several studies have demonstrated the association between selenium deficiency and HT,<sup>33,53,54</sup> and the impact of selenium on decreasing autoimmune laboratory parameters in HT.<sup>45,55–58</sup> While laboratory parameters did improve in many studies, results remain controversial, and more importantly the clinical significance of this impact is not yet well established.

A 2003 randomized controlled trial (RCT) designed to assess the impact of 6 months of selenium

supplementation in conjunction with levothyroxine administration in patients with autoimmune thyroiditis demonstrated a significant decrease in anti-TPO antibodies in the intervention ( $n=35$ ) versus control ( $n=30$ ) group, but did not impact thyroid hormone levels, or anti-Tg levels.<sup>59</sup> The study did report significant increases in overall mood and feelings of well being in the intervention group, consistent with earlier findings.<sup>59</sup> Previous work suggests changes in mood with selenium supplementation may be the results of altered dopamine or serotonin metabolism.<sup>55</sup>

A similar 2002 study demonstrated a significant reduction in anti-TPO in the intervention group ( $n=36$ , 200 µg of selenium selenite and L-T(4) to TSH normalization for 6 months) versus those in a control group treated with L-T(4) only. The study reported the most dramatic reduction in anti-TPO occurring in individuals with the highest initial antibody levels. Those with anti-TPO levels over 1200 IU/mL experienced a mean reduction of 40%, while those under 1200 IU/mL experienced a mean reduction of 10%.<sup>61</sup> A similar study involving anti-TPO positive euthyroid patients supplemented for 6 months with 200 µg of selenium showed no reduction in anti-TPO or quality of life benefit.<sup>62</sup>

Although there are a number of small intervention trials demonstrating significant reduction in anti-TPO antibodies with selenium supplementation, factors including baseline selenium status and population homogeneity limit the applicability of results to varied populations. Although four studies included in a 2013 Cochrane Review demonstrated significant decreases in anti-TPO levels, with one study reporting subjective improvements in quality of life, reviewers concluded insufficient evidence for clinical application due to unclear blinding strategies, and the absence of health-related quality of life scores.<sup>37</sup>

Currently, a multi-centred RCT is underway to assess the impact of 12 months of selenium supplementation in patients with autoimmune thyroiditis treated with levothyroxine (Trial Registry Number: NCT02013479). The CATALYST study (the chronic autoimmune thyroiditis quality of life selenium trial) is taking place across four clinic sites in Denmark involving 472 participants, and will be the first to assess quality of life as a primary outcome.<sup>63</sup>

## GRAVES' DISEASE

GD is an autoimmune disorder primarily associated with hyperthyroidism, but it also involves non-thyroid associated outcomes including pretibial myxedema, acropachy, and most commonly Graves' ophthalmopathy (GO).<sup>64</sup> The complete etiology of GD is unknown, but it is thought it is due to a complex interaction between genetic risk, infections, environmental factors (including smoking), stress, and nutrient deficiency.<sup>65</sup> The pathogenesis of GD involves autoimmunity as in HT, but rather than lead to tissue destruction, the immune dysfunction leads to antibodies against TSH receptors resulting in increased thyroid activity and thyroid hormone production. This overproduction causes thyroid enlargement via thyroid follicular cell hyperplasia.<sup>66</sup> Owing to its multifaceted role in thyroid health, selenium has long drawn attention as a possible treatment option for both GO and GD itself.<sup>67,68</sup>

There are a number of possible mechanisms through which selenium may positively influence the course of GD and GO. As an important component of both GPx and TRx, selenium may influence the regulation of T3 levels in GD.<sup>69</sup> There is an elevation in oxidative stress in the course of GD as H<sub>2</sub>O<sub>2</sub> levels rise with increased TSH receptor stimulation, leading to a higher requirement of selenium containing enzymes.<sup>8,70</sup> Along with increased H<sub>2</sub>O<sub>2</sub> production, GD leads to the up-regulation of inflammatory cytokines. Selenium helps to decrease these inflammatory cytokines via NF-kappa-B inhibition, thereby attenuating the inflammatory response in GD (Trial Registry Number: NCT01611896).<sup>71,72</sup>

While there are no RCTs assessing direct benefit of selenium in the treatment of GD, there is an ongoing double-blind placebo controlled clinical trial, the Graves' Disease Selenium Supplementation trial (GRASS), taking place involving seven Danish medical centres which aims to establish the clinical role of selenium in the treatment of GD (Trial Registry Number: NCT01611896).<sup>73</sup>

## GRAVES' OPHTHALMOPATHY

GO is the most common extrathyroidal outcome of GD, occurring in up to 60% of cases, and involves

serious reduction in quality of life.<sup>74</sup> It should be noted the significant effect smoking has on risk and course of GD, and the notable, dramatic increase in GO occurrence with smoking.<sup>74</sup> Smoking has been shown to increase both the differentiation of orbital preadipocytes<sup>75</sup> and glycosaminoglycan production,<sup>76</sup> two processes leading to the notable exophthalmia defining GO. Interestingly, plasma selenium concentrations have been shown to be lower in smokers versus non-smokers.<sup>77</sup>

Case-controlled studies have demonstrated that selenium levels are significantly lower in GD patients who develop GO, compared with those with GD alone, suggesting selenium deficiency may be an independent risk factor for GO development in GD.<sup>78</sup> Typical treatment options for GO include corticosteroids, radiotherapy, surgical decompression, and immunotherapy,<sup>74</sup> and there is increasing evidence that selenium supplementation is beneficial in preventing, stabilizing, and reducing GO.<sup>79,80</sup>

A 2011 double-blind RCT demonstrated that supplementation with 200 µg of selenium per day significantly decreased GO, improved quality of life, and decreased worsening of disease.<sup>68</sup> The benefit of supplementation remained even after therapy was withdrawn for 6 months. It should be noted these results occurred in a population in a selenium-deficient region.<sup>79</sup> Based on these results, it may be clinically appropriate to recommend selenium supplementation in individuals with GO for 6 months – especially those with low selenium status.

## MATERNAL HEALTH

Selenium supplementation has shown benefit in the treatment of both male and female infertility,<sup>81</sup> and has become a therapy of interest in reproductive health due to evidence of decreased risk of maternal thyroid dysfunction and postpartum thyroiditis with supplementation.

A 2007 study demonstrated that supplementation with selenomethionine 200 µg/day during pregnancy and the postpartum period in euthyroid women with anti-TPO antibodies decreased the risk of permanent hypothyroidism and postpartum

thyroiditis compared with placebo. Anti-TPO antibody levels were significantly reduced in the treatment groups, and thyroid ultrasound showed improved echogenicity patterns.<sup>46</sup> A 2014 study demonstrated that mild to moderate iodine deficient women experienced a decrease in free T4 and TSH compared with controls when supplemented with 60 µg of selenium starting at 12 weeks' gestation.<sup>47</sup> This change occurred only in women who were already thyroid antibody positive, but there was no statistically significant change in anti-TPO antibodies.<sup>47</sup> Observational studies have also demonstrated an association between low serum selenium levels and incidence of hyperthyroidism during pregnancy,<sup>82</sup> suggesting selenium status may be a risk factor for both hyper- and hypothyroidism. Moreover, animal models suggest that maternal supplementation of selenium not only decreased thyroid dysfunction in treated mice, but also benefited health parameters in their breast-fed offspring.<sup>83</sup>

A 2013 Cochrane review of treatment strategies for hypothyroidism before and during pregnancy concluded that selenium did demonstrate positive impact on both postpartum thyroid function and rates of postpartum thyroiditis, but found no differences in rates of pre-eclampsia or preterm birth.<sup>84</sup>

## CONCLUSION

Selenium supplementation decreases anti-TPO antibodies in autoimmune thyroiditis with varying impact based on baseline thyroid function and initial anti-TPO levels. While several studies report increases in subjective well-being and mood, there remains unclear evidence regarding the clinical impact of lowering anti-TPO on quality of life outcomes. Ongoing studies reporting on changes in health-related quality of life outcomes will offer more definitive guidelines of clinical applications of selenium supplementation in Hashimoto's thyroiditis and if broad recommendations for supplementation are warranted. Currently, the combined safety profile and probable benefit would reasonably suggest the consideration of selenium supplementation in patients is warranted. Selenium status is

an indicator of risk for development of Graves' ophthalmopathy in patients with Graves' disease, and has shown benefit in both reducing risk of GO development and treatment of mild to moderate pre-existing condition. In pregnant women with anti-TPO antibodies, supplementation with 200 µg of selenium should be recommended

during pregnancy and in the postpartum period. Individuals in populations with low iodine status should avoid selenium supplementation until iodine levels are normalized.

## DISCLOSURE OF INTEREST

The author has nothing to report.

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