REVIEW PAPER

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The effect of selenium deficiency on thyroid deiodinase activity and the severity of oxidative stress in autoimmune thyroid diseases: a review of the literature

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ABSTRACT

Background. Selenium is a trace element of crucial importance for thyroid physiology, acting mainly through its incorporation into functionally specialised proteins, including the iodothyronine deiodinases and several enzymes engaged in antioxidant defence. Growing clinical and experimental data link suboptimal selenium status with an increased risk of autoimmune thyroid diseases (AITDs), particularly Hashimoto's thyroiditis, Graves' disease and postpartum thyroid dysfunction.

Material and methods. A structured search of the PubMed/MEDLINE database was performed using keywords related to selenium, deiodinases, oxidative stress and autoimmune thyroid disorders. The analysis primarily included English-language articles, with one regionally relevant Polish publication. Priority was given to randomised controlled trials, meta-analyses and large observational studies. Animal studies were included only where human data were insufficient.

Results. Selenium deficiency lowers DIO1 and DIO2 activity, impairing peripheral conversion of thyroxine to the active triiodothyronine. A concurrent decline in glutathione peroxidase and thioredoxin reductase activ-

ity promotes oxidative stress in thyrocytes and may amplify immune-mediated tissue injury. Clinical trials show that selenium supplementation (100–200 µg/day) can reduce anti-thyroid peroxidase antibody titres in Hashimoto's thyroiditis, improve mild Graves' orbitopathy and decrease postpartum thyroid dysfunction in women with positive thyroid antibodies.
Conclusions. Adequate selenium status is essential for thyroid hormone homeostasis and for limiting oxidative damage in AITDs. Selenium supplementation may benefit certain patients, particularly those in selenium-deficient populations. Nevertheless, its narrow therapeutic window and considerable genetic variability in selenium metabolism require individualised supplementation.

1. Introduction

Selenium contributes to antioxidant defence, immune regulation and thyroid hormone metabolism [1]. It helps maintain cellular redox balance, limits oxidative damage, and participates in DNA synthesis and repair, all of which support genomic stability [2]. The thyroid has the highest selenium concentration of any adult tissue. Although needed only in trace amounts, selenium plays a major role in thyroid homeostasis through selenocysteine-containing proteins [3].

The main dietary organic forms are selenomethionine (SeMet) and selenocysteine (Sec). SeMet is incorporated directly into methionine-containing proteins and serves as a cellular selenium reservoir [4]. Proteins with Sec at their active sites are termed selenoproteins, and the iodothyronine deiodinases (DIOs) and glutathione peroxidases (GPxs) are among their best-characterised representatives – both essential for protection against oxidative damage and prevention of autoimmunity [1]. The deiodinases convert tetraiodothyronine (T4) into its active form, triiodothyronine (T3); low selenium availability reduces their activity, thereby diminishing the production of active hormones [5]. Low selenium concentrations have also been linked to a higher risk of autoimmune thyroiditis, Graves' disease and goitre [6].

Thyroid disorders are closely tied to oxidative stress. Thyrocytes generate reactive oxygen species (ROS) as part of normal function: T4 and T3 biosynthesis, catalysed by thyroid peroxidase (TPO), requires the controlled availability of ROS – particularly hydrogen peroxide (H_2O_2) – for iodination of tyrosine residues. Because the gland physiologically depends on ROS for hormone synthesis, it is also unusually vulnerable to oxidative damage [7]. The clinical course of thyroid disease is therefore largely shaped by the redox status of the gland, which is in turn regulated by trace elements that act as antioxidant cofactors [8].

Despite considerable progress, the roles of selenium in deiodinase activity and of oxidative stress in autoimmune thyroid diseases (AITDs) remain unclear. The optimal dose, duration, formulation, genetic variation, and clinical recommendations remain unresolved. The present review summarises current knowledge on the role of selenium in thyroid physiology. It outlines the consequences of selenium deficiency on deiodinase activity and oxidative stress, and discusses the clinical relevance of selenium supplementation in the most common AITDs, Hashimoto's thyroiditis, Graves' disease, postpartum thyroid dysfunction, and goitre, as well as thyroid cancer.

2. Materials and methods

Relevant studies were identified through a structured search of the PubMed/MEDLINE database. The primary search term used was "selenium and thyroid", covering publications from March 2003 to May 2026. The initial search yielded 854 records. Additionally, three publications of institutional or regional relevance were identified from sources outside the searched databases. The search results were subsequently refined using PubMed filters for Clinical Study, Meta-Analysis, Randomised Controlled Trial and Systematic Review, resulting in 131 records eligible for abstract screening. Titles and abstracts were evaluated for relevance to selenium status, selenoprotein function, oxidative stress, thyroid physiology, autoimmune thyroid diseases, Hashimoto thyroiditis, Graves' disease, postpar-

tum thyroiditis and thyroid hormone metabolism. During this stage, 42 records were excluded because they did not meet the predefined inclusion criteria. The remaining 89 full-text articles were assessed for eligibility. After a detailed evaluation, 15 studies were excluded, primarily due to insufficient methodological quality, lack of clinically relevant outcome data, limited applicability to human thyroid pathophysiology, or duplication of evidence already covered in higher-quality reviews. Together with the three publications identified outside the searched databases, 77 studies were included in the present review. Preference was given to recent original studies, randomised controlled trials, systematic reviews and meta-analyses. Most animal studies were excluded, but selected studies were retained for mechanistic insights into selenium metabolism and selenoprotein function. The study selection process is summarised in **Figure 1**.

3. Selenium

3.1. Functions and forms of selenium

Selenium occupies a distinctive position in biology: selenocysteine is inserted co-translationally at a recoded UGA codon, a mechanism conserved in bacteria, archaea, and eukaryotes, pointing to an early evolutionary origin of selenoprotein-based redox catalysis [2]. Selenium (Se) is an essential trace element that supports human health by maintaining redox homeostasis and benefiting cardiovascular and metabolic functions. Moreover, selenium supplementation reduces inflammation in autoimmune thyroid disorders and promotes neuronal function, female fertility and spermatogenesis. Furthermore, selenium regulates inflammatory and cytoskeletal genes, inhibits cancer cell migration and angiogenesis. It also enhances the activity of macrophages, neutrophils, and natural killer cells and promotes lymphocyte proliferation and differentiation. However, both selenium deficiency and excess can harm health, making optimal selenium status essential [5].

Dietary selenium content is determined by geographically variable, soil-dependent concentrations. Selenium reaches the body in organic forms (selenomethionine – SeMet, methylselenocysteine, selenocystamine) and inorganic forms (selenite, selenate, selenide) [9]. SeMet, the predominant dietary form, occurs in cereals, legumes, nuts and animal-derived products [10].

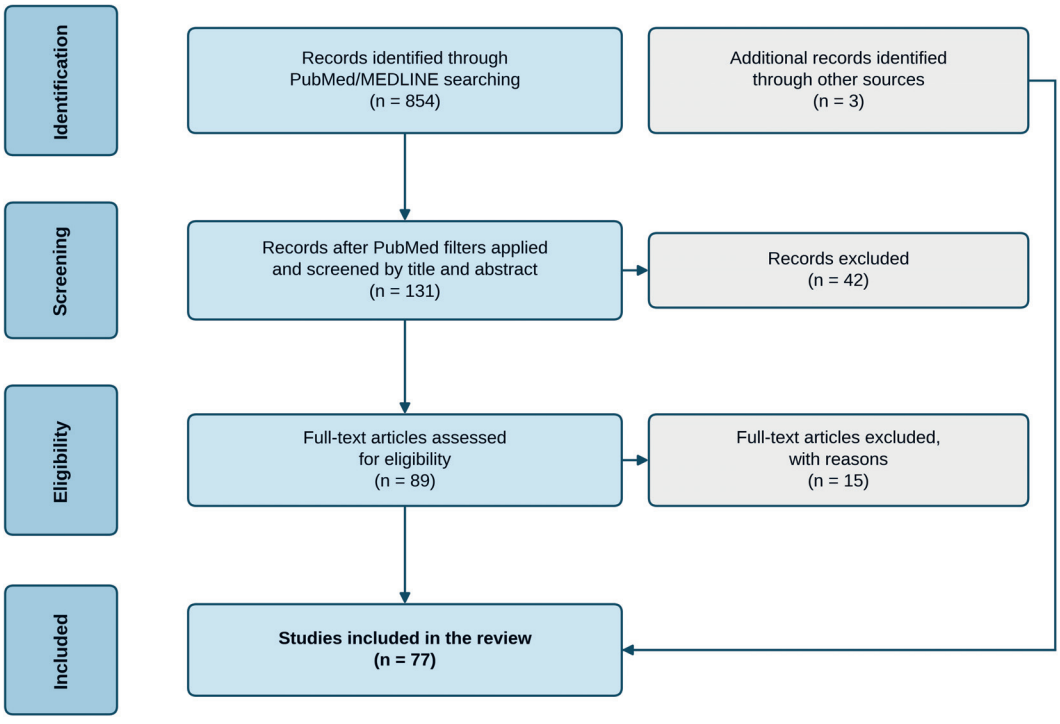


Figure 1. Scheme of review and identification of works

3.2. Selenium absorption and distribution

Roughly 80% of dietary selenium is absorbed, depending on the source [11]. Status is most commonly assessed from plasma, serum or whole-blood concentrations: plasma levels are inflammation-sensitive, whereas erythrocyte concentrations better reflect long-term status [12]. Selenium is distributed throughout tissues, bound within selenoproteins as selenocysteine (Sec) or stored as SeMet [13]. During selenium deficiency, selenium is redistributed according to tissue hierarchy. The brain, thyroid gland, testes, and skeletal muscle preferentially retain selenium, whereas its levels decline in the liver and skin [14]. Selenium requirements change across the lifespan. Children and adolescents need a higher intake to support somatic growth and neurodevelopment [15].

3.3. Sex differences in Se metabolism and supplementation

Sex differences in selenium metabolism may affect the response to supplementation, as sex hormones regulate trans-selenation, thereby influencing selenomethionine metabolism and selenoprotein synthesis. Sex-dependent glutathione peroxidase (GPx) polymorphisms are linked to lower GPx activity in men, while women have higher circulating GPx activity despite similar selenium levels. In addition, in premenopausal women, plasma selenium and GPx activity correlate with estrogen levels, suggesting that estrogen regulates selenium status. Women retain circulating selenium more efficiently and excrete more selenium in urine after supplementation, indicating sex differences in selenium handling. Sex should be considered when assessing selenium metabolism, selenoproteins, and related outcomes [16].

3.4. Challenges in selenium supplementation

3.4.1. Narrow therapeutic window

Selenium supplementation has a narrow therapeutic window, as both insufficient and excessive intake may disrupt thyroid regulation and redox homeostasis. Doses recommended for thyroid disorders are typically 100–200 µg/day for deficient individuals, with an upper limit of approximately 400 µg/day for adults [1]. Acute selenosis causes gastrointestinal, cardiovascular, pulmonary, and neurological symptoms, while chronic selenosis manifests with nail, hair, tooth, skin, and neuromuscular abnormalities [17].

Serum or plasma selenium is commonly used to assess selenium status but does not fully reflect functional selenoprotein saturation. Selenoprotein P (SELENOP), the main plasma selenium transporter, is a more informative biomarker and plateaus at selenium levels of approximately 110–125 µg/L when selenoprotein synthesis is maximised. Combined selenium, SELENOP, and GPx assessment helps identify deficiency, optimal status, and excess exposure, improving safety monitoring during prolonged high-dose supplementation [18].

3.4.2. Genetic variability in selenium metabolism

The response to selenium supplementation varies due to genetic differences. Polymorphisms in BHMT, CBS, GPX1, SELENOP and DIO influence selenium utilisation and bioavailability. As a result, some individuals benefit from Se therapy, whereas others show little or no improvement despite adequate intake. The DIO2 Thr92Ala variant (rs225014) may reduce deiodinase activity and local triiodothyronine (T3) availability. This variant is associated with poorer psychological well-being, reduced response to levothyroxine therapy, and persistent hypothyroid symptoms despite normal serum thyroid-stimulating hormone (TSH) and thyroxine (T4) levels. Variants in DIO1 (e.g., rs11206244 and rs2235544) affect peripheral thyroid hormone conversion, while polymorphisms in SELENOP (e.g., rs3877899 and rs7579) may impair Se transport and antioxidant defence. Likewise, the GPX1 Pro198Leu (rs1050450) variant is linked to reduced antioxidant activity and increased oxidative stress. Genetic variability highlights the need for personalised Se supplementation based on genotype and thyroid status. This also suggests that genetic variability among the studied populations may affect clinical trial results and the effectiveness of supplementation. Future insights into these associations may enable the development of molecular diagnostic markers and personalised treatments based on individual polymorphisms [1,19,20]. The most relevant polymorphisms are summarised in **Table 1.**

Table 1. Selected genetic polymorphisms influencing selenium metabolism and selenoprotein function (based on [1,19,20])

Gene / locus	Chromosomal location	Functional relevance
BHMT	5q14	Affects selenium utilisation via homocysteine and methylation pathways
CBS	21q22.3	Encodes cystathionine beta-synthase; homocysteine metabolism and indirect regulation of selenium bioavailability
GPX1	3p21.31	Variants linked to altered antioxidant enzyme activity and oxidative stress susceptibility
SELENOP	5p12	Variants linked to altered plasma selenium and tissue selenium delivery
DIO2 (Thr92Ala, rs225014)	14q31	Affects thyroid hormone activation; among the most studied polymorphisms influencing responsiveness to selenium

3.4.3. Effectiveness of selenium supplements

Supplement efficacy and safety depend on selenium form: differences in absorption, metabolism and distribution determine its bioavailability [21]. Organic forms are preferred in a balanced diet because of their lower toxicity and higher bioavailability compared with inorganic forms [22]. Direct comparisons of how individual selenium species affect DIO1, DIO2 and DIO3 expression are still lacking, so form-specific dosing rests on bioavailability rather than on documented effects on deiodinase expression [13,21].

3.5. Selenium nanoparticles

Selenium nanoparticles (SeNPs) have been explored as a means of improving absorption and bioavailability. Functionalised SeNPs have lower cytotoxicity and offer advantages over conventional sources thanks to their nanoscale dimensions, porous structure and favourable biodispersion. SeNPs exhibit antimicrobial, anticancer, antidiabetic, antiparasitic and antioxidant activities [23]. Selenium compounds reduce metal-induced oxidative damage by binding to copper and iron, with their metal-binding capacity potentially reflecting antioxidant efficacy better than GPx activity alone [22]. Smaller, more homogeneous SeNPs exhibit enhanced antioxidant activity [24] and potential chemopreventive and antimicrobial effects [23]. The unique physicochemical properties of SeNPs, including their high surface-area-to-volume ratio and reactive oxygen species (ROS)-responsive design, contribute to their therapeutic potential. Lentinan-modified SeNPs lead to GPx1 activation and enhanced scavenging of ROS and lipid hydroperoxides. Through this, SeNPs may suppress inflammation-driven adipogenesis in thyroid eye disease [25]. Furthermore, SeNPs show potential as drug carriers and anticancer agents, with transferrin-conjugated, doxorubicin-loaded SeNPs enhancing drug delivery and inducing apoptosis in cancer cells, warranting further research [26]. Future research should focus on personalised Se-based therapies using genomics and nanotechnology [1].

3.6. Selenoproteins

Selenocysteine-containing proteins regulate cellular defence, hydrogen peroxide (H_2O_2)-dependent biosynthetic reactions and thyroid hormone activation. Their imbalance disrupts the hypothalamic–pituitary–thyroid axis, contributing to autoimmune thyroid disorders (AITDs) and metabolic diseases [27]. The human genome encodes 25 selenoproteins, mainly involved in redox balance [28].

Most selenoproteins – including GPxs, thioredoxin reductases (TrxRs) and iodothyronine deiodinases (DIOs) – have oxidoreductase activity and serve as key intracellular antioxidants [14]. Several selenoproteins – selenoprotein F (SELENOF), S (SELENOS), M (SELENOM), T (SELENOT), N (SELENON), K (SELENOK), H (SELENOH) and W (SELENOW) – contribute to redox sensing and calcium homeostasis. SELENOP is the principal plasma selenium transporter and a reliable biomarker of status [29,30]. GPx activity declines at low-normal plasma selenium levels, with an optimal level around 90 µg/L [31].

Iodothyronine deiodinases are membrane-associated selenoproteins that occur in three isoforms – DIO1, DIO2, and DIO3 — with distinct tissue distributions and physiological roles (**Table 2**) [32,33]. Deiodinases regulate intracellular and circulating thyroid hormone levels [33], and selenium deficiency may compromise their activity, disturbing hormone metabolism [27]. Iodine is also an essential micronutrient involved in the synthesis of the thyroid hormones T3 and T4. During hormone production, iodination of thy-

Table 2. Characteristics of iodothyronine deiodinases (DIO1, DIO2, DIO3): tissue distribution, catalytic activity and physiological role (based on [15,32])

Enzyme	Tissue distribution	Catalytic activity	Main physiological role
DIO1	Liver, kidneys, thyroid gland	Outer-ring and inner-ring deiodination (bidirectional)	Conversion of T4 to T3; inactivation of T3 to 3,3′-T2; major contributor to circulating T3
DIO2	Pituitary gland, thyroid, skeletal muscle, brain, brown adipose tissue	Outer-ring deiodination	Conversion of T4 to active T3; main source of intracellular T3 in target tissues
DIO3	Cerebral cortex, placenta, skin; absent in thyroid tissue	Inner-ring deiodination	Inactivation of thyroid hormones: T4 to rT3 and T3 to 3,3′-T2

roglobulin forms monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT and DIT combine to produce T3, whereas two DIT molecules form T4 [34]. DIO1 shows bidirectional activity, contributing to T4-to-T3 activation and to T3-to-3,3′-T2 inactivation. DIO2 predominantly catalyses outer ring deiodination, converting T4 into active T3 [31]. DIO3 mainly mediates inner-ring deiodination, inactivating thyroid hormones by converting T4 to reverse T3 (rT3) and T3 to 3,3′-diiodothyronine (3,3′-T2) [15]. Selenium is essential for T3 synthesis via DIO1 and DIO2. Se deficiency reduces T4-to-T3 conversion and may increase rT3, disrupting thyroid hormone balance [1].

Selenoproteins differ in their sensitivity to selenium availability: stress-related selenoproteins (GPX1, SELENOW, SELENOH) are strongly regulated by selenium status, while housekeeping selenoproteins (GPX4, TXNRD1, TXNRD3) remain relatively stable [14]. Individual differences in deiodinase activity despite similar selenium levels may be explained by thyroid status, growth factors, cytokines, diseases, trace elements (iodine, iron), tissue-specific T3 production, hormone transport, half-life, and DIO gene variants. For example, the rs225014 A/G Thr92Ala DIO2 polymorphism leads to decreased DIO1 activity under stress conditions [35]. Chronic inflammation alters deiodinase activity by linking oxidative stress with T3 metabolism. Elevated interleukin (IL)-6 increases ROS, reduces DIO1 and DIO2 activity, and induces DIO3 expression [36].

3.7. The antioxidant effect of selenium

Oxidative stress occurs when ROS production exceeds antioxidant capacity [37]. ROS are by-products of cellular metabolism, generated mainly by mitochondrial electron leakage and oxidative phosphorylation enzymes. ROS, particularly H_2O_2, are generated during thyroid hormone synthesis and are essential for thyroid peroxidase (TPO)–mediated T4 and T3 production. Excess ROS induces oxidative stress, causing DNA and protein damage, lipid peroxidation, and thyroid cell death. Excessive H_2O_2 causes irreversible oxidation of cysteine residues, leading to permanent protein damage. Guanine is the DNA base most susceptible to oxidation because of its low redox potential. Its product, 8-oxo-2′-deoxyguanosine, is a biomarker of oxidative DNA damage and carcinogenesis [1,5,7].

About half of selenoproteins display antioxidant properties. GPx detoxifies ROS, thereby protecting membrane integrity. TrxR, together with thioredoxin (Trx) and NADPH, forms a major cellular antioxidant system that maintains reduced Trx, which repairs disulfide bonds, detoxifies H_2O_2, and enhances antioxidant defence [1,7,15]. It also reduces ribonucleotides, regulates redox-sensitive enzymes, and provides hydrogen for ribonucleotide reductase in DNA synthesis and repair [37]. Selenium deficiency reduces TrxR1 activity, increasing ROS accumulation, oxidative damage, and impaired thyroid function, contributing to autoimmune thyroid dysfunction [1,7].

Reduced glutathione levels indicate oxidative stress in Hashimoto's thyroiditis, which is linked to thyroid hormone deficiency, inflammation, and autoimmunity. Oxidative DNA damage contributes to Graves' disease. Thyroid-stimulating antibodies (TSAb) promote oxidative processes, with untreated patients showing increased DNA damage and lipid peroxidation. Moreover, oxidative stress markers correlate with TSAb levels, and ROS-induced DNA damage promotes genomic instability and carcinogenesis, including thyroid cancer [7].

3.7.1. Selenium as a regulator of redox-sensitive NF-κB and Nrf2 pathways

By inhibiting nuclear factor kappa B (NF-κB) and regulating nuclear factor erythroid 2-related

factor 2 (Nrf2) transcription, selenium controls immune and antioxidant responses [38]. Under oxidative stress, ROS activates IκB kinase (IKK), triggering IκB degradation and NF-κB translocation to the nucleus. By enhancing GPx and TrxR activity, selenium reduces ROS, NF-κB activation, and the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. The TrxR–thioredoxin system also regulates the redox state of NF-κB, influencing its DNA-binding and transcriptional activity. Selenium deficiency impairs GPx and TrxR, enhancing NF-κB signalling, inflammation, and immune dysregulation. GPx and TrxR also indirectly regulate the Nrf2 pathway, a key regulator of the cellular antioxidant response. Under oxidative stress, Nrf2 dissociates from Keap1 (kelch-like ECH-associated protein 1), translocates to the nucleus, and binds to antioxidant response elements, DNA sequences that encode antioxidant and detoxification enzymes. Selenium regulates Nrf2 activity, enhancing the cellular oxidative stress response [39].

4. Role of selenium in thyroid diseases

Epidemiological data link suboptimal selenium status with an increased thyroid disorder risk [10]. Selenium intake varies by region: Europe, including Poland (50–80 µg/L serum selenium), generally has lower levels than selenium-rich regions such as the US, Japan, and Venezuela (>100 µg/L), which may contribute to higher autoimmune thyroid disease (AITD) prevalence [5, 15, 40]. Comparisons between such populations are further complicated by concurrent differences in iodine intake, because selenium-dependent deiodinases act on an iodine-derived substrate pool [34].

Wu et al. studied two adjacent counties in Shaanxi, China, with different soil selenium levels. Serum selenium was nearly twofold higher in the selenium-adequate county (103.6 vs 57.4 µg/L), where thyroid disorders were less prevalent (18.0% vs 30.5%) [41]. The association was stronger in women, in whom selenium status reduced thyroid volume, goitre, and tissue damage; no comparable effect was observed in men [42]. Pirola et al. found that 31.3% of patients with autoimmune thyroiditis and mild subclinical hypothyroidism achieved euthyroidism after 4 months of 83 µg/day selenomethionine, suggesting selenium's role in normalising thyroid function [43].

5. Autoimmune thyroid diseases (AITDs)

AITDs involve immune dysregulation and thyroid autoantibodies, driven by genetic predisposition, oestrogens, adipokines, body mass index, smoking, iodine exposure, selenium/vitamin D deficiency, infections, stress, and diet [44,45]. Loss of immune tolerance initiates thyroid autoimmunity, with antigen-presenting cells (APCs) activating $CD4^+$ T cells and directing their differentiation through cytokine and transcription factor signals [46,47]. $CD4^+$ T helper cells were divided into Th1 and Th2; Th1 cells secrete interferon γ (IFN-γ), supporting cell-mediated responses [48]. IFN-γ drives macrophage polarisation toward the pro-inflammatory M1 phenotype and enhances antigen presentation, thereby promoting persistent autoimmune responses [49].

Pro-inflammatory Th17 lymphocytes secrete IL-17, which stimulates macrophages, fibroblasts, and epithelial cells to release pro-inflammatory cytokines such as IL-1 and IL-6, promoting leukocyte recruitment and thyrocyte apoptosis [50]. Serum and tissue IL-17 levels correlate with anti-thyroid peroxidase (TPOAb) and anti-thyroglobulin (TGAb) titres, as well as early fibrotic changes [51]. IL-6 and IL-1β promote Th17 differentiation while inhibiting Treg development, whereas Tregs suppress immune responses through the release of IL-10 and TGF-β (transforming growth factor β) [51,52]. AITD is characterised by reduced Treg function, resulting in increased Th17 activity. The loss of Treg $CD4^+CD25^+Foxp3^+$ cells impairs suppression of Th1 and Th2 responses, promoting cytotoxic and antibody-mediated immunity that contributes to thyroiditis [50]. Th2 cells produce IL-4, IL-5 and IL-13, promoting B-cell maturation and immunoglobulin G antibody production, including TSH receptor-stimulating antibodies. Genetic and environmental factors can disrupt T-cell subsets, B cells and APCs, and trigger thyroid autoimmunity [46].

Selenium contributes to AITD pathogenesis through selenoprotein-mediated regulation of T-cell function and redox homeostasis. The protective effect of selenium supplementa-

tion on thyrocytes results from both enhanced antioxidant defence and direct modulation of immune cell function [52,53]. Selenoproteins regulate inflammation and oxidative stress through diverse mechanisms. SELENOS controls inflammatory cytokine production, SELENOW supports macrophage responses, SELENOK regulates immune calcium signalling, and SELENOM maintains calcium homeostasis and antioxidant protection [20]. Selenium supplementation reduces IL-6 production, enhances antioxidant defences, and promotes Treg cell expansion, helping restore the Treg/Th17 balance [48]. Adequate selenium status promotes T-cell proliferation, natural killer cell activity, macrophage function, and antibody production, whereas selenium deficiency impairs innate and adaptive immunity [53]. Zuo et al. confirmed an association between selenium levels and AITD activity; selenium supplementation significantly reduced serum FT3 (free triiodothyronine), FT4 (free thyroxine), and TPOAb in AITD patients, with no effect on TSH or TGAb [49]. A dose-dependent decrease in TPOAb has been reported, with 100 µg/day required to achieve maximal GPx activity [31]. Key clinical studies are summarised in **Table 3.**

5.1. Hashimoto's thyroiditis

Hashimoto's thyroiditis is a common organ-specific autoimmune disease characterised by T- and B-lymphocyte infiltration and the production of anti-TPO and anti-TG antibodies, leading to thyroid dysfunction [60]. The lymphocytic infiltrate progressively destroys thyroid follicular cells, and patients frequently present with low FT4 and FT3 levels. The disease involves impaired antioxidant defence, and selenium deficiency may reduce thyrocyte protection against oxidative damage [61]. Socha et al. reported that mean serum selenium in patients with Hashimoto's disease (63.03 ± 17.31 µg/L) was significantly lower than in controls (75.16 ± 19.92 µg/L). Several clinical studies in AITD patients have shown that six months of supplementation at 200 µg/day raises serum selenium from 70–75 µg/L to 86–125 µg/L and may improve thyroid function [62]. Mazokopakis et al. found that 200 µg/day of oral L-selenomethionine reduced anti-TPO by 5.6% at three months and 9.9% at six months. Extending treatment for another 6 months led to a further 8% decrease, whereas discontinuation led to a 4.8% rebound [54]. By contrast, lowering the dose from 200 to 100 µg/day did not maintain

Table 3. Summary of key clinical studies on selenium supplementation in autoimmune thyroid diseases

Author, year	Disease	Sample size	Se dose / form	Duration	Main outcome
Mazokopakis et al., 2007 [54]	Hashimoto's thyroiditis	80	L-selenomethionine 200 µg/day	12 months	Significant reduction in anti-TPO (5.6% at 3 months, 9.9% at 6 months, additional 8% at 12 months); rebound after discontinuation
Turker et al., 2006 [55]	Hashimoto's thyroiditis	88	Sodium selenite 200 vs. 100 µg/day	9 months	200 µg/day reduced TPOAb; dose reduction to 100 µg/day did not maintain effect
Toulis et al., 2010 [56]	Hashimoto's (meta-analysis)	4 RCTs	Selenomethionine or selenite 200 µg/day	3–6 months	Significant decrease in TPOAb titres; improvement in mood and well-being
Pirola et al., 2016 [43]	Subclinical hypothyroidism with autoimmune thyroiditis (AIT)	196	Selenomethionine 83 µg/day	4 months	Restoration of euthyroidism in 31.3% of patients
Negro et al., 2007 [57]	Pregnant women with positive TPOAb	151	Selenomethionine 200 µg/day	Pregnancy + 12 months postpartum	Reduction in postpartum thyroid dysfunction (28.6% vs. 48.6%) and permanent hypothyroidism (11.7% vs. 20.3%)
Mantovani et al. (SERENA), 2019 [58]	AITD during pregnancy and postpartum	60	Selenomethionine 83 µg/day	Pregnancy + 6 months postpartum	Significant postpartum reduction in TPOAb and TGAb; antibody rebound in placebo group
Marcocci et al., 2011 [59]	Mild Graves' orbitopathy	159	Sodium selenite 200 µg/day	6 months	Significant improvement of ocular involvement, quality of life and disease progression compared with placebo
Zuo et al., 2021 [49]	AITD (meta-analysis)	Multiple RCTs	Selenium-containing therapies	Various	Significant reduction in FT3, FT4, and TPOAb; no significant change in TSH or TGAb

the TPOAb reduction [55]. The systematic review and meta-analysis by Toulis et al. found that supplementation was associated with significant reductions in TPOAb and improvements in mood and well-being [56]. More recent meta-analyses, including large Cochrane reviews of trials, confirm selenium's TPOAb-lowering effect, but its impact on long-term thyroid outcomes remains uncertain [46]. A meta-analysis by Huwiler et al. showed that selenium supplementation reduced TPOAb levels but had no significant effect on FT3, FT4, total T3, total T4, TGAb, thyroid volume, or inflammatory cytokines (IL-2 and IL-10). This suggests that although selenium attenuates the autoimmune response, it does not restore thyroid volume and hormone synthesis, likely because hormone production depends on the amount of remaining functional thyroid tissue rather than antibody levels alone [63].

5.2. Graves' disease

Graves' orbitopathy (GO) is an autoimmune disorder of orbital and retrobulbar tissues [64]. Its pathophysiology involves immune cells, cytokines, interleukins and enhanced oxidative stress [65]. Th17 lymphocytes and their signature cytokine IL-17 play a substantial role in Graves' disease. Li et al. showed that serum IL-17 levels were highest in patients with intractable Graves' disease (54.4 ± 36.0 pg/mL), followed by untreated patients (33.6 ± 23.1 pg/mL) and patients in remission (19.0 ± 7.5 pg/mL). Elevated IL-17 appears to track with active, severe disease, and IL-17 may represent a therapeutic target in intractable cases [48]. Owji et al. demonstrated an inverse relationship between serum selenium and T3, T4 and TSH in patients with Graves' disease accompanied by orbitopathy. In patients without ocular involvement, selenium was significantly inversely associated with T4 and TSH, but not with T3 [66]. In a retrospective case-control study, Kim et al. observed that mean serum selenium levels were significantly lower in patients with Graves' disease, both with and without orbitopathy. Patients with orbitopathy had marginally lower mean levels, and selenium correlated with eyelid retraction [67]. The multicentre trial by Marcocci et al. (EUGOGO selenium study) showed that sodium selenite at 200 µg/day for six months significantly improved ocular manifestations, quality of life and disease course in mild GO compared with placebo. Quality of life improved through better visual function, appearance, eyelid condition, soft tissue status, reduced proptosis, and improved eye muscle motility [59]. Owing to its anti-inflammatory and antioxidant properties, supplementation seems particularly useful in reducing the signs of ophthalmopathy in patients from selenium-deficient regions [64, 68].

5.3. Postpartum thyroid dysfunction

The postpartum period (first 12 months after delivery) involves immune reactivation after pregnancy-induced tolerance, which may exacerbate existing AITD or trigger new disease onset [69]. Postpartum thyroid dysfunction (PPTD) is defined by abnormal TSH. Early-pregnancy TPOAb positivity carries a 5.7-fold higher risk of PPTD compared with TPOAb-negative women [70].

Negro et al. observed that selenium given during pregnancy and the postpartum period reduced TPOAb and lowered the incidence of PPTD (28.6% vs 48.6%) and of permanent postpartum hypothyroidism (11.7% vs 20.3%) compared with placebo [57]. The SERENA study evaluated selenium in autoimmune thyroiditis during pregnancy and after delivery; women on selenomethionine (83 µg/day) showed a significant postpartum decline in TPOAb and TGAb, whereas the placebo arm experienced an antibody rebound. These findings echo Negro et al. and confirm that selenium during pregnancy and the postpartum period is both safe and effective in lowering thyroid autoantibody titres [58].

In TPOAb-positive pregnant women, selenium may reduce autoantibodies and lower postpartum thyroiditis risk [71]. Selenium-deficient pregnant women with autoimmune thyroiditis have higher risks of adverse outcomes and postpartum hypothyroidism, warranting monitoring during and after pregnancy [72]. Despite these encouraging results, routine selenium use in all TPOAb-positive pregnant women remains debated. The 2014 European Thyroid Association (ETA) guideline did not recommend universal supplementation. More recent data support its safety and efficacy in this setting and favour individualised decisions based on selenium status and antibody titres [31,58,71].

5.4. Goitre

Goitre is defined as abnormal thyroid enlargement and may be diffuse or nodular; it can occur

in euthyroidism, hypothyroidism or hyperthyroidism [41]. Goitre pathogenesis involves chronic TSH stimulation, which promotes follicular cell proliferation and enhances H_2O_2 generation. Under selenium deficiency, GPx and TrxR activities decrease, promoting impaired H_2O_2 detoxification and ROS accumulation in thyrocytes [7]. Oxidative stress may promote fibrosis and nodular changes, while reduced DIO1 and DIO2 activity impairs T4-to-T3 conversion and induces compensatory hyperplasia. [1].

Epidemiological evidence supports a link between low selenium levels and higher goitre prevalence. Wu et al. showed that thyroid enlargement was less prevalent in a selenium-adequate Chinese county than in a selenium-deficient one [41]. Derumeaux et al. observed among French adults aged 35–60 that higher serum selenium levels were inversely associated with thyroid volume and goitre, particularly in women [42].

Selenoenzymes maintain thyroid redox balance, and their reduced activity promotes apoptosis, remodelling, and nodular goitre. Selenium status assessment is relevant in selenium-deficient regions, such as Central and Eastern Europe. Further trials are needed to determine whether targeted supplementation can reduce thyroid enlargement or prevent nodular progression [41,42].

5.5. Thyroid cancer

Thyroid cancer is the most common endocrine malignancy, with low selenium linked to higher risk and possible anticarcinogenic effects. In papillary thyroid carcinoma (PTC), GPx1 and TrxR1 are reduced, while DIO3 expression and activity are increased. Elevated DIO3 expression correlates with metastases, highlighting the dual role of selenoproteins in tumour progression [73]. Hao et al.'s meta-analysis found significantly lower serum selenium levels in patients with thyroid cancer than in controls [74]. Other studies have reported lower selenium levels in blood, thyroid tissue, and serum, particularly in follicular and papillary carcinomas [75]. A recent study demonstrated that GPx3 activity was decreased in PTC patients, suggesting that low serum selenium levels are significantly associated with carcinogenesis [76]. Ge et al. found lower serum selenium levels in PTC patients, particularly in women and those with bilateral or multifocal tumours. In addition, lower selenium levels were associated with a greater number of lymph node metastases, suggesting a potential protective role of selenium in PTC. Further studies are needed to define selenium's role in PTC progression and selenoprotein regulation in thyroid cancer [73, 77].

6. Future perspectives

Four priorities follow from the evidence reviewed here. First, selenium status should be assessed using functional biomarkers rather than total serum selenium, because SELENOP and GPx activity plateau at concentrations that total serum selenium alone cannot detect [18,31]. Second, supplementation trials should be stratified by DIO2, GPX1 and SELENOP genotype, so that discrepant results can be attributed to genetic background rather than to dose or formulation [1,19,20]. Third, engineered selenium nanoparticles warrant controlled evaluation in thyroid autoimmunity [23,25,26]. Fourth, trials should report clinically meaningful endpoints, including thyroid volume, progression to overt hypothyroidism and quality of life, rather than antibody titres alone [46,63].

7. Conclusions

Taken together, the evidence reviewed here points to selenium as a trace element of unusual importance for the thyroid. Acting primarily through its incorporation into selenoproteins – notably the iodothyronine deiodinases and the antioxidant enzymes glutathione peroxidase and thioredoxin reductase – it influences both hormone activation and thyrocyte redox balance. When selenium is in short supply, peripheral T4-to-T3 conversion is impaired and the capacity to neutralise ROS declines; both consequences plausibly contribute to AITD onset and progression. Clinical data from the past two decades indicate that supplementation, usually 100–200 µg/day for at least three to six months, can lower autoantibody titres in Hashimoto's thyroiditis, ease ocular manifestations of mild Graves' orbitopathy and reduce postpartum thyroid dysfunction. Selenium status also appears relevant to gland integrity in patients at risk of goitre and thyroid cancer. At the same

time, the narrow therapeutic window, marked genetic variability in metabolism, and substantial regional differences in baseline status make uniform recommendations difficult. Larger, well-designed randomised trials are needed to define the optimal dose, treatment duration and patient subgroups most likely to benefit, and to clarify the long-term safety of supranutritional intake.

8. Limitations

This review has several limitations that should be considered when interpreting the findings. Potential selection bias and heterogeneity in selenium preparations, doses, treatment duration, and study populations limit the comparability and interpretation of findings. A non-indexed Polish publication and a PubMed/MEDLINE-only search may have introduced selection bias and limited the retrieval of studies.

List of abbreviations

AIT – autoimmune thyroiditis
AITD – autoimmune thyroid disease
APC – antigen-presenting cell
DIO – iodothyronine deiodinase
DIT – diiodotyrosine
3,3'-T2 – 3,3'-diiodothyronine
ETA – European Thyroid Association
EUGOGO – European Group on Graves' Orbitopathy
FT3 – free triiodothyronine
FT4 – free thyroxine
GO – Graves' orbitopathy
GPx – glutathione peroxidase
H_2O_2 – hydrogen peroxide
IFN-γ – interferon γ
IKK – inhibitor of κB kinase
IL – interleukin
Keap1 – kelch-like ECH-associated protein 1
MIT – monoiodotyrosine
NF-κB – nuclear factor kappa B
Nrf2 – Nuclear factor erythroid 2-related factor 2
PPTD – postpartum thyroid dysfunction
PTC – papillary thyroid carcinoma
ROS – reactive oxygen species
rT3 – reverse triiodothyronine
Se – selenium
Sec – selenocysteine
SELENOF – selenoprotein F
SELENOH – selenoprotein H
SELENOK – selenoprotein K
SELENOM – selenoprotein M
SELENON – selenoprotein N
SELENOP – selenoprotein P
SELENOS – selenoprotein S
SELENOT – selenoprotein T
SELENOW – selenoprotein W
SeMet – selenomethionine
SeNPs – selenium nanoparticles
T3 – triiodothyronine
T4 – thyroxine
TGAb – anti-thyroglobulin antibodies
TGF-β – transforming growth factor β
TNF-α – tumour necrosis factor α
TPO – thyroid peroxidase
TPOAb – anti-thyroid peroxidase antibodies
Trx – thioredoxin
TrxR – thioredoxin reductase
TSAb – thyroid-stimulating antibodies
TSH – thyroid-stimulating hormone

Statements

Authors' contribution
[MM, MW, GW]: conceptualisation, methodology, literature search, investigation, writing – original draft. [MB and EZ]: literature search, data curation, writing – review & editing. [GW]: supervision, project administration, writing – review & editing. All authors have read and approved the final version of the manuscript.

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