

The Role of Iodine and Selenium in Autoimmune Thyroiditis

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Key words

- iodine
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Abstract

Iodine and selenium (Se) are both essential elements to thyroid hormone economy, while they represent key players in the development of autoimmune thyroiditis.

Chronic high iodine intake has been associated in various studies with increased frequency of autoimmune thyroiditis. In susceptible individuals, iodine excess increases intra-thyroid infiltrating Th17 cells and inhibits T regulatory (TREG) cells development, while it triggers an abnormal expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in thyrocytes, thus inducing apoptosis and parenchymal destruction. As was shown in a mouse model, high iodine supply leads to changes in the immunogenicity of the thyroglobulin molecule, upregulation of vascular intercellular adhesion molecule-1 (ICAM-1), and reactive oxygen species (ROS) generation in the thyrocytes. Serum Se levels were found decreased

in Hashimoto thyroiditis and especially in Graves' disease as well as in thyroid-associated ophthalmopathy patients, the levels being related to the pathogenesis and outcome. Selenium is strongly involved, via the variable selenoproteins, in anti-oxidant, redox, and anti-inflammatory processes. Selenium enhances CD4⁺/CD25⁺ FOXP3 and T regulatory cells activity while suppressing cytokine secretion, thus preventing apoptosis of the follicular cells and providing protection from thyroiditis. Selenium supplementation may be useful in autoimmune thyroid diseases, though, while usually well-tolerated, it should not be universally recommended, and it is also likely to be helpful for those with low Se status and autoimmunity. Broadly speaking, the achievement and maintenance of "selenostasis" as well as adequate urinary iodine excretion are mandatory to control disease, while, putatively, they may additionally be critical to preventing disease.

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Introduction

Autoimmune thyroiditis (AIT), including Hashimoto Thyroiditis (HT) which is the most common form, is an organ-specific disorder characterized by a profound interaction between genetic and environmental factors [1,2]. The incidence of AIT is on the rise in many parts of the world. It exhibits a prevalence of about 12% depending on age (more frequent in postmenopausal women), gender (10 times more frequent in women) and race, being more common in Caucasians than in Blacks [3].

For a wide-ranging and analytic presentation of the environmental factors and their interaction with genetics, the reader is referred to several recent overviews [4–9]. This review discusses the pivotal role that both iodine and selenium may play in the development of AIT, while the main

focus will be an update of the molecular mechanisms involved in the complex pathogenetic interactions of AIT.

Iodine

Environmental iodine deficiency, long a cause of iodine deficiency disorders round the world, has been substantially reduced thanks to the implementation of programs of mandatory food iodine fortification in numerous countries. However, while this endeavor has led to the virtual eradication in these regions of severe iodine deficiency, it has in parallel resulted in an increase in the prevalence of AIT. Meanwhile, it has recently been noted in various parts of the world that a decrease in iodine intake results in a lowering of the incidence of AIT [10].

The effect of a cautious iodization program aiming to adjust iodine intake to a low recommended level was evaluated in 2 identical cross-sectional population studies before and 4–5 years after mandatory iodine fortification of salt implemented in Denmark [11]. An increase in the prevalence of both thyroid peroxidase antibody (TPOAB) and thyroglobulin antibody (TgAB) was observed 4–5 years after initiation of the program mostly in young women and at low concentrations of antibodies [11].

Excessive iodine intake for a period of 5 years in a population-based study with 1085 participants in Sao Paulo resulted in excessive median urinary iodine excretion (MUIE) above 300 µg/l and 400 µg/l, in 45.6 and 14.1%, of the participants, respectively [12]. Additionally, an increase in the prevalence of AIT to 17% has been reported, 8% of the individuals being detected with hypothyroidism, while incidence of hyperthyroidism amounted to 3.3% of the study population.

More crucially, excessive iodine intake (MUIE > 300 µg/l) could well become a serious public health concern because of its ability to substantially increase subclinical hypothyroidism and AIT rates [13]. This was recently documented in 2 Chinese communities manifesting both high (261 µg/l) and normal (145 µg/l) iodine intake levels [14], as well as in the Pescopagano survey in Italy. In the latter study conducted in a southern Italian village, 1411 people were examined in 1955 and 1148 in 2010 following the introduction of the salt iodization program [15]. The prevalence of hypothyroidism was found to be higher in 2010 vs. 1995 (5.0 vs. 2.8%, $p < 0.005$), chiefly due to an increased rate of subclinical hypothyroidism (SCH) in subjects younger than 15 years old. In parallel, TPOAB levels (19.5 vs. 12.6%; $p < 0.0001$) and HT rates (14.5 vs. 3.5%; $p < 0.0001$) were higher in 2010 than in 1995 [15].

It is therefore evident that even small differences in iodine intake can result in quite large differences in prevalence of thyroid diseases, given that iodine intakes both slightly below and above the recommended levels have been shown to be associated with an increase in disease risk [16]. Based on the above data, the best approach would be adherence to a narrow iodine intake interval so that a given population may achieve prevention of IDD and minimalization of the risk of autoimmune thyroid disease.

In various animal models, such as the BioBreeding/Worcester (BB/W) rat [17] and especially the nonobese diabetic (NOD) mouse [18], an autoimmune thyroiditis-prone animal model, the administration of iodine significantly enhanced and accelerated, in a dose-dependent manner, the incidence of AIT and thus corroborated the results that excess iodine is associated with thyroid autoimmunity.

Iodine and Autoimmune Thyroiditis: Mechanisms of Induction

The importance of Tg, which was the first thyroid-specific susceptibility gene to be identified, challenged by iodine in the induction of AIT has been well known since 1956 [19]. In 1992 it was demonstrated that a high iodine diet in the BB/W rat, which results in spontaneous development of type 1 diabetes mellitus and lymphocytic thyroiditis, increases significantly the incidence of thyroiditis, while a low iodine diet has the opposite effect [20]. The authors also observed that the extent of Tg iodination is responsible for inducing lymphocytic thyroiditis in rat. Since then, it has been established that iodine triggers autoim-

munity by inducing the generation of “cryptic peptides” within the Tg molecule, which in turn encompass “cryptic epitopes” on Tg with immunostimulatory properties [21]. In this line of evidence, it was demonstrated that TgABs are directed to the epitope B of Tg more frequently in iodized salt consumers than in nonconsumers [22]. Moreover, while autoreactive T cells may proliferate in response to normal Tg, no reaction was seen in non-iodinated Tg [23,24]. Iodine excess upregulates the expression of vascular intercellular adhesion molecule-1 (ICAM-1) on the surface of cell types including thyrocytes [25]. During the process of iodine organification in the thyroid, the generated reactive oxygen species (ROS), and especially hydrogen peroxide (H₂O₂), can influence ICAM-1 expression and activate its transcription synergistically with iodine via the MAPK pathway [26,27].

In HT, an immunologic reaction is triggered in thyrocytes induced by the production of inflammatory cytokines, particularly interferon-γ (IFN-γ), from T helper (Th)1 type lymphocytes [28]. It has thus been hypothesized that IFN-γ induces MHC class II expression on hemopoietic and epithelial cells and activates macrophages and ICAM-1, leading to leukocyte recruitment to the site of inflammation [29]. This postulated promotion of autoimmune disease activity by IFN-γ is, however, till now controversial, since it was shown that IFN-γ may possess disease-suppressing activities [30]. NOD.H-2h4 transgenic mice, which had serum IFN-γ levels similar to wild-type mice, showed upregulation of MHC class II on thyrocytes but failed to develop spontaneous thyroiditis. Immunization with murine thyroglobulin resulted in milder disease and decreased frequency of activated CD4+ lymphocytes in the cervical lymph nodes [31]. The latter suppressive effect was confirmed, as blockade of systemic IFN-γ enhanced disease activity suggesting a local disease-limiting role of IFN-γ in autoimmune thyroiditis. Potential mechanisms for this activity might be a decrease of the amount of thyroid antigens available for uptake by thyroid-resident antigen presenting cells (APCs), as well as the induction of regulatory proteins, which are members of the suppressor of the cytokine signaling (SOCS) family, particularly SOCS-1, that alleviate or terminate immunostimulatory signals [32].

On the other hand, IFN-γ induces protein 10 (IP-10), which was identified as a chemokine exerting its function through binding to chemokine (C-X-C motif) receptor 3 (CXCR3) [33]. IP-10 and its receptor, CXCR3, appear to contribute to the pathogenesis of various organ-specific autoimmune diseases such as HT and Graves' disease (GD). It has been suggested that IP-10 levels might be a marker of the severity of the autoimmune process, as they were reported significantly higher in patients with a hypoechoic ultrasonographic pattern, which is a sign of a more severe lymphomonocytic infiltration in patients with thyroiditis [33]. These results are supported by an experimental study showing that high iodine intake in rats was associated with increased CD4(+) T cells and serum IP-10, indicating that high iodine consumption aggravates the inflammatory reaction in the thyroid by increasing serum IP-10 levels after induction of AIT with bovine thyroglobulin [34].

Other studies in NOD.H-2h4 mice have revealed a major role of Th17 cells in iodine-excess-induced AIT, given that they are capable of promoting an inflammatory reaction, which is negatively regulated by Th1, T helper type 2 (Th2), and regulatory T (TREG) cells [35,36]. Thus, high iodine intake facilitates the production of Th17 cells from T cells and inhibits the development

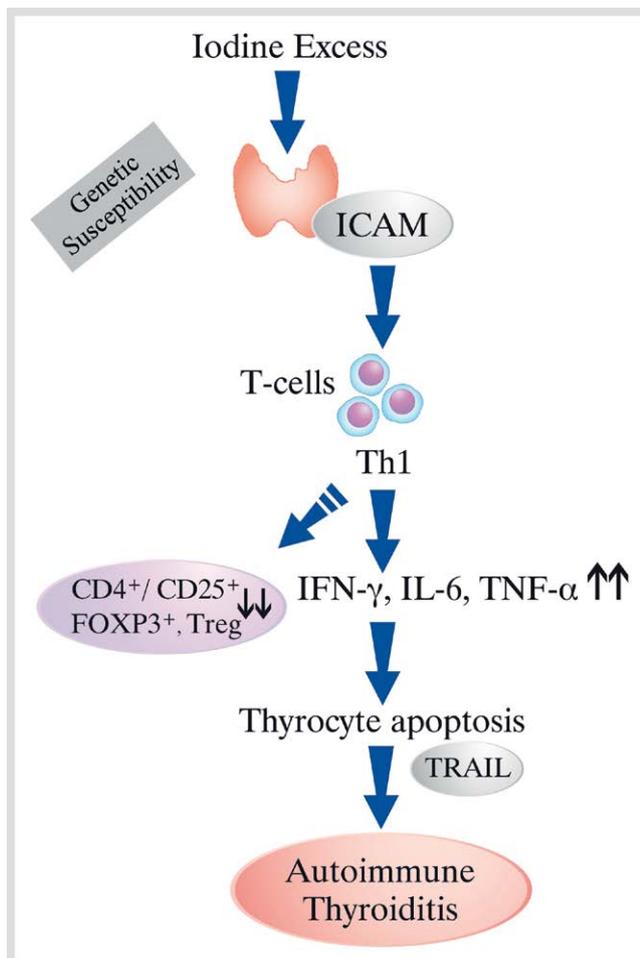


Fig. 1 High iodine intake may in susceptible individuals lead to an increased expression of ICAM-1 on thyroidal follicle cells, induce T helper cells to differentiate towards T helper 1 (Th1), decrease CD4+/CD25+, FOXP3 and TREG, increase cytokine secretion, induce apoptosis via abnormal TRAIL expression and mediate thyroid destruction. ICAM: Intracellular adhesion molecule; TRAIL: Tumor necrosis factor (TNF) related apoptosis-inducing ligand (TRAIL); FOXP3: Forkhead/winged helix transcription factor p3 (FOXP3). (Color figure available online only).

of TREG cells. Interestingly, the increased concentration of serum IL-17 was inversely correlated with patients' residual thyroid function, while the expressed intra-thyroid IL-17 was correlated with the degree of local fibrosis [36]. The increased Th17:Th10 ratio that was found in HT patients after stimulation with thyroid specific self-antigens, together with an elevated baseline production of interleukin-6 (IL-6), of tumor growth factor- β 1 (TGF- β 1) and of mRNA encoding forkhead/winged helix transcription factor p3 missing exon 2 (FOXP3 Δ 2), may contribute to the skewing towards Th17-cell responses in HT [36]. Furthermore, the expression of signal transducer and activator of transcription 3 (STAT3) was much higher, while the expression of forkhead/winged helix transcription factor p3 (FOXP3) was seen to be significantly lower and the proportion of Th17 cells much larger [37] (○ Fig. 1). Here, emphasis should be placed on the key role of the FOXP3 gene in the development of TREG cells, in view of the fact that mutations in the FOXP3 gene cause severe systemic autoimmune diseases in humans and in mice, while polymorphisms of the FOXP3 gene may alter FOXP3 function and/or expression and drive the genetic susceptibility to AITD [37].

Elevated iodine supplementation (315 μ g and 615 μ g daily, respectively) in transgenic antibody-devoid mice, TAZ10, which are immunologically prone to AIT, alters the immune cell profile [CD8⁺ and TREG cells, natural killer (NK) cells] and cytokine production, without affecting disease progression [38]. In contrast, enhanced iodide intake in NOD.H2(h4) mice accelerates the incidence and severity of spontaneous autoimmune thyroiditis, most probably via apoptosis of thyrocytes by CD4 and CD8 T cells and subsequently disruption of the immunoregulatory mechanisms [39]. A number of apoptosis signaling pathways, including Fas ligand and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), are thought to be implicated in destructive thyroiditis. It is thus probable that excessive iodine induces TRAIL abnormal expression in the thyroid, promotes follicular cells apoptosis, and mediates thyroid destruction [40].

Selenium and Autoimmune Thyroiditis

In organisms, selenium either exists as low-molecular weight compounds, such as selenite, selenomethionine, methylselenol or selenomethylselenocysteine, or is assimilated as selenocysteine (amino acid; Sec) into selenium-containing proteins (selenoproteins). The thyroid contains more Se g/tissue than any other organ. Selenium is essential for the deiodination process of thyroxine by deiodinases (DIOs), and for the degradation of excessive generation of H₂O₂, via glutathione peroxidases (GPXs) and thioredoxin reductase (TRX) [41,42]. Therefore, many studies have been conducted in AIT patients in several countries with variable Se content in the soil with the aim of examining the effects of Se administration on the AIT markers [43]. Most of the studies, which applied organic selenium in the form of selenomethionine, showed a decrease of the TPOAB, while several other studies, using the inorganic form selenite, did not document any effect on the thyroid antibodies as compared to placebo. Two meta-analyses have confirmed a positive effect of Se on TPOAB and improvement of mood in HT [44,45], while another meta-analysis in the Cochrane library concluded that the evidence to support or refute the efficacy of selenium supplementation in patients with HT is incomplete [46]. In a very recent double-blind, randomized, placebo-controlled study including 230 women with singleton pregnancies, it was shown that low-dose Se (60 μ g/day) supplementation did not affect TPOAB but tended to change thyroid function, by decreasing TSH and FT₄, in thyroid antibody positive patients [47]. The divergent results of the various studies may be due to the inhomogeneity of the groups of patients as well as to the variability of the basal Se and iodine state, the duration of the study time and the Se compounds applied [48].

Serum Se levels have been reported slightly lower in patients with AIT than in controls in a study performed in lower Austria [49]. Also, in another study designed in Denmark, patients with newly diagnosed AIT, especially GD, had significantly lower serum Se concentrations compared with random controls, indicating a potential link between inadequate selenium supply and overt autoimmune thyroid disease, especially GD [50].

In the same line of evidence, serum Se levels were found low, as compared to controls, in HT and especially in GD patients, while high Se levels (>120 μ g/l) were associated with remission and better outcome [51]. Moreover, serum Se levels were lower in patients with thyroid associated orbitopathy (TAO) as compared

with GD in an Australian study population with marginal selenium status [52]. These findings underscore the association of Se deficiency and thyroid autoimmunity and strongly indicate that low Se levels may reflect an increased risk factor for TAO in patients with Graves' disease. Se supplementation in GD patients with mild TAO statistically significantly improved ocular involvement and Quality of Life, while it slowed disease progression following 3 and 6 months treatment [53].

These results thus point to the possibility that patients might benefit from an improvement in their Se status, both as a means of reducing the individual autoimmunity risk as well as to remedy a Se deficiency, which often develops during the course of illness.

Mechanisms of Selenium Action

Selenium has variably been linked to thyroid autoimmunity. Besides the regulatory role that Se possesses in the deiodination of thyroid hormones, being a central constitutional element of the DIOs, Se neutralizes, via GPX1 and GPX3, the diffusion and activity of overproduced H_2O_2 and thus, it conserves the integrity of the thyrocytes [54,55]. Accordingly, it was shown that by means of a conditional gene knockout strategy, ablation of Sec tRNA[Ser]Sec results in the loss of expression of the whole selenoprotein set, or selenoproteome, in both hepatocytes and T cells [56].

CD4+T cells can differentiate into either Th1 or Th2 cells, based on the activation of a pro-Th1 or a pro-Th2 environment [57]. High dietary Se may trigger an oxidative burst in response to T cell receptor (TCR) stimulation [57]. It is known that Th0 and Th1 clones may function as helper T cells, leading to production of autoantibodies against Tg and TPO [58]. TCR induces differentiation of CD+T cells into FOXP3 + TREG cells, which might be influenced by high dietary Se levels [59]. The reduction or functional abnormality of CD25+CD4+ TREG cells leads to the development of autoimmune disease. It is notable that, as was demonstrated in human leucocyte antigen DR3 (DRB1*0301) transgenic class II-knock-out nonobese diabetic mice, depletion of CD4+CD25+TREG cells prior to sodium iodide treatment induced destructive thyroiditis (68%) and exacerbates serum anti-Tg antibodies [60]. In an experimental study, inorganic Se inhibited in a dose-dependent manner the expression of HDL-DR molecules by reducing the radical oxygen species (ROS) in cultures of human thyrocytes exposed to IFN- γ [61]. Se supplementation in patients with AIT affects dose-dependently IL-2 and other cytokines variably involved in the pathogenesis of AIT [62] (• Fig. 2).

Selenium may indirectly inhibit TNF activation and cytokine release. It is noteworthy, that by increasing Se supplementation, receptor activator for nuclear factor- κ B ligand (RANKL) that is related to TNF- α activation may be reduced [57]. In this line of evidence, in an experimental study investigating the effects of SeMet on proinflammatory cytokines release from monocyte and lymphocytes of patients with untreated HT, a significant inhibition of IFN- γ and IL-2 by SeMet was demonstrated, an effect that was potentiated when combined treatment with LT4 and SeMet was applied [63]. Thus, Se exhibits directly and indirectly anti-inflammatory and antioxidative actions, which have been variably revealed in studies on immune cells from humans and animals. In this connection, Se supplementation as selenite (50 μ g/day or 100 μ g/day) increased both GPX1 and GPX4 activ-

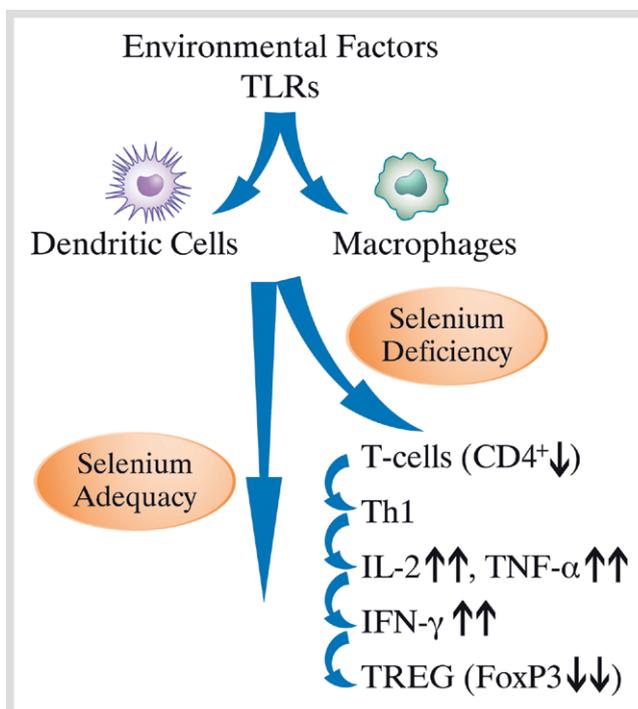


Fig. 2 Increased Se intake induces, via activation of the T cell receptor (TCR), differentiation of CD4+T cells into CD25+Foxp3+T regulatory cells (TREG). Adequate levels of Se intake do not affect T cells and T helper cells (Th0) vs. Th1 or Th2 differentiation. In contrast, Se deficiency, as an environmental factor, increases T-cell activation, while the T helper-1 (Th1)/T helper-2 (Th2) ratio may shift to a Th1-type response, increasing such cytokines as IL-2, TNF- α , IFN- γ , thereby reducing CD25+T regulatory cells (TREG)+Foxp3 and in parallel inhibiting an activation of dendritic cells and macrophages by Toll-like receptor (TLR) cells [57, 61]. TREG likely responds to different ligands for TLRs, thus the TLRs may exert different effects on TREG, depending on the degree of inflammation, resulting in more suppression or, in contrast, abrogation of suppression [68]. (Color figure available online only).

ity in lymphocytes from supplemented individuals compared to controls [63].

Macrophages, a class of myeloid leukocytes with phagocytic activity, detect the presence of signature molecules associated with microbial infection and tissue damage signaling properties [64]. An experimental study recently demonstrated that the enhanced release of H_2O_2 by macrophages after zymosan stimulation could be directly attributable to loss of glutathione peroxidase (GSH-Px) activity, thus leading to reduced peroxide breakdown [65]. Moreover, the influence of a selenium-deficient diet in mice and rats has been studied via investigation into the GSH-Px and secretory activities of peritoneal macrophages, mitogenesis of spleen cells, and adjuvant arthritis. Macrophage GSH-Px activity was significantly reduced by 9 weeks on the selenium-deficient diet. Interestingly, this reduction was associated with enhanced macrophage H_2O_2 release following zymosan stimulation after 12 weeks on the diet, this accompanied by a similar trend in chemiluminescence and reduced mitogenesis of spleen cell cultures to T and B cell mitogens after 8 weeks on the diet [65].

Mouse macrophages treated with lipopolysaccharide (LPS) demonstrated an increase in TXNRD1 expression, while the mRNA or protein expression of other selenoproteins, including GPX enzymes, was less affected, suggesting a significant role of TXNRD1 in the regulation of redox status in macrophages [66].

The incorporation of radiolabeled selenium into protein during LPS stimulation revealed TRXND1 as the only LPS-inducible selenoprotein in macrophages. In mice, macrophage-specific ablation of TRXND1 results in a drastic decrease in the expression of VSIG4, a B7 family protein known to suppress T cell activation [66]. These results suggest a link between selenium metabolism and immune signaling and identify TRXND1 as both a regulator and a regulated target in the macrophage gene expression network [66].

A significant association between the SEPS1–105 GA and AA genotypes and HT was found in a study investigating the role of polymorphisms in the promoter region of selenoprotein S, and SEPS gene, in the risk for developing HT [67]. It is of interest that male patients with HT represent a 3.94 times increased risk for carrying the A allele than women. This was the first study showing polymorphisms of selenoproteins associated with the risk of HT. To conclude, this review underlines the significance of the 2 essential elements, iodine and Se, for thyroid function and the fact that both excess and deficiency are intimately related with thyroid autoimmunity. It is thus apparent that dietary intake should imply maintenance of normal iodine and Se levels while avoiding either increased or diminished serum and/or urine excretion levels.

Conflict of Interest



The author declares no conflict of interest.

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