JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS·Nicolaus Copernicus University in Toruń

Cite as: RYBIŃSKA Marcelina, RZEPKA Hanna, STĘPOWSKI Paweł, TAJSTER Mateusz. Diet and Oral Supplementation as Adjuncts to Pharmacological Treatment in Thyroid Diseases: A Narrative Review. Journal of Education, Health and Sport. 2026;95:73649. https://doi.org/10.12775/JEHS.2026.95.73649

ARTICLE TIMELINE
Received: 23.06.2026 Revised: 15.08.2026
Accepted: 02.09.2026 Published: 14.09.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 246387
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2026.

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Diet and Oral Supplementation as Adjuncts to Pharmacological Treatment in Thyroid Diseases: A Narrative Review

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Keywords: thyroid diseases; Hashimoto's thyroiditis; Graves 'disease; hypothyroidism; hyperthyroidism; selenium; iodine; vitamin D; zinc; myo-inositol; gluten-free diet; dietary supplementation; levothyroxine; autoimmune thyroid disease

Abstract:

Background: Thyroid diseases, including hypothyroidism, hyperthyroidism, Hashimoto's thyroiditis, and Graves 'disease, represent a major global health burden. Despite the established efficacy of pharmacological treatments such as levothyroxine and antithyroid drugs, a proportion of patients experience residual symptoms, suboptimal biochemical control, or progressive autoimmunity. Growing evidence suggests that dietary modifications and oral supplementation with specific micronutrients may serve as clinically relevant adjuncts to standard pharmacotherapy, modulating thyroid hormone metabolism, immune regulation, and antioxidant defence.

Objective:

The aim of this narrative review is to critically evaluate and synthesise the current evidence on the efficacy and safety of dietary modifications and oral supplementation specifically selenium, iodine, vitamin D, zinc, magnesium, myo-inositol, and a gluten-free diet as adjuncts to pharmacological treatment in patients with thyroid diseases across all age groups.

Materials and Methods:

This paper presents a narrative review of the scientific literature assessing the role of diet and oral supplementation in the management of thyroid diseases. The aim of this work was to collect and analyse scientific data regarding dietary factors, micronutrient supplementation, and lifestyle modifications that may complement pharmacological treatment in patients with thyroid disorders, including hypothyroidism, hyperthyroidism, Hashimoto's thyroiditis, and Graves' disease. The literature is focused on the principal nutrients and dietary interventions namely selenium, iodine, vitamin D, zinc, magnesium, myo-inositol, and a gluten-free diet and their impact on thyroid function, autoantibody titres, and overall disease management.

Scientific articles were retrieved from electronic databases, including PubMed/MEDLINE and Google Scholar, as well as from publicly available websites dedicated to the dissemination of reliable medical and scientific information.

The analysis included preclinical studies, clinical trials, systematic reviews, and meta-analyses.

Only publications written in English were included. The literature review and article selection process were conducted in February 2026.

Introduction

Thyroid disorders represent one of the most prevalent endocrine conditions worldwide, affecting an estimated 200 million individuals globally, with a significantly higher incidence among women and older populations. The spectrum of thyroid pathology encompasses a broad range of conditions, including hypothyroidism, hyperthyroidism, autoimmune thyroid diseases such as Hashimoto's thyroiditis (HT) and Graves' disease (GD), as well as structural abnormalities including nodular goitre and thyroid neoplasms. Among these, autoimmune thyroid diseases constitute the most common aetiology of both hypothyroidism and hyperthyroidism in iodine-sufficient regions. The chronic, often lifelong nature of these conditions imposes a considerable burden on patients and healthcare systems alike, necessitating a comprehensive and multidisciplinary approach to management.

The cornerstone of pharmacological management in hypothyroidism is levothyroxine (LT4) replacement therapy, which aims to restore euthyroidism and alleviate symptoms associated with thyroid hormone deficiency. In hyperthyroid states, antithyroid drugs (ATDs) — primarily thiamazole and propylthiouracil — are employed to inhibit thyroid hormone synthesis, either as definitive therapy or as a bridge to radioiodine ablation or surgical intervention. Despite the general efficacy of these pharmacological strategies, a subset of patients continue to experience residual symptoms, suboptimal biochemical control, or adverse effects associated with long-term pharmacotherapy. This clinical reality has prompted growing interest in adjunctive therapeutic strategies that may complement conventional pharmacological treatment.

The thyroid gland is uniquely dependent on a range of micronutrients for optimal function. Iodine, as the fundamental substrate for thyroid hormone biosynthesis, has long been recognised as essential to thyroid physiology. However, accumulating evidence suggests that additional micronutrients — including selenium, zinc, magnesium, inositol, and vitamin D — play critical roles in modulating thyroid hormone metabolism, immune regulation, and antioxidant defence within the thyroid gland. Selenium, in particular, is integral to the activity of deiodinases and glutathione peroxidases, enzymes central to the peripheral conversion of thyroxine (T4) to the biologically active triiodothyronine (T3) and to the mitigation of oxidative stress. Zinc participates in the regulation of thyroid hormone receptor signaling and has been implicated in

thyroid hormone synthesis. Vitamin D, beyond its classical role in calcium homeostasis, exerts immunomodulatory effects and has been associated with the pathogenesis of autoimmune thyroid diseases. Inositol, particularly myo-inositol, has emerged as a second messenger in thyrotropin (TSH) receptor signaling, with preliminary evidence suggesting a role in thyroid hormone production.

Beyond individual micronutrients, dietary patterns have garnered attention as potential modulators of thyroid function and autoimmunity. A gluten-free diet has been proposed as a beneficial intervention in patients with concurrent autoimmune thyroid disease and coeliac disease or non-coeliac gluten sensitivity, based on the hypothesis of shared immunological mechanisms and the potential for dietary antigens to perpetuate thyroid autoimmunity. Additionally, goitrogenic foods, dietary fibre, calcium, coffee, and soy products have been identified as factors that may interfere with levothyroxine absorption or thyroid hormone metabolism, highlighting the importance of dietary counselling in the clinical management of thyroid diseases.

Despite the increasing body of literature examining the relationship between nutritional status, dietary habits, and thyroid disease, existing evidence remains heterogeneous, with considerable variability in study design, patient populations, interventions, and outcome measures. To date, no comprehensive narrative review has synthesized the available evidence on the combined role of dietary interventions and oral supplementation as adjuncts to pharmacological treatment across the full spectrum of thyroid diseases. Addressing this gap is essential to inform evidence-based clinical practice and to guide future research priorities in the field of nutritional endocrinology.

The aim of the present narrative review is to critically evaluate and synthesize the current evidence regarding the efficacy and safety of dietary modifications and oral supplementation including selenium, iodine, vitamin D, zinc, magnesium, myo-inositol, and gluten-free dietary interventions as adjunctive strategies to standard pharmacological treatment in patients with thyroid diseases. The review encompasses all age groups and both sexes, and addresses outcomes including thyroid function parameters, thyroid autoantibody titers, quality of life, and safety profiles.

Results:

Selenium

Selenium (Se) is an essential trace element that exerts its biological functions primarily through its incorporation into selenoproteins as the amino acid selenocysteine - sometimes referred to as the 21'st amino acid. To date, 25 selenoprotein families have been identified in humans, among which the most relevant to thyroid physiology are the glutathione peroxidases (GPx), the thioredoxin reductases (TrxR), and the iodothyronine deiodinases (DIO). The thyroid gland contains the highest concentration of selenium per gram of tissue of any organ in the human body, reflecting the critical dependence of thyroid homeostasis on adequate selenium availability. The DIO enzymes - comprising three isoforms (DIO1, DIO2, and DIO3) - are selenocysteine-containing enzymes responsible for the peripheral activation and inactivation of thyroid hormones: DIO1 and DIO2 catalyze the conversion of the prohormone thyroxine (T4) into the biologically active triiodothyronine (T3), while DIO3 inactivates both T4 and T3. In parallel, GPx1, GPx3, and thioredoxin reductase 1 (TrxR1) protect thyrocytes from oxidative damage generated during thyroid hormone synthesis, particularly from hydrogen peroxide (H2O2) produced in large quantities by thyroid peroxidase (TPO) during iodine organification. Selenium deficiency therefore disrupts thyroid hormone metabolism at multiple levels, impairing both T3 production and antioxidant defense, ultimately predisposing to thyroid dysfunction and autoimmunity.

The most extensively studied clinical application of selenium supplementation in thyroid disease refers to Hashimoto's thyroiditis (HT). Multiple randomized controlled trials and several meta-analyses have examined the effect of selenium - primarily in the form of selenomethionine or sodium selenite at a dose of 200 μg/day - as an addition to levothyroxine (LT4) therapy in patients with HT. A meta-analysis (Kong et al., 2023) which pooled data from 21 RCTs involving 1,610 subjects, demonstrated that selenium supplementation significantly reduced serum thyroid peroxidase antibody (TPOAb) levels at both three months and six months. Thyroglobulin antibody (TgAb) name also decreased significantly at three months, though the effect was not sustained at six months. Notably, a significant reduction in TSH levels was observed after six months of supplementation. A more recent and methodologically rigorous systematic review and meta-analysis (Huwiler et al., 2024) including 35 RCTs, further confirmed these findings. This analysis demonstrated a significant TSH-lowering effect of selenium, but exclusively in HT patients not receiving thyroid hormone replacement therapy

(THRT), suggesting that the benefit may be more pronounced in patients in the earlier, non-hypothyroid phases of the disease. No significant effect on free T4 or free T3 levels was observed across the majority of included studies, suggesting that selenium's primary mechanism of action in HT is immunomodulatory rather than directly related to hormone synthesis.

The clinical efficacy of selenium supplementation appears to be influenced by the chemical form of selenium used, the administered dose, and the baseline selenium status of the patient. Organic forms of selenium, particularly selenomethionine (SeMet), are generally preferred in clinical practice due to their superior bioavailability and more favorable toxicity profile compared with inorganic forms such as sodium selenite. SeMet is stored in body proteins - particularly muscle proteins - and is released gradually in accordance with protein turnover, thereby providing a more sustained supply of selenium. In contrast, inorganic selenium forms have a narrower therapeutic window and a greater potential for cumulative toxicity. A dose of 200 μg/day of selenomethionine has been most consistently employed in clinical trials and appears necessary for maximal induction of GPx activity; studies using 100 μg/day have reported less consistent reductions in autoantibody names. Baseline selenium status is a critical determinant of treatment response: among 18 studies that measured serum selenium at baseline in HT patients, approximately 50% reported severe deficiency and 39% mild deficiency, with only 11% of participants being selenium-sufficient. This suggests that much of the observed benefit may reflect correction of underlying deficiency rather than a pharmacological effect of supraphysiological selenium dosing.

The evidence for selenium supplementation in Graves' disease (GD) and Graves' orbitopathy (GO) is both distinct and clinically significant. The landmark randomized, double-blind, placebo-controlled trial conducted by the European Group on Graves' Orbitopathy (EUGOGO) - published in the New England Journal of Medicine in 2011 - demonstrated that sodium selenite (100 μg twice daily for six months) significantly improved quality of life, reduced eye involvement, and slowed the progression of mild GO compared to placebo, with the benefit sustained at 12-month follow-up. This trial, conducted in European countries with marginal selenium status, established selenium as the first evidence-based pharmacological adjunct in mild GO and has since influenced international clinical guidelines. A subsequent meta-analysis of four RCTs confirmed these findings, reporting that selenium was superior to placebo at six months in reducing the Clinical Activity Score and improving GO-specific quality of life. In patients with Graves' hyperthyroidism without orbitopathy, the evidence is less conclusive. A 2019 meta-analysis incorporating ten RCTs and 796 GD patients suggested that adjuvant

selenium accelerates the restoration of biochemical euthyroidism when combined with antithyroid drugs (ATDs), primarily methimazole. However, the long-term GRASS trial - a multicenter Danish RCT of selenium supplementation in GD - reported that supplemental selenium did not significantly affect remission rates or recurrence after ATD discontinuation, highlighting the need for larger and longer-term trials in selenium-sufficient populations.

Selenium supplementation at doses of 100 to 200 μg/day is generally well tolerated. Adverse events reported in clinical trials have been mild and transient, including gastrointestinal disturbances, and have not differed significantly from placebo groups. However, selenium has a narrow therapeutic index and chronic intake exceeding 400 μg/day - the tolerable upper intake level established by the European Food Safety Authority - may result in selenosis, characterized by nail changes, alopecia, gastrointestinal symptoms, and neurological problems. It is therefore of clinical importance to assess baseline selenium status before initiating supplementation, and to avoid routine supplementation in selenium-sufficient individuals. Based on the available evidence, the 2022 European Thyroid Association (ETA) guidelines recommend selenium supplementation (200 μg/day selenomethionine) as an adjunct to LT4 in patients with HT, particularly those with elevated autoantibodies and selenium deficiency. For mild GO, selenium supplementation (200 μg/day sodium selenite for six months) is recommended by both EUGOGO and the ETA, with the condition that efficacy in selenium-sufficient populations requires further investigation.

Iodine

Iodine is the only micronutrient with a clearly defined, non-substitutable role in human physiology: it serves as the essential substrate for the biosynthesis of thyroid hormones. The adult thyroid gland contains approximately 70–80% of the total body iodine content, maintaining an intrathyroidal concentration of approximately 8,000 μg. The recommended dietary allowance (RDA) for iodine in non-pregnant adults is 150 μg/day, rising to 220–250 μg/day during pregnancy and 290 μg/day during lactation, reflecting the substantially increased demand for thyroid hormone production, fetal iodine supply, and transfer of iodine into breast milk. The biosynthetic pathway of thyroid hormones is critically dependent on adequate iodine availability: dietary iodide is absorbed in the small intestine, transported into thyrocytes via the sodium-iodide symporter (NIS) at the basolateral membrane, and subsequently oxidized by thyroid peroxidase (TPO) in the presence of hydrogen peroxide (H_2O_2) at the apical membrane-follicular lumen interface. TPO catalyzes the organification of iodide into tyrosyl residues

within thyroglobulin (Tg) to form monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are subsequently coupled to produce thyroxine (T4, from two DIT molecules) and triiodothyronine (T3, from one DIT and one MIT). The mature, iodinated thyroglobulin is stored as colloid within the follicular lumen and undergoes proteolysis upon TSH stimulation to release T4 and T3 into the circulation.

Iodine deficiency (ID) remains the most common preventable cause of thyroid dysfunction and neurodevelopmental impairment worldwide. Despite significant progress in global iodine nutrition through universal salt iodisation (USI) programs, an estimated 1.9 billion individuals worldwide are at risk of iodine deficiency disorders (IDDs). In regions of severe deficiency, insufficient iodine availability for thyroid hormone synthesis leads to compensatory TSH hypersecretion, thyroid hyperplasia, and ultimately the development of endemic goiter and hypothyroidism. In mild-to-moderate iodine deficiency, the thyroid can maintain euthyroidism in most individuals through adaptive mechanisms including increased iodine uptake efficiency, preferential T3 synthesis, and enhanced recycling of intrathyroidal iodine; however, this compensatory activity results in chronic TSH stimulation and a progressive increase in the prevalence of nodular goiter and autonomous thyroid function. In patients already receiving levothyroxine (LT4) therapy for hypothyroidism, coexisting iodine deficiency may impair residual thyroid function and increase LT4 dose requirements, while also contributing to thyroid volume enlargement. The WHO defines adequate iodine status in the general population as a median urinary iodine concentration (UIC) of 100–199 μg/L; in pregnant women, the recommended median UIC is 150–249 μg/L.

The relationship between iodine and thyroid function follows a U-shaped curve, whereby both deficiency and excess are associated with adverse thyroid outcomes. Iodine excess - whether from dietary sources such as seaweed, iodinated contrast media, amiodarone, or supplementation - triggers the Wolff-Chaikoff effect, an intrinsic autoregulatory mechanism in which acute elevation of intrathyroidal iodide concentration transiently inhibits TPO-mediated organification of iodine, thereby suppressing thyroid hormone synthesis. In healthy individuals, this inhibitory effect is transient and lasts approximately 24–48 hours, after which an escape phenomenon occurs mediated by downregulation of NIS expression, reducing iodide transport and restoring organification. However, in patients with underlying autoimmune thyroid disease - including Hashimoto's thyroiditis and those previously treated for Graves' disease with radioiodine or surgery - the escape from the Wolff-Chaikoff effect may fail to occur, resulting in clinically significant iodine-induced hypothyroidism. Conversely, in patients with

longstanding multinodular goiter or autonomous thyroid nodules - conditions more prevalent in chronically iodine-deficient populations - iodine loading may precipitate hyperthyroidism via the Jod-Basedow phenomenon, reflecting unregulated hormone synthesis by autonomously functioning nodular tissue. These bidirectional risks render iodine supplementation in thyroid disease patients a nuanced clinical decision.

In iodine-sufficient populations, routine iodine supplementation as an adjunct to LT4 or antithyroid drug therapy is not recommended, as supplemental iodine confers no additional benefit and may precipitate thyroid dysfunction in susceptible individuals. The therapeutic role of iodine supplementation is principally confined to correction of deficiency states. In pregnant women, adequate iodine intake is of paramount importance: the WHO and the American Thyroid Association (ATA) recommend a daily iodine intake of 250 μg/day and 150 μg/day supplementation, respectively, for pregnant and lactating women, due to the critical role of maternal thyroid hormones in fetal neurodevelopment during the first trimester, prior to the onset of fetal thyroid function at approximately 12 weeks of gestation. A systematic review (Taylor et al.) concluded that iodine supplementation in mildly-to-moderately deficient pregnant women reduced maternal thyroid volume and thyroglobulin concentrations, though effects on TSH and free T4 were inconsistent and evidence for neurodevelopmental benefit in offspring remained insufficient. For hypothyroid pregnant women already receiving LT4 therapy, careful monitoring of iodine status via urinary iodine concentration measurement is advisable, and targeted supplementation should be considered when deficiency is confirmed, as iodine deficiency in this population may impair the adequacy of thyroid hormone replacement and compromise fetal outcomes.

The relationship between iodine intake and thyroid autoimmunity is complex and not fully elucidated. Epidemiological data suggest that rapid increases in population iodine intake following the introduction of salt iodisation programs are associated with a transient rise in the prevalence of subclinical hypothyroidism and elevated thyroid autoantibodies, attributable to increased iodination of thyroglobulin rendering it more immunogenic. In Hashimoto's thyroiditis patients receiving LT4, high iodine intake should be actively avoided, as excess iodine may exacerbate thyrocyte destruction by augmenting oxidative stress through increased H_2O_2 generation, and the failure of the Wolff-Chaikoff escape mechanism in these patients can precipitate or worsen hypothyroidism, necessitating LT4 dose adjustment. Similarly, in patients with Graves' disease treated with antithyroid drugs, excessive iodine intake can blunt the therapeutic response to methimazole or propylthiouracil by providing excess substrate for

hormone synthesis, and should be minimized during the active treatment phase. In clinical practice, assessment of iodine status should therefore be an integral component of the nutritional evaluation of all patients with thyroid disease, and any supplementation must be individualized based on verified deficiency status, underlying thyroid pathology, and concurrent pharmacological treatment.

Vitamin D

Vitamin D is a fat-soluble steroid hormone that exists in two principal dietary forms: ergocalciferol (VitD2, of plant and fungal origin) and cholecalciferol (VitD3, synthesised in the skin upon ultraviolet B radiation exposure and found in animal-derived foods). Both forms undergo sequential hepatic hydroxylation to 25-hydroxyvitamin D (25(OH)D) — the main circulating storage form used to assess nutritional status - and subsequent renal hydroxylation by the enzyme CYP27B1 to the biologically active metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$, calcitriol). The classical biological role of vitamin D encompasses the regulation of calcium and phosphorus homeostasis and the maintenance of bone mineralization. However, the discovery that the vitamin D receptor (VDR) and the enzyme CYP27B1 are expressed in virtually all immune cells - including dendritic cells, macrophages, monocytes, natural killer cells, and both T and B lymphocytes - has led to a substantial expansion of understanding of vitamin D as a critical immunomodulatory hormone. This local conversion of 25(OH)D into calcitriol within immune tissues enables autocrine and paracrine immunoregulatory effects that are largely independent of circulating calcitriol concentrations, explaining why vitamin D status may influence immune function even in patients with apparently normal serum calcium levels.

The immunomodulatory mechanisms of vitamin D are particularly relevant to autoimmune thyroid disease. Calcitriol, via VDR activation, exerts a broad immunosuppressive effect on the adaptive immune response: it inhibits the maturation and antigen-presenting capacity of dendritic cells, thereby reducing T-cell activation; it suppresses the differentiation and proliferation of pro-inflammatory Th1 and Th17 lymphocyte subsets, reducing the production of cytokines including IFN-γ, IL-2, IL-17, and TNF-α; and it promotes the differentiation of $CD4^+FoxP3^+$ regulatory T cells (Tregs), which are central to the maintenance of immune tolerance. In Hashimoto's thyroiditis, the pathological process is driven predominantly by a Th1/Th17-dominant immune response leading to lymphocytic infiltration and progressive thyrocyte destruction; restoration of the Th17/Treg balance by vitamin D is therefore a mechanistically plausible and experimentally supported therapeutic target. Additionally, VDR

activation downregulates HLA class II gene expression in thyroid tissue, thereby reducing antigen presentation to autoreactive lymphocytes, and inhibits B-cell differentiation into plasma cells, attenuating autoantibody production. VDR gene polymorphisms (notably at the BsmI, ApaI, FokI, and TaqI loci) modulate VDR expression and signaling efficiency and have been associated with both susceptibility to autoimmune thyroid disease and differential responsiveness to vitamin D supplementation.

Vitamin D deficiency (defined as serum 25(OH)D < 20 ng/mL) is highly prevalent in patients with autoimmune thyroid disease. A frequently cited observational study comparing thyroid disease patients and healthy controls found that vitamin D deficiency was present in 63% of all thyroid disease patients versus 30% of controls ($p < 0.001$), with the highest prevalence in Hashimoto's thyroiditis (79%) compared to non-autoimmune thyroid conditions. A meta-analysis (Wang et al.) of 20 case-control studies comprising 3,603 participants found that patients with autoimmune thyroid disease had significantly lower serum 25(OH)D levels compared to controls and were nearly three times more likely to be vitamin D deficient. Whether this deficiency represents a causative factor in disease pathogenesis, a consequence of chronic immune activation, or a component of a self-perpetuating vicious cycle remains a matter of ongoing investigation, as prospective and Mendelian randomization studies have yielded inconsistent results.

Multiple randomized controlled trials and meta-analyses have examined the effect of vitamin D supplementation on thyroid autoantibody levels and thyroid function in patients with Hashimoto's thyroiditis, predominantly as an adjunct to levothyroxine therapy. A meta-analysis (Zhang et al., 2021) - pooling data from eight RCTs - found that vitamin D supplementation significantly reduced both TPOAb name and TgAb name using a random-effects model, with subgroup analysis indicating that treatment duration exceeding three months showed a more pronounced and statistically significant reduction in TPOAb. A more recent and comprehensive meta-analysis (Tang et al.,2023), including 18 RCTs with data collected from inception to August 2023, confirmed a significant reduction in TPOAb and TgAb levels following vitamin D supplementation, with the greatest effect observed in patients with baseline 25(OH)D levels below 20 ng/mL. Furthermore, a 2023 meta-analysis of studies specifically examining vitamin D supplementation effects on thyroid autoantibodies in autoimmune thyroid disease, including patients across both HT and Graves' disease subgroups, confirmed that at least six months of vitamin D treatment was associated with a significant decrease in serum TPOAb levels. Effects on TSH, free T3, and free T4 were generally non-significant across most meta-analyses,

consistent with the notion that vitamin D exerts its primary benefit through immunomodulatory mechanisms rather than direct effects on thyroid hormone synthesis or metabolism. Notably, the landmark VITAL trial - a large-scale RCT of 25,871 participants - demonstrated that daily supplementation with 2000 IU vitamin D3 for five years was associated with a 22% reduction in the risk of developing any autoimmune disease, including autoimmune thyroid disorders.

The optimal dose and formulation of vitamin D supplementation in thyroid disease patients have not been definitively established and currently lack formal endorsement in major endocrinology guidelines. Most clinical trials have employed doses of cholecalciferol (VitD3) ranging from 1,000 to 4,000 IU/day, with some studies using weekly or monthly bolus regimens. A dose of 2,000–4,000 IU/day has been suggested as the therapeutic window most consistently associated with meaningful reductions in autoantibody names, particularly in vitamin D-deficient patients, with the caveat that doses up to 4,000 IU/day remain within the tolerable upper intake level established by most regulatory authorities. Higher-dose regimens (exceeding 10,000 IU/day) carry a risk of vitamin D toxicity, characterized by hypercalcaemia, nephrocalcinosis, and soft tissue calcification, and should be avoided without biochemical monitoring. In clinical practice, assessment of baseline 25(OH)D concentration is recommended prior to initiating supplementation, both to confirm deficiency and to guide appropriate dosing. For hypothyroid patients receiving LT4 therapy, vitamin D supplementation may be considered as an evidence-supported adjunct in those with confirmed deficiency, with the aim of achieving a serum 25(OH)D target of at least 30 ng/mL (75 nmol/L). The clinical benefit of supplementation in vitamin D-replete patients remains less clearly established.

Zinc

Zinc (Zn) is the second most prevalent trace element in the human body and serves as an essential cofactor or structural component in more than 300 enzymatic reactions, including those involved in DNA synthesis, immune function, and cellular signaling. Its interaction with thyroid hormone metabolism is multifaceted and operates at several levels of the hypothalamic-pituitary-thyroid (HPT) axis. At the hypothalamic level, zinc mediates the binding of triiodothyronine (T3) to its nuclear receptor, thereby facilitating T3-dependent gene transcription of thyrotropin-releasing hormone (TRH) - the primary driver of the HPT axis. At the pituitary level, zinc participates in the synthesis and secretion of thyrotropin (TSH) by thyrotroph cells. Within the thyroid gland itself, zinc is required for the activity of thyroid

transcription factor 2 (TTF-2), a zinc finger protein that binds to the promoter regions of the thyroglobulin and thyroid peroxidase (TPO) genes, thereby regulating thyroid hormone biosynthesis at the transcriptional level. At the peripheral level, zinc functions as a cofactor of type 1 and type 2 iodothyronine deiodinases (DIO1 and DIO2), which are responsible for the conversion of thyroxine (T4) to the biologically active T3 in the liver, kidney, and skeletal muscle; zinc deficiency has been shown to reduce hepatic DIO1 activity by up to 67%, impairing peripheral T3 generation. Finally, zinc is integral to the structural conformation of the thyroid hormone nuclear receptor (TR): the T3 receptor contains zinc finger domains that are required to adopt the biologically active configuration necessary for DNA binding and transcriptional activation, meaning that zinc deficiency may impair T3 signaling at the cellular level even in the presence of normal circulating T3 concentrations.

Clinical and epidemiological data consistently support a bidirectional relationship between zinc status and thyroid function. Zinc deficiency has been associated with reduced serum T3 and T4 concentrations, elevated reverse T3 (rT3), and impaired TSH response to TRH stimulation, consistent with a functional hypothyroid state attributable to deficient peripheral T4-to-T3 conversion and reduced HPT axis activity. Conversely, hypothyroidism itself can reduce intestinal zinc absorption - as thyroid hormones regulate the expression of zinc transporters in the gastrointestinal mucosa - creating a self-perpetuating cycle in which hypothyroidism worsens zinc deficiency, which in turn further impairs thyroid function. A systematic review and meta-analysis (Talebi et al., 2020) evaluated trace element status in hypothyroid patients and reported that serum zinc levels were significantly lower in hypothyroid individuals compared to euthyroid controls. A further systematic review by Beserra et al. (2021), specifically examining the relationship between zinc and thyroid hormones in humans across 18 studies, confirmed a positive correlation between serum zinc concentrations and circulating T3 levels, while highlighting the heterogeneity of available evidence and the limited number of high-quality interventional studies.

The most methodologically reliable evidence for zinc supplementation as an adjunct to thyroid pharmacotherapy comes from a randomized, double-blind, placebo-controlled trial by Nishiyama et al., in which hypothyroid patients with confirmed zinc deficiency received oral zinc sulphate supplementation for 12 months. Following supplementation, levels of serum free T3 and total T3 normalized, serum reverse T3 (rT3) decreased, and the TRH-stimulated TSH response normalized, suggesting restoration of both peripheral T4-to-T3 conversion and HPT axis responsiveness. A subsequent RCT (Mahmoodianfard et al., 2015) randomized 68

overweight or obese hypothyroid women on stable LT4 therapy to four groups: zinc alone (30 mg/day zinc gluconate), selenium alone (200 μg/day), zinc plus selenium, or placebo for 12 weeks. The zinc-alone group demonstrated a significant increase in serum FT3 and a reduction in TSH compared to placebo, while the combination group showed significant improvements in both FT3 and FT4. A randomized controlled trial (Rabbani et al., 2021) further evaluated co-supplementation with zinc (30 mg/day), magnesium, and vitamin A in 86 hypothyroid patients over 10 weeks, reporting a significant increase in serum FT4 and a reduction in hs-CRP in the intervention group compared to placebo, suggesting concomitant anti-inflammatory effects. Additionally, a pediatric RCT examining zinc supplementation (25 mg elemental zinc daily for 12 weeks) in children and adolescents with autoimmune thyroid disease demonstrated significant reductions in both TPOAb and TgAb names, with a favorable effect on oxidative stress markers, indicating a potential immunomodulatory role for zinc in the context of autoimmune thyroid disease.

The interplay between zinc and selenium is of particular clinical relevance in the context of thyroid disease. Both micronutrients share overlapping metabolic roles - particularly in deiodinase activity and antioxidant defense - and their deficiencies frequently co-occur in patients with autoimmune thyroid disease and in populations consuming selenium- and zinc-poor diets. Animal studies have demonstrated positive bidirectional interactions between selenium and zinc status, with selenium administration partially correcting zinc deficiency and vice versa. In the clinical context, data from the NHANES 2007–2012 cohort study demonstrated that low dietary zinc intake was independently associated with an increased risk of new-onset hypothyroidism, and that the interaction between low selenium and low zinc intake further amplified this risk. A systematic review of RCTs (Zavros et al., 2023) concluded that zinc supplementation increased FT3 levels in hypothyroid patients, although this finding was based on limited evidence, and the effects of combined zinc-selenium supplementation on thyroid function remained inconclusive due to the small number of available studies and significant methodological heterogeneity.

The clinical application of zinc supplementation in thyroid disease requires careful consideration of dose, formulation, and patient zinc status. The RDA for zinc is 8–11 mg/day in adults, with a tolerable upper intake level of 40 mg/day established by the Institute of Medicine. Therapeutic doses employed in clinical trials of thyroid disease have ranged from 25 to 30 mg/day of elemental zinc, commonly administered as zinc gluconate or zinc sulphate. Chronic supplementation at doses exceeding 40 mg/day carries a risk of copper deficiency -

attributable to competition between zinc and copper for intestinal absorption via the metal transporter ZIP4 - which may paradoxically impair thyroid function given copper's role in ceruloplasmin-mediated iron transport and mitochondrial function. Assessment of baseline serum zinc concentrations is therefore advisable prior to supplementation, and routine zinc supplementation in zinc-replete thyroid patients is not currently supported by evidence. Importantly, the overall evidence base for zinc supplementation in thyroid disease remains limited by the small number of RCTs, short study durations, heterogeneous patient populations, and variable outcome measures; larger, well-designed trials with longer follow-up are required before definitive clinical recommendations can be issued.

Magnesium and Myo-Inositol

Magnesium (Mg) is the fourth most abundant mineral in the human body and serves as a cofactor in over 300 enzymatic reactions, including those involved in ATP synthesis, nucleic acid stabilization, protein synthesis, and membrane ion transport. Its relationship with thyroid function is mediated through several interconnected mechanisms. At the mitochondrial level, magnesium is an obligatory cofactor of the mitochondrial ATP synthase (Complex V), directly linked to ATP production via oxidative phosphorylation. Adequate intracellular magnesium is therefore essential for the energy-dependent processes of thyroid hormone biosynthesis, including the active transport of iodide into thyrocytes via the sodium-iodide symporter (NIS), which is driven by the Na^+/K^+-ATPase gradient. Experimental evidence from animal models has demonstrated that magnesium supplementation significantly augments radioactive iodine uptake by thyroid cells, while magnesium deficiency impairs iodide transport and reduces thyroid hormone synthesis, consistent with the critical role of ATP availability in NIS-mediated iodide accumulation. In addition, magnesium modulates the bioavailability and activity of vitamin D by serving as a cofactor for the hydroxylation enzymes CYP2R1 and CYP27B1 responsible for the sequential activation of cholecalciferol to calcitriol; magnesium deficiency may therefore impair the anti-inflammatory and immunomodulatory actions of vitamin D in thyroid tissue, highlighting the interconnected nature of micronutrient status in thyroid autoimmunity.

The relationship between magnesium and thyroid function is well established in both experimental and clinical literature. Serum magnesium levels are characteristically elevated in hypothyroidism and decreased in hyperthyroidism, a pattern attributable to the influence of thyroid hormones on magnesium renal clearance and cellular distribution. In hyperthyroid

patients, elevated thyroid hormone levels accelerate magnesium excretion and reduce magnesium retention, leading to a catabolic state of relative hypomagnesaemia; indeed, the symptomatology of magnesium deficiency - including neuromuscular excitability, tachycardia, anxiety, and fatigue - closely parallels that of thyrotoxicosis, a clinical overlap noted as early as the mid-twentieth century. A large cross-sectional study of 3,748 adults in Tianjin, China, (Wang et al., 2018) demonstrated that severely low serum magnesium (≤0.55 mmol/L) was independently associated with a significantly increased risk of positive TgAb, the prevalence of Hashimoto's thyroiditis, and (subclinical) hypothyroidism. Notably, non-severely low magnesium (0.55–0.85 mmol/L) was not associated with autoantibody levels or thyroid function, suggesting a threshold effect at which only severe depletion materially impairs thyroid immune regulation. In patients with latent Hashimoto's thyroiditis with elevated TPOAb and mild iodine deficiency, co-reductions in serum calcium, magnesium, and zinc have been described, indicative of a broader pattern of concurrent micronutrient depletion in active thyroid autoimmunity.

Myo-inositol (MYO) is the most abundant and physiologically active stereoisomer of the inositol family, a group of cyclic polyols bearing six hydroxyl groups. It is a precursor of phosphoinositide's - specifically phosphatidylinositol (PtdIns) and its phosphorylated derivatives - which serve as essential second messengers in multiple intracellular signalling cascades. In thyroid physiology, the TSH receptor (TSHR) signals through two principal G-protein-coupled pathways: the adenylate cyclase/cAMP/PKA pathway and the phospholipase C (PLC)/inositol trisphosphate (IP3)/Ca^{2+}/diacylglycerol (DAG) pathway. Myo-inositol is the immediate precursor of phosphatidylinositol 4,5-bisphosphate (PIP_2), the substrate of PLC, which upon TSH receptor activation generates IP_3 and DAG as second messengers. IP_3 triggers intracellular calcium release and activates NADPH oxidase (DUOX2), which generates the hydrogen peroxide (H_2O_2) required for TPO-mediated thyroid hormone biosynthesis. It follows that depletion of intracellular myo-inositol, or impairment of the PLC-dependent inositol phosphate signalling cascade, reduces the capacity of thyrocytes to produce H_2O_2 in response to TSH stimulation, thereby attenuating thyroid hormone synthesis and predisposing to hypothyroidism. This mechanistic framework has been comprehensively reviewed (Benvenga et al., 2021) and provides a compelling rationale for clinical investigation of myo-inositol as an adjunct to thyroid pharmacotherapy.

The clinical evidence for myo-inositol supplementation in thyroid disease derives principally from studies examining its use in combination with selenium in patients with autoimmune

thyroid disease-related subclinical hypothyroidism (SCH). The inaugural RCT in this field was published by Nordio and Pajalich in 2013, in which 48 women with AITD-related SCH (TSH 4.01–9.99 mIU/L, positive TPOAb and TgAb) were randomized to receive either 600 mg/day myo-inositol plus 83 μg/day selenomethionine (MYO+Se) or selenomethionine alone for six months. The MYO+Se group demonstrated a 31% reduction in TSH (from 4.4 to 3.0 mIU/L; $p < 0.001$), a 36% reduction in TPOAb, and a 25% reduction in TgAb, while the selenium-only group showed improvements limited primarily to autoantibody names without significant TSH normalization, suggesting an additive and mechanistically distinct contribution of myo-inositol to the selenium-mediated effect. A subsequent and larger RCT by Nordio and Basciani (2017), enrolling 168 patients with Hashimoto's thyroiditis and TSH 3–6 mIU/L randomized to MYO+Se or Se alone, confirmed these findings: TSH, TPOAb, and TgAb levels were all significantly decreased in the combined treatment group, with restoration of euthyroidism reported in a substantial proportion of participants. A further study (Ferrari et al., 2017) demonstrated that MYO+Se treatment reduced the risk of progression from subclinical to overt hypothyroidism in patients with autoimmune thyroiditis compared to selenium alone, suggesting a potential disease-modifying benefit. Additionally, a study (Pace et al., 2020) reported that combined myo-inositol and selenium supplementation was associated with slower progression of thyroid autoimmunity and a reduction in thyroid volume in patients with Hashimoto's thyroiditis over 24 months of follow-up.

The therapeutic regimen most consistently employed across clinical studies combines myo-inositol (600 mg/day) with selenomethionine (83–200 μg/day), typically administered orally as a fixed-dose combination for a minimum of six months. Myo-inositol is well tolerated at these doses, with no clinically significant adverse effects reported in any of the published trials; it is a naturally occurring molecule synthesized endogenously and present in a wide range of dietary sources including fruits, beans, grains, and nuts, with an estimated average daily dietary intake of approximately 1 gram. The evidence base for magnesium supplementation as an independent adjunct to thyroid pharmacotherapy remains considerably more limited: while the mechanistic rationale is sound and observational data consistently demonstrate an association between magnesium deficiency and thyroid dysfunction, dedicated interventional RCTs evaluating isolated magnesium supplementation on thyroid outcomes are scarce. The available interventional evidence is largely derived from multi-micronutrient co-supplementation trials - such as the Rabbani et al., 2021 RCT of zinc, magnesium, and vitamin A - which do not allow attribution of effects to magnesium alone. Assessment of serum magnesium concentration in

patients with autoimmune thyroid disease is therefore clinically advisable, and correction of confirmed deficiency should be considered as part of a comprehensive nutritional management approach. The combination of myo-inositol and selenium represents the most evidence-supported nutritional adjunct specifically targeting the TSH signaling pathway, and may be of particular benefit in patients with HT-related SCH who do not yet meet criteria for pharmacological LT4 initiation.

Gluten-Free Diet

The association between coeliac disease (CD) and autoimmune thyroid disease (AITD) is among the most clinically relevant and well-documented comorbidity patterns in autoimmune endocrinology. Coeliac disease, a chronic immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (wheat, barley, and rye) in genetically susceptible individuals, affects approximately 1% of the general population in Western countries, though the prevalence of undiagnosed CD may be considerably higher. Epidemiological studies consistently demonstrate a significantly increased prevalence of AITD - particularly Hashimoto's thyroiditis - among patients with CD, with estimates ranging from 2% to 9% of CD patients carrying concurrent AITD, compared to approximately 1–3% in the general population. Conversely, the prevalence of CD among patients with AITD is elevated at 1.5‰3.2% compared to approximately 0.5–1% in age-matched controls without autoimmune disease. A systematic review and meta-analysis by Sun et al. (2016), pooling data from 10 studies encompassing 12,042 CD patients, confirmed a significantly increased incidence of thyroid disease in CD patients, supporting the clinical recommendation to screen all patients with confirmed CD for thyroid dysfunction at diagnosis and during follow-up.

The mechanistic basis for the co-occurrence of CD and AITD is multifactorial and not yet fully elucidated, but appears to involve at least three interconnected pathways: shared genetic susceptibility, intestinal barrier dysfunction, and molecular mimicry. From a genetic standpoint, both CD and AITD are associated with the human leukocyte antigen (HLA) DQ2 (encoded by DQA1*05/DQB1*02) and DQ8 (encoded by DQA1*03/DQB1*0302) haplotypes, as well as with non-HLA immune regulatory genes, most notably the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) gene, PTPN22, and CD40, all of which play central roles in the regulation of immune self-tolerance. Second, active, untreated CD is characterized by increased intestinal permeability - commonly referred to as 'leaky gut '- attributable to dysregulation of tight junction proteins by the cytokine zonulin and by inflammatory mediators such as IFN-γ. This

increased gut permeability facilitates the translocation of luminal antigens, gliadin peptides, and microbial products into the systemic circulation, thereby triggering and amplifying systemic immune activation, which may perpetuate or exacerbate thyroid autoimmunity. Third, molecular mimicry has been proposed as a mechanism whereby structural similarities between gliadin peptides and thyroid antigens (notably tissue transglutaminase, which shares immunogenic epitopes with thyroid transglutaminase) may induce cross-reactive autoimmune responses, resulting in the generation of anti-thyroid antibodies in genetically susceptible individuals exposed to gluten.

In patients with confirmed coeliac disease and concurrent autoimmune thyroid disease, adherence to a strict gluten-free diet (GFD) has been associated with several clinically relevant benefits, including improved intestinal absorption of levothyroxine, reduction in LT4 dose requirements, and — in some studies — reduction in thyroid autoantibody names. The impairment of LT4 absorption in patients with untreated CD is well established: intestinal villous atrophy reduces the absorptive surface area of the proximal small intestine where LT4 is principally absorbed, resulting in increased LT4 dose requirements and TSH instability despite apparently adequate oral dosing. Krysiak et al., 2019) conducted a prospective pilot study enrolling 34 women with HT and positive anti-tissue transglutaminase (anti-tTG) antibodies, 16 of whom adhered to a GFD for six months. The GFD group demonstrated a significant reduction in both TPOAb and TgAb titers, a slight increase in serum 25(OH)D levels, and an improvement in thyroid secretory capacity (as measured by the SPINA-GT index) compared to the non-dietary group, suggesting a thyroid-specific benefit of gluten elimination beyond the restoration of intestinal integrity. Similarly, Sategna-Guidetti et al. demonstrated that patients with CD who maintained strict GFD adherence for at least 12 months showed normalization of previously elevated anti-thyroid antibodies in a proportion of cases, accompanied by restoration of normal TSH levels, providing early clinical evidence for the thyroid-directed benefit of GFD in patients with overt CD.

The more contentious and clinically relevant question pertains to whether a gluten-free diet confers benefit in patients with Hashimoto's thyroiditis in the absence of confirmed CD or non-coeliac gluten sensitivity (NCGS). This question has gained clinical urgency given the widespread and often self-initiated adoption of GFD among HT patients, frequently without prior serological or histological evaluation for CD. A meta-analysis by Piticchio et al., 2023) - the most comprehensive quantitative synthesis to date, adhering to MOOSE guidelines and including four studies with a total of 87 HT patients without confirmed CD or histological

intestinal changes — reported a trend towards reduction in both TgAb and TPOAb that narrowly missed statistical significance over a mean GFD period of approximately six months. Notably, TSH was significantly reduced and FT4 was significantly increased, while FT3 showed no significant change. Subgroup analyses revealed that the reduction in autoantibody names reached statistical significance specifically in patients with confirmed gluten-related conditions (GRC), including NCGS (TgAb $p = 0.02$; TPOAb $p = 0.02$), but not in those without GRC. These data suggest that the thyroid-directed benefit of GFD in HT patients without CD may be confined to the subgroup with underlying gluten sensitivity, and that routine adoption of GFD in unselected HT patients is not supported by the currently available evidence.

From a practical clinical standpoint, the current evidence supports the following approach to gluten restriction in patients with thyroid disease. First, all patients with AITD - particularly those with HT or Graves ’disease - should be screened for CD using serological testing (anti-tissue transglutaminase IgA with total IgA measurement to exclude IgA deficiency) at the time of thyroid diagnosis, given the significantly elevated prevalence of undiagnosed CD in this population. In patients with confirmed CD, strict and lifelong adherence to a GFD is mandatory and is expected to improve intestinal LT4 absorption, stabilize TSH, and potentially reduce thyroid autoantibody titers. In patients with AITD without confirmed CD but with clinical features suggestive of NCGS (including functional gastrointestinal symptoms, extraintestinal manifestations, or persistently elevated anti-gliadin antibodies without villous atrophy), a supervised trial of GFD may be clinically warranted, with monitoring of thyroid function and autoantibody levels as objective outcome measures. However, the routine recommendation of GFD to all HT patients in the absence of CD or NCGS is not currently justified by evidence and carries potential risks including nutritional inadequacy (reduced dietary fiber, B vitamins, iron, calcium, and zinc), increased food cost, and social burden, as well as the risk of inadvertently increasing dietary intake of naturally gluten-free but nutrient-poor processed foods. Screening for CD should precede any recommendation to adopt a GFD, as withdrawal of gluten prior to diagnostic evaluation will normalize serological markers and impair the sensitivity of biopsy-based diagnosis.

Discussion

The present narrative review synthesizes the available evidence on the role of dietary modifications and oral supplementation as adjuncts to pharmacological treatment in thyroid diseases. Collectively, the reviewed literature demonstrates that nutritional status is not merely

a passive determinant of thyroid function, but an active and modifiable factor that may meaningfully influence the clinical course of thyroid disorders, the efficacy of pharmacotherapy, and the degree of thyroid autoimmunity. The six interventions examined — selenium, iodine, vitamin D, zinc, magnesium/myo-inositol, and a gluten-free diet — operate through distinct yet frequently overlapping mechanisms, including modulation of thyroid hormone biosynthesis and peripheral metabolism, regulation of immune cell differentiation and autoantibody production, preservation of antioxidant defense mechanisms within the thyroid gland, and optimization of drug absorption and pharmacodynamic response. Taken together, the evidence supports the concept of an integrative nutritional approach to thyroid disease management, complementary to — rather than substituting for — established pharmacological treatment.

Among all the interventions reviewed, selenium emerges as the best evidenced and most clinically actionable nutritional adjunct in thyroid disease. The consistent reduction of TPOAb and TgAb titers observed across multiple meta-analyses, coupled with the landmark EUGOGO trial establishing sodium selenite as an evidence-based treatment for mild Graves ʾorbitopathy, has translated into formal guideline recommendations from both the European Thyroid Association and the European Group on Graves ʾOrbitopathy. However, a critical and frequently overlooked nuance is that the therapeutic benefit of selenium appears to be primarily confined to selenium-deficient individuals: when baseline selenium status is adequate, as in several Northern and Central European populations, the incremental benefit of supplementation is substantially attenuated. This observation has important implications for clinical practice in Poland and Central Europe, where marginal selenium status is prevalent, and where supplementation is most likely to confer benefit. Furthermore, the differential response to organic selenomethionine versus inorganic sodium selenite - the former being preferable for chronic immunomodulatory use in HT, the latter employed in the EUGOGO GO protocol - underscores the importance of matching the selenium form to the specific clinical indication.

Iodine occupies a unique position among thyroid-related micronutrients in that it is simultaneously indispensable and potentially harmful, with a narrow optimal range that varies by the underlying thyroid condition. The U-shaped dose-response relationship between iodine intake and thyroid function - encompassing the risks of both deficiency-related hypothyroidism and goiter on the one hand, and iodine-induced hypothyroidism via the Wolff-Chaikoff mechanism and Jod-Basedow-mediated hyperthyroidism on the other - renders iodine the most

clinically nuanced of the nutritional adjuncts reviewed. Critically, the widespread practice of recommending iodine supplementation to all patients with thyroid disease, irrespective of etiology and iodine status, is not only unsupported by evidence but potentially harmful. Patients with Hashimoto's thyroiditis are particularly vulnerable to iodine excess, given the impaired Wolff-Chaikoff escape mechanism and the enhanced immunogenicity of iodinated thyroglobulin. Conversely, iodine-deficient hypothyroid patients - including pregnant women - represent a specific population in whom targeted supplementation is both appropriate and essential. The clinical imperative is therefore individualized assessment of iodine nutritional status, ideally via urinary iodine concentration measurement, as the prerequisite for any supplementation decision.

Vitamin D and zinc share a complementary immunomodulatory role in the context of thyroid autoimmunity. Both micronutrients are deficient in a substantial proportion of patients with autoimmune thyroid disease, and both exert anti-inflammatory and immune-regulatory effects that mechanistically oppose the Th1/Th17-predominant pathological process underlying Hashimoto's thyroiditis. The meta-analytic evidence for vitamin D supplementation reducing TPOAb and TgAb titers is more robust and consistent than that for zinc, reflecting the larger body of RCTs available for vitamin D. Nonetheless, the interaction between these two micronutrients - illustrated by the finding that magnesium deficiency impairs vitamin D activation, and that combined zinc-selenium supplementation yields greater improvements in FT3 than either alone - highlights the importance of a comprehensive micronutrient assessment rather than a single-nutrient approach. Clinicians should be aware that correcting one micronutrient deficiency in isolation may yield a suboptimal response if co-existing deficiencies in other thyroid-relevant micronutrients remain unaddressed, a phenomenon increasingly recognised in the nutritional endocrinology literature as the 'multi-micronutrient interaction 'paradigm.

The combination of myo-inositol and selenomethionine represents a particularly promising and mechanistically well-grounded nutritional strategy in patients with Hashimoto's thyroiditis-related subclinical hypothyroidism (SCH). By simultaneously targeting the $PLC/IP_3/H_2O_2$ limb of TSH receptor signaling (myo-inositol) and the selenoprotein-dependent antioxidant and deiodinase systems (selenium), this combination addresses two complementary pathophysiological processes simultaneously. The clinical significance of this is greatest in the large and often clinically challenging population of HT patients with SCH (TSH 4–6 mIU/L)

who do not yet meet the threshold for pharmacological LT4 initiation according to current guidelines, yet who experience symptoms attributable to suboptimal thyroid function. In this population, MYO+Se supplementation may represent a safe, evidence-supported, non-pharmacological strategy to restore euthyroidism, reduce autoantibody titers, and potentially slow the progression to overt hypothyroidism, thereby delaying or obviating the need for LT4 initiation. Future RCTs should specifically evaluate this combination in well-defined SCH populations with long-term follow-up and include patient-reported quality-of-life outcomes.

The gluten-free diet remains the most debated of the nutritional interventions discussed in this review, reflecting the tension between the mechanistically plausible and epidemiologically supported CD-AITD association on one hand, and the limited and methodologically heterogeneous evidence for GFD benefit in HT patients without confirmed gluten-related conditions on the other. The current evidence justifies GFD only in clearly defined clinical contexts: patients with confirmed CD and concurrent AITD, and potentially patients with HT and confirmed or clinically suspected NCGS. The routine adoption of GFD by unselected HT patients - a practice that has become increasingly widespread in the context of social media-driven dietary trends - is not supported by the available data and carries non-trivial risks including micronutrient depletion, increased dietary costs, and the potential to mask or delay the diagnosis of CD if adopted prior to serological evaluation. The clinical priority is therefore universal CD screening in all AITD patients, followed by targeted dietary guidance based on confirmed diagnosis rather than empirical dietary restriction.

A clinically important dimension of nutritional adjunct therapy in thyroid disease concerns the interactions between dietary and supplemental interventions and concurrent pharmacological treatment. The absorption of levothyroxine is subject to interference by a broad range of dietary factors: calcium, iron, dietary fiber, coffee, soy products, and certain dietary supplements (including calcium carbonate, ferrous sulphate, and antacids) can significantly impair LT4 bioavailability when ingested concurrently, and patients should be consistently advised to take LT4 on an empty stomach at least 30–60 minutes before breakfast or at least 4 hours after the last meal or offending supplement. Conversely, correction of intestinal malabsorption - whether through adherence to a GFD in CD patients or through repletion of vitamin D deficiency, which itself regulates intestinal calcium and mineral transporter expression - may improve LT4 absorption and necessitate downward dose adjustment to prevent iatrogenic thyrotoxicosis. Similarly, for patients with Graves ’disease, dietary iodine restriction during antithyroid drug

therapy and avoidance of iodine-containing supplements, including certain seaweed-derived products and high-dose iodine-containing multivitamins, is advisable to optimize pharmacological efficacy. These pharmacokinetic and pharmacodynamic interactions reinforce the necessity of integrating nutritional assessment into the routine clinical management of thyroid disease.

Several important limitations of the existing evidence base must be acknowledged. Firstly, the majority of RCTs included in meta-analyses on selenium, vitamin D, and zinc supplementation are characterized by small sample sizes, short follow-up durations (typically three to six months), and heterogeneous patient populations, limiting the generalizability and clinical translation of their findings. Secondly, baseline micronutrient status is inconsistently measured and reported across studies, making it difficult to determine whether observed therapeutic effects reflect genuine pharmacological benefits or merely correction of pre-existing deficiencies. Thirdly, the concurrent use of multiple nutritional interventions in real-world clinical practice — as opposed to the single-intervention design of most RCTs — introduces complex interaction effects that are poorly characterized in the available literature. Fourthly, patient-reported outcome measures, including symptom burden, fatigue, quality of life, and psychological wellbeing, are underreported as primary outcomes in nutritional intervention trials in thyroid disease, despite their central importance to patients. Future research should prioritise large, well-powered, multi-arm RCTs with long-term follow-up, standardized baseline micronutrient profiling, patient-reported outcomes, and head-to-head comparison of combination nutritional strategies, ideally conducted in collaboration with thyroid disease patient advocacy groups to ensure the relevance and feasibility of trial designs.

Conclusions

The present narrative review demonstrates that dietary modifications and oral supplementation represent clinically relevant and evidence-supported adjuncts to pharmacological treatment in thyroid diseases, provided that their application is guided by individual patient assessment, confirmed micronutrient deficiency, and the specific thyroid condition being managed. The evidence is strongest and most clinically actionable for selenium supplementation, which is supported by multiple meta-analyses and formal guideline recommendations in both Hashimoto's thyroiditis and Graves 'orbitopathy, with the greatest benefit observed in selenium-deficient individuals. Vitamin D supplementation has demonstrated consistent reductions in thyroid autoantibody names in patients with autoimmune thyroid disease and

confirmed deficiency, with an emerging body of evidence supporting its immunomodulatory role via the Th17/Treg axis. Zinc, while mechanistically well-integrated into thyroid hormone metabolism at multiple levels of the HPT axis, remains supported by a more limited interventional evidence base, and its use is most appropriate in patients with confirmed deficiency. The combination of myo-inositol and selenium offers a mechanistically compelling and clinically promising strategy specifically in patients with Hashimoto's thyroiditis-related subclinical hypothyroidism who do not yet meet pharmacological treatment thresholds, with early RCT data suggesting a potential to restore euthyroidism and slow disease progression.

Iodine represents a unique case among the reviewed micronutrients: both its deficiency and its excess are associated with significant thyroid dysfunction, necessitating careful individualized assessment of iodine nutritional status before any supplementation is considered. In iodine-sufficient populations, routine supplementation as an adjunct to thyroid pharmacotherapy is not recommended and may be harmful in patients with autoimmune thyroid disease or autonomous nodular thyroid function. The gluten-free diet is indicated as a mandatory and potentially thyroid-protective intervention in patients with confirmed coeliac disease and concurrent autoimmune thyroid disease; however, its adoption in HT patients without confirmed CD or non-coeliac gluten sensitivity is not currently supported by robust evidence and carries the risk of nutritional inadequacy if implemented without proper dietary supervision.

From a broader clinical perspective, the findings of this review support the integration of comprehensive nutritional assessment - encompassing serum selenium, 25(OH)D, zinc, magnesium, and urinary iodine concentration - into the routine evaluation of patients with thyroid disease, alongside serological screening for coeliac disease in all patients with autoimmune thyroid conditions. Nutritional adjunct therapy should be considered as part of a personalized, multidisciplinary approach to thyroid disease management, complementing rather than replacing established pharmacological treatment with levothyroxine or antithyroid drugs. Clinicians should also be vigilant regarding the pharmacokinetic interactions between dietary factors and levothyroxine absorption, providing structured counselling to optimize drug bioavailability.

The current evidence base, while growing and mechanistically compelling, is still limited by the relatively small number of high-quality randomized controlled trials, short study durations, and heterogeneous patient populations. Larger, well-designed, multi-arm randomized controlled trials with long-term follow-up, standardized micronutrient profiling at baseline, and

inclusion of patient-reported quality-of-life outcomes are urgently needed to strengthen the evidence base and enable the formulation of specific, evidence-graded nutritional recommendations within future thyroid disease management guidelines. Until such evidence is available, the nutritional adjuncts reviewed herein should be applied selectively, with appropriate diagnostic evaluation, at evidence-based doses, and under the supervision of a qualified clinician.

Author's Contribution:

Conceptualization: MR,HRZ,PS,MT

Methodology: MR,HRZ,PS,MT

Formal analysis: MR,HRZ,PS,MT

Investigation: MR,HRZ,PS,MT

Supervision: MR,HRZ,PS,MT

Writing-rough preparation: MR,HRZ,PS,MT

Writing review and editing: MR,HRZ,PS,MT

Receiving founding: not applicable

All authors have read and agreed with the published version of the manuscript.

Funding:

The article did not receive any founding.

Institutional Review and bread Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Conflict of Interest Statement:

Not applicable.

AI:

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

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