FOOD BIOCHEMISTRY & NUTRITION

Editors
İrem KILINÇ
Yusuf Kenan HASPOLAT
Berna KILINÇ



orient

FOOD BIOCHEMISTRY & NUTRITION

Editors
İrem KILINÇ
Yusuf Kenan HASPOLAT
Berna KILINÇ

© Orient Yayınları. All right to this book are reserved and vested in Orient Yayınları.
No part of this book may be reproduced, or published in photocopying and electronic media without permission of the publisher.

FOOD BIOCHEMISTRY & NUTRITION

Editors
İrem KILINÇ
Yusuf Kenan HASPOLAT
Berna KILINÇ

Orient Publications: 293
2025

Editor-in-Chief: Serhat Buhari BAYTEKİN
Executive Editor: Üzeyir TEKİN
Editorial Director: Ayşen ALPASAR
Page and Cover Design: Toprak GÜNDOĞDU

Orient Publications
Certificate No: 17590
Cevizlidere Mahallesi, 1245. Sokak, 8/A
Çankaya/ANKARA
www.orientyayinlari.com

LIBRARY CARD

KILINÇ, İrem; HASPOLAT, Yusuf Kenan; KILINÇ, Berna
FOOD BIOCHEMISTRY & NUTRITION
16x24 cm
258 pages, references included
e-ISBN: 978-625-5976-31-4
1. Health, 2. Biochemistry, 3. Nutrition

Orient Publications is a brand of Enderun Publicity Service.
Printed in Türkiye
Scientific and legal responsibility of the articles belongs to the authors.

FOOD BIOCHEMISTRY & NUTRITION

Editors
İrem KILINÇ
Yusuf Kenan HASPOLAT
Berna KILINÇ

Orient

CONTRIBUTERS

Dr. İhsan SOYTEMİZ (Biologist) President of the Turkish Biologists Association	**Dr. Öznur KARACA VURAL, MD.** Department of Pediatrics, Ankara Etlik City Hospital, Ankara, Turkey
Dr. Ali Kansu TEHÇİ, MD. Department of Pediatrics, Ankara Etlik City Hospital, Ankara, Turkey	**Dr. Sanem SERT, MD.** Department of Pediatrics, Ankara Etlik City Hospital, Ankara, Turkey
Dr. Merve KAYA, MD. Dermatology and Venereology Specialist Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey	**Dr. Merve AKAY, MD.** Dermatology and Venereology Resident Ankara Bilkent City Hospital, Ankara,Turkey
Dr. Havva Nur PELTEK KENDİRCİ, MD. Department of Pediatric Endocrinology, Faculty of Medicine, Hitit University, Çorum, Turkey	**Dr. Ceren CEYLAN KIRAÇ, MD.** Department of Pediatrics, Faculty of Medicine, Balıkesir University, Balıkesir, Turkey
Dietitian, Dr. Şule BÖLÜKBAŞ ÖZDEMİR Hitit University Erol Olçok Training and Research Hospital Pediatric Diet Department, Çorum, Turkey	**Dietitian, Dr. İdil KARADEDE** Department of Nutrition and Dietetics, Yeditepe University, İstanbul, Turkey

Prof. Dr. Berna KILINÇ Department of Seafood Processing, Faculty of Fisheries, Ege University, İzmir, Turkey	**Assoc. Prof. Dr. Hülya HOŞGÖREN** Department of Biology, Faculty of Science, Dicle University, Diyarbakır, Turkey
Prof. Dr. Sema AGÜLOĞLU FİNCAN Department of Molecular Biology and Genetics, Faculty of Science, Dicle University, Diyarbakır, Turkey	**Assoc. Prof. Dr. İbrahim Halil GEÇİBESLER** Department of Occupational Health and Safety, Faculty of Health Sciences, Bingöl University, Bingöl, Turkey
Assoc. Prof. Dr. Serap TOPRAK DÖŞLÜ Department of Nutrition and Dietetics, Faculty of Health Sciences, Mardin Artuklu University, Mardin, Turkey	**Assoc. Prof. Dr. Gozde HASBAL CELIKOK** Department of Biochemistry, Faculty of Pharmacy, Istanbul University, Istanbul, Turkey
Lecturer. Dr. Nurten CENGİZ Department of Food Engineering, Faculty of Engineering, Adana Alparslan Türkeş Science and Technology University, Adana, Turkey	**Res. Asst. Dr. Müberra ÖZCAN** Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Süleyman Demirel University, Isparta, Turkey
İrem KILINÇ (Food Engineer) Department of Seafood Processing, Faculty of Fisheries, Izmir Katip Celebi University, Izmir, Turkey	**Nurgizem KAYNARCA (Biologist)** Institute of Graduate Studies in Health Sciences, Istanbul University, Istanbul, Turkey

CONTENTS

FOOD BIOTECHNOLOGY 1
SEMA AGÜLOĞLU FİNCAN

FOOD ADDITIVES, FOOD SUPPLEMENTS AND THEIR EFFECTS ON HEALTH 11
ŞULE BÖLÜKBAŞ ÖZDEMİR
HAVVA NUR PELTEK KENDİRCİ

COMPLEMENTARY FEEDING: BIOCHEMICAL FOUNDATIONS, NUTRITIONAL REQUIREMENTS AND CLINICAL PRACTICE 26
ALİ KANSU TEHÇİ

BIOCHEMICAL DYNAMISM AND NUTRITIONAL VALUE OF HUMAN MILK 50
SANEM SERT

BIOCHEMICAL FOUNDATION AND CLINICAL UTILIZATION OF PEDIATRIC FORMULAS 64
ÖZNUR KARACA VURAL

SELENIUM SUPPLEMENTATION AND HASHIMOTO'S THYROIDITIS: A REVIEW OF CURRENT EVIDENCE 92
GOZDE HASBAL CELIKOK
NURGİZEM KAYNARCA

NUTRITION PROBLEMS AND EPIDEMIOLOGY IN SOCIETY 108
HÜLYA HOŞGÖREN

DIETARY HABITS AND CONSUMER PREFERENCES.....119
İDİL KARADEDE

RESISTANT STARCH: BIOCHEMICAL STRUCTURE, PREBIOTIC EFFECT AND ROLE IN HUMAN NUTRITION.....135
İHSAN SOYTEMİZ

THE ARTICHOKE (CYNARA SCOLYMUS L.) IN THE MEDITERRANEAN DIET: BIOCHEMICAL COMPOSITION, NUTRITIONAL EFFECTS, AND HEALTH ASPECTS.....152
İREM KILINÇ

THE IMPORTANCE OF MEDICINAL AROMATIC PLANTS IN NUTRITION: OCIMUM BASILICUM 'PURPURASCENS'.....163
NURTEN CENGİZ
SERAP TOPRAK DÖŞLÜ

RHUBARB (RHEUM RIBES) AS A FUNCTIONAL FOOD.....176
İBRAHİM HALİL GEÇİBESLER

THE IMPACT OF HIGH GLYCEMIC INDEX DIET ON SKIN HEALTH 191
MERVE KAYA
MERVE AKAY

TOXICOLOGICAL ASPECTS OF MICRO AND NANOPLASTICS: SOURCES, BIOCHEMICAL EFFECTS AND FOOD EXPOSURE.....208
MÜBERRA ÖZCAN

SMOKED SEAFOOD: BIOCHEMISTRY, NUTRITION & HEALTH IMPACTS 220
BERNA KILINÇ
İREM KILINÇ

NUTRITION AND FOOD BIOCHEMISTRY IN CHILDREN RECEIVING ANTIEPILEPTIC TREATMENT 236
CEREN CEYLAN KIRAÇ

SELENIUM SUPPLEMENTATION AND HASHIMOTO'S THYROIDITIS: A REVIEW OF CURRENT EVIDENCE

GOZDE HASBAL CELIKOK
NURGİZEM KAYNARCA

1. Introduction

Hashimoto's thyroiditis (HT), the most prevalent autoimmune thyroid disorder, is characterized by chronic inflammation and gradual destruction of the thyroid gland. While levothyroxine (L-T4) replacement therapy remains the cornerstone of treatment, the potential role of adjunctive therapies, such as selenium (Se) supplementation, has garnered increasing interest. Se, an essential trace element, plays a crucial role in thyroid hormone metabolism and antioxidant defence. This review examines the current evidence, with a focus on research published in recent years, regarding the impact of Se supplementation on HT, exploring its effects on thyroid function, autoantibody levels, and overall disease management.

1.1. Hashimoto's thyroiditis (HT)

HT, Also known as chronic lymphocytic thyroiditis (CAT), representing the most prevalent specific manifestation of autoimmune thyroid disease (AITD), is the most prevalent autoimmune disorder affecting the thyroid gland (1,2). As the leading cause of hypothyroidism, HT is characterized by chronic inflammation and lymphocytic infiltration of the thyroid parenchyma, ultimately leading to this condition in approximately 20-30% of patients (3,4). This inflammation results in an increase in thyroid volume and the presence of antibodies against thyroid-specific antigens (5). While the exact etiopathogenesis of HT remains incompletely defined (6), it is widely recognized as a primary example of an autoimmune thyroid disease.

In 1912, the Japanese physician, Hakaru Hashimoto, provided the initial description of the key pathological features of HT, documenting cases characterized by atrophy of thyroid follicular cells, lymphocytic infiltration, goitre, and fibrosis (3,4,7).

HT has demonstrated a marked increase in incidence in recent decades (4). It is now recognized as one of the most prevalent thyroid disorders, affecting 0.3-1.5 per 1000 individuals annually (8). Notably, HT exhibits a striking female predominance, with over 10% of women presenting positive thyroid antibodies and a 4-10 times greater likelihood of developing AITD compared to men (3,4,6). The incidence of HT is also influenced by age, with a peak observed in middle age, and geographical location, with higher rates reported in iodine-sufficient regions. Furthermore, antithyroid antibody prevalence varies across racial groups, demonstrating both age-related increases and reductions associated with smoking (1). While HT can occur at any age, incidence peaks in middle age (6). Epidemiological studies consistently indicate a strong genetic predisposition to HT. Evidence suggests AITD has familial clustering with significant concordance rates in monozygotic twins, and the presence of circulating thyroid autoantibodies in siblings of affected individuals (9,10).

While the precise etiology of the increased prevalence of AITDs in females remains elusive, it is hypothesized that hormonal influences and X-chromosome inactivation (XCI) play significant roles. Specifically, the location of certain thyroid self-antigens on the X-chromosome suggests that XCI may modulate the incidence of these diseases. This hypothesis is further supported by the observation of skewed XCI patterns in female patients with AITDs (11,12,13). The pathogenesis of HT involves multiple genes, including those within the HLA complex and various immunoregulatory genes such as *CTLA-4*, *PTPN22*, *CD14*, *CD40*, and *IL2R*, with single nucleotide polymorphisms in these genes contributing to disease susceptibility (14).

The pathogenesis of HT is closely associated with autoantibody production and significant lymphocytic infiltration, including B and T cells, within the thyroid tissue, highlighting the role of both cellular and humoral immunity in disease development. T cell dysfunction contributes to the breakdown of immune homeostasis against thyroid tissue (15,16). In addition to genetic factors, recent epidemiological shifts suggest that environmental factors, including the hygiene hypothesis, may also significantly contribute to disease development (4). Exogenous factors, such as interferon-alpha therapy and hepatitis C virus infection, have been reported to increase the risk of AITD, particularly in women with elevated anti-thyroid peroxidase (AbTPO) levels, potentially through direct thyroid cell toxicity or the induction of destructive immune responses (17,18). HT, the leading cause of hypothyroidism in iodine-sufficient regions globally, exhibits a complex correlation with iodine intake: While adequate iodine is essential for thyroid hormone synthesis, excessive iodine consumption is associated with a higher prevalence of AITD, evidenced by studies showing a 1.3% AITD incidence in populations with excessive iodine intake in China compared to 0.3% in mildly iodine-deficient areas, and conversely,

iodine-deficient regions generally demonstrate a lower AITD prevalence. This is likely due to excessive iodine's ability to stimulate thymus development, modulate immune cell function, induce cytokine and chemokine production, increase oxidative stress, and enhance the immunogenicity of thyroglobulin, all of which can contribute to thyroid autoimmunity. Therefore, careful monitoring of iodine status is crucial to avoid both deficiency and excess, particularly in HT patients where excessive iodine intake or supplementation is not recommended (3,6,8,19,20,21). Furthermore, increasingly prevalent dietary selenium (Se) deficiency in Europe is reported to be implicated in the potential exacerbation of HT due to selenium's critical role in thyroid function and redox regulation through selenoproteins (22). In addition to iodine and Se, research indicates that vitamin D deficiency may contribute to the development or exacerbation of HT by influencing immune function and potentially affecting thyroid autoantibody levels (23).

As a result of the chronic inflammation and gradual destruction of thyroid tissue, HT can manifest with a wide range of symptoms, often attributable to the resulting hypothyroidism. These symptoms are frequently nonspecific and can vary in intensity depending on the severity of the disease (6). Commonly reported manifestations include chronic fatigue and general weakness, nervousness, mood swings, concentration problems, and a variety of gastrointestinal issues (2,5). Beyond these, HT can affect multiple systems, leading to local and systemic manifestations impacting the cardiovascular, pulmonary, hematopoietic, reproductive, neuropsychiatric systems, and even the skin. Patients may also experience dry skin and changes in body weight (2,6). Because the symptoms are so varied and often resemble those of other conditions, diagnosis can sometimes be challenging.

The diagnosis of HT relies on a combination of biochemical and imaging findings. The presence of circulating thyroid autoantibodies, specifically AbTPO and anti-thyroglobulin antibodies (AbTg), is a key diagnostic feature (3,5,6). AbTPO are more sensitive, detected in approximately 90% of HT patients, while AbTg are less sensitive and specific, found in 60-80% of cases (8). Biochemical evaluation also includes measuring thyroid stimulating hormone (TSH) levels, which are often elevated, and free thyroxine (fT4), which may be normal or low, especially in early stages (2,3). Ultrasonography is a crucial imaging tool, typically revealing a hypoechogenic and inhomogeneous thyroid parenchyma, reflecting the characteristic lymphocytic infiltration and follicular destruction (2,5). This infiltration appears as reduced echogenicity on ultrasound (6). These combined findings contribute to a comprehensive diagnosis.

The primary treatment for HT focuses on addressing the associated hypothyroidism through thyroid hormone replacement therapy (THRT). Levothyroxine (L-T4), a synthetic form of thyroid hormone, is the cornerstone of this treatment (5,6). It is typically administered orally daily, with a recommended dosage of 1.6-1.8 micrograms per kilogram of body weight (2). This replacement therapy is generally lifelong to maintain normal TSH levels (6). While L-T4 tablets are the most common formulation, liquid solutions and soft gel capsules are also available

(24). These alternative formulations can be particularly beneficial for patients with malabsorption issues (e.g., atrophic gastritis, lactose intolerance, bariatric surgery, gastric paresis) or those taking medications that interfere with L-T4 absorption (e.g., proton pump inhibitors, sucralfate, calcium) (24). Such diverse formulations allow for personalized therapy to achieve and maintain stable biochemical euthyroidism (3). In rare cases, thyroidectomy may be considered for HT patients experiencing severe local compression symptoms, nodular disease suspicious for malignancy, or for cosmetic reasons related to goitre size (3). In addition to L-T4 therapy, dietary modifications and supplementation may also play a supportive role in the management of HT (6).

1.2. Selenium (Se)

Se, a metalloid trace element named after the moon goddess Selene, is essential for human health due to its incorporation into selenoproteins, which play crucial roles in various cellular processes, including antioxidant defence and thyroid metabolism (25). However, it is vital to note that Se, while essential, can also be toxic if ingested in excessive amounts (26). Se status is assessed via plasma/serum (short-term), whole-blood (mid-term), or toenail (long-term) analyses. Plasma/serum is the most common method; whole blood reflects erythrocyte Se, and toenails indicate annual status (27,28,29).

Dietary intake is the primary source of Se for humans (30). Systemic Se levels are predominantly determined by dietary habits, exhibiting significant inter-population variability due to geographical factors, notably soil composition, which influences Se content in food sources (31). While Se content in food is subject to fluctuations based on soil concentration, climate, and specific food type, epidemiological data indicate a global prevalence of Se deficiency (32). Within the diet, Se is primarily present as selenocysteine (SeCys) and selenomethionine (SeMet), with SeMet being the predominant form in plant-based sources, particularly cereals and grains (33,34). Additional significant sources include meat, fish, eggs, and dairy products (33), with Brazil nuts being exceptionally rich, containing levels ranging from approximately 0.03 to 512 μg/g (26). Dietary supplements commonly incorporate Se in both organic (SeMet and SeCys) and inorganic (selenite and selenate) forms (25,35). SeMet, being incorporated into body proteins in place of methionine, is considered highly bioavailable, making it a preferred form for supplementation (36). Se enters the human food chain primarily through plants, seafood (via algae), and meat products, leading to substantial variation in individual Se intakes worldwide, ranging from deficient (7 μg/day) to toxic (4,990 μg/day) levels. These variations are largely attributed to differences in soil Se content, Se speciation, soil pH, and organic matter content, which ultimately affect the Se content of crops and fodder (35).

Selenium's critical role in thyroid function was initially understood through studies of myxedematous endemic cretinism, linked to combined iodine and Se deficiencies, emphasizing selenium's importance for normal thyroid development and function (37). The thyroid gland is recognized as a selenium-rich tissue (38)

and incorporates Se into various selenoproteins essential for thyroid hormone homeostasis. Thyroid cells express a range of selenoproteins, including deiodinase isozymes (DIOs), glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs), and selenoproteins (F, P, K, N, and S), which collectively contribute to optimal thyroid function (39). DIOs (D1, D2, D3) modulate thyroid hormone levels by catalysing the conversion of thyroxine (T4) to active triiodothyronine (T3) and facilitate the inactivation of thyroid hormones via T4 to reverse T3 (rT3) conversion (40,41). GPxs, highly expressed in the thyroid, protect the gland from oxidative stress by scavenging reactive oxygen species generated during hormone synthesis (41,42). TrxRs contribute to redox regulation and transcription factor modulation (43). SeCys, the incorporated form of Se in most selenoproteins, is crucial for their catalytic activity, with all selenoproteins, except selenoprotein P, possessing at least one SeCys residue. Selenoprotein P, the principal Se transporter in plasma, ensures adequate Se delivery to the thyroid (44,45).

Maintaining optimal Se levels is crucial for proper thyroid function, as low Se status is an independent risk factor for thyroid diseases (35). The thyroid gland's capacity to retain Se, even during periods of scarcity, highlights its indispensable role in maintaining thyroid health. Despite historical misclassification as a carcinogen, Se is now recognized as a vital nutrient, essential for normal thyroid function (46).

Se supplementation has become a common practice, particularly in regions with documented Se deficiencies. The recognition of selenium's therapeutic potential dates back to the 1980s, when supplementation with sodium selenite proved effective in treating chondrodystrophy (Kashin-Beck disease) and juvenile cardiomyopathy (Keshan disease), both linked to Se deficiency. While Se supplementation can benefit individuals with inadequate Se levels, it's crucial to note that supplementation in those with sufficient Se status may increase the risk of certain diseases (47). Given that an estimated 15% of the global population experiences Se deficiency and considering the wide variation in Se intake worldwide (46), supplementation can play a vital role in addressing this nutritional gap. Se supplements are widely available, often in the form of selenate or selenite, providing a mixture of different Se species (48). These supplements, available as stand-alone products or within multivitamin/multimineral formulations, can contribute an average additional intake of 5-30 μg/day, which can be particularly valuable in Se-deficient regions (32). Human Se deficiency is typically defined as a dietary intake below 40 μg/day, whereas toxicity, known as selenosis, can occur with daily levels exceeding 400 μg (49).

Selenosis, although rare, has been reported in epidemiological studies of populations residing in areas with high soil Se concentrations and can result from acute poisoning or prolonged exposure to elevated Se levels (31). Clinical manifestations of Se toxicity include nausea, vomiting, abdominal pain, diarrhoea, hair loss, brittle nails, peripheral neuropathy, and a characteristic garlic odour in sweat and breath (31,47). As the human body is incapable of synthesizing Se, consistent dietary intake or appropriate supplementation is requisite to meet physiological requirements. Consequently, Se supplementation in individuals with suboptimal

baseline Se status has garnered research interest as a potential strategy to mitigate disease incidence and progression. However, it is equally critical to emphasize that excessive Se intake, through either diet or supplementation, can precipitate adverse health outcomes and Se toxicity (47).

Se deficiency has significant implications for thyroid health, increasing the risk of several conditions, including increased thyroid gland volume, hypothyroidism, HT, and thyroid nodules (50). Se deficiency impairs thyroid hormone synthesis by reducing the activity of selenoproteins, particularly DIOs, which are responsible for converting T4 to the active T3 (31). The resultant decrease in T3 production triggers an increase in TSH levels, which, paradoxically, amplifies hydrogen peroxide (H_2O_2) production due to reduced GPxs activity. The accumulated H_2O_2 damages thyroid cells, potentially leading to fibrosis (31). Furthermore, Se deficiency reduces both GPxs and DIOs activity, hindering H_2O_2 disposal and impairing thyroid hormone metabolism (40). Consequently, the oxidative stress characteristic of autoimmune disorders like HT is exacerbated (51). While Se supplementation has been proposed as a potential therapy for AITD due to its antioxidant and anti-inflammatory properties, both Se deficiency and excess can negatively impact thyroid function and overall health (52). As evidenced by pertinent research, optimal GPxs activity necessitates plasma Se concentrations of approximately 90 μg/L (53). In individuals diagnosed with HT, a reduction in AbTPO levels may require elevated Se dosages exceeding 100 μg/day to maximize GPxs activity (54). Furthermore, achieving maximal selenoprotein P concentrations is contingent upon plasma Se levels of approximately 120 μg/L (55).

2. Evaluation of Recent Clinical Trials and Meta-analysis

The role of Se supplementation in the management of HT has long been a topic of interest. This section will examine various clinical trials and meta-analyses assessing the effects of Se on HT. Selenium's role in HT has been extensively studied, with several trials exploring the effects of Se supplementation on thyroid function and autoimmunity. Winther et al. (56) conducted a 5-year, randomized, double-blind, placebo-controlled trial in a Danish population (without known thyroid disease) to investigate the effect of Se supplementation on thyroid function in 361 participants. Participants were equally divided into 3 group and administered doses of 100 μg, 200 μg, and 300 μg respectively, In addition to this, there were 126 participants in the placebo group. Se supplementation significantly increased plasma Se concentrations. While no impact of Se was seen on plasma TSH levels of treatment and placebo group, oppose to this increasing Se dose decreased TSH and fT4 concentrations. No effect of Se was found on fT3 or the fT3:fT4 ratio. The study concluded that Se supplementation dose-dependently decreased TSH and fT4 in this population without known thyroid disease. In contrast, Esposito et al. (57) investigated the effects of six months of Se supplementation (166 μg/day L- SeMet) on 76 untreated euthyroid patients with HT residing in a Se-deficient region (Campania district, Italy), compared to placebo. Thirty-eight patients received Se, while 38 received a placebo. The study measured TSH, fT3, fT4, as well

as AbTPO, AbTg, CXCL10 (Interferon-gamma-inducible protein 10; IP-10), and thyroid echogenicity at baseline, 3, and 6 months. Se supplementation significantly increased fT3 levels at 3 and 6 months and transiently decreased fT4 at 3 months, but did not affect TSH, thyroid antibodies, echogenicity, or CXCL10. The study suggests Se may influence thyroid hormone levels without significantly modulating autoimmunity or CXCL10 in early HT. Pirola et al. (58) investigated the effect of 4 months of Se supplementation (83 mcg/day of SeMet) on 192 patients (163 female, 29 male, mean age 32.2±7.0 years) with subclinical hypothyroidism due to AITD. The study measured fT4, TSH, and AbTPO levels. Se supplementation restored euthyroidism in 31.3% of supplemented patients compared to 3.1% in the control group. AbTPO significantly decreased only in supplemented patients. The study suggests Se supplementation can restore euthyroidism in a subset of patients with subclinical hypothyroidism due to HT. These studies suggest that Se can influence thyroid hormone levels, with the specific effects on TSH and fT4 varying significantly depending on the presence of HT, baseline selenium status, and the dosage and duration of supplementation

In addition to these studies, a larger body of research has examined the effects of Se on thyroid autoimmunity, specifically by measuring thyroid antibody levels. De Farias et al. (59) conducted a 3-month, randomized, double-blind, placebo-controlled trial investigating the impact of 200 μg/day of SeMet supplementation on 55 AbTPO positive HT patients, with follow-up at 6 months. The study assessed AbTPO and AbTg levels, as well as GPx1 genotypes, Se and GPx1 activity levels, thyroid function, and echogenicity. Se supplementation significantly increased Se and GPx1 activity, and significantly decreased AbTPO levels at 6 months, but not at 3 months. Notably, AbTg levels exhibited no statistically significant variation between both groups throughout the study. Interestingly, the SeMet group exhibited a significant increase in TSH levels at 3 months, which persisted at 6 months. The authors concluded that Se supplementation is associated with decreased AbTPO levels in HT patients, independent of GPx1 genotype. Similarly, Hu et al. (60) conducted a 6-month, prospective, randomized controlled trial investigating the effects of 200 μg/day of selenious yeast tablet supplementation. The study enrolled 126 participants, including 90 with HT, who were randomized into a Se-treated group (n=43) and a control group (n=47) receiving no supplementation. Comparisons were made between the Se-treated and control groups, as well as with a cohort of 36 healthy controls. The study measured thyroid antibodies, as well as thyroid hormones, Se levels, GPx3 and selenoprotein P1 concentrations, and regulatory T cell (Treg) populations, including their subsets and Helios/PD-1 expression. Se supplementation significantly increased Se, GPx3, and selenoprotein P1 levels, and decreased AbTPO and AbTg levels, with a trend towards decreased TSH. Subgroup analysis revealed greater reductions in AbTPO, AbTg, and TSH in patients with subclinical hypothyroidism. Furthermore, Se supplementation significantly increased the proportion of activated Treg cells (aTregs) and Helios expression in Treg cells, particularly in aTregs, after 6 months of treatment. The authors conclud-

ed that Se supplementation can effectively modulate thyroid autoimmunity and Treg populations in HT patients, especially those with subclinical hypothyroidism. Furthermore, Mantovani et al. (61) conducted the SERENA study, a randomized, double-blind, placebo-controlled trial investigating the effects of 83 mcg/day of L- SeMet supplementation on 45 pregnant women with thyroid autoimmunity (positive AbTg and/or AbTPO). Participants were evaluated at 10±2 weeks, 36±2 weeks of gestation, and 6 months postpartum. Se supplementation significantly attenuated the postpartum increase in AbTg and AbTPO compared to placebo, while not affecting thyroid hormones, echogenicity, or volume. The study concluded that Se supplementation during and after pregnancy is safe and beneficial in reducing thyroid autoantibody titers and postpartum thyroiditis recurrence. These studies converge on the finding that Se supplementation can modulate thyroid autoimmunity by reducing thyroid antibody titers, but the specific time course and target antibody may differ.

Additional studies have broadened the understanding of selenium's impact on HT. Rostami et al. (62) investigated the relationship between serum Se status and thyroid function/antioxidant defence biomarkers in 49 women with HT and 50 healthy controls. The study measured thyroid hormones, thyroid antibodies, thyroglobulin, Se, glutathione, GPx3 activity, thyroid volume, and urinary iodine concentration. HT patients had lower Se, glutathione, T4, T3, fT3, and fT4, and higher thyroglobulin, GPx3, TSH, T3-uptake, AbTPO, AbTg, and thyroid volume compared to controls. Se deficiency in HT patients was associated with increased thyroid volume, AbTPO, AbTg, TSH, and urinary iodine. The study suggests Se deficiency plays a role in oxidative stress and thyroid dysfunction in HT, even with optimal iodine status. Finally, Zheng et al. (63), using data from the National Health and Nutrition Examination Survey 2007-2012, investigated the relationship between dietary Se intake and HT in 8,756 US adults (49.25% male, average age 44.35). Among the participants, 940 (10.74%) had HT. The study found that higher dietary Se intake was associated with a reduced risk of HT across all analysed models. In the fully adjusted model, the odds ratio (OR) was 0.65 (95% confidence interval [CI] 0.51-0.83). Furthermore, dietary Se intake demonstrated a negative correlation with AbTPO levels and a non-linear correlation with AbTg levels. These findings suggest that sufficient dietary Se intake may offer protection against HT. Wu et al. (64) conducted a 6-year prospective cohort study of 1254 individuals in two regions of China to investigate the association between Se deficiency and HT incidence. One region had adequate Se levels, while the other had low Se levels. The study measured serum and nail Se, TSH, T4, T3, AbTPO, and urinary iodine concentration. Individuals in the low-Se region had a significantly higher incidence of HT and AbTPO seroconversion compared to those in the adequate-Se region. Lower baseline Se concentrations were associated with a higher rate of AbTPO seroconversion. The study suggests a causal relationship between Se deficiency and HT risk, highlighting the protective effect of sufficient Se intake. These studies highlight the importance of maintaining adequate Se levels for thyroid health and emphasize its potential protective role in HT.

Several meta-analyses have investigated the effects of Se supplementation on HT, yielding somewhat variable results. Huwiler et al. (65) conducted a systematic review and meta-analysis of 35 studies (32 included in the meta-analysis) to evaluate the effects of Se supplementation in HT. The meta-analysis revealed a significant decrease in TSH levels in patients without THRT, but no significant change in TSH in the overall population or in those with THRT. While fT4 levels remained unchanged overall, a subgroup analysis showed an increase in fT4 in adults. No significant change was observed for fT3 levels. Se supplementation significantly decreased AbTPO levels, but not AbTg levels (though a decrease was noted in HT patients without THRT). Thyroid echogenicity decreased in some studies, but no significant effect was found on thyroid volume. Se did not significantly affect IL-2, IL-10, or adverse events, but it did significantly decrease malondialdehyde. The authors concluded that Se supplementation is safe and shows potential as a disease-modifying factor for HT-associated hypothyroidism, particularly in reducing TSH levels in euthyroid and subclinically hypothyroid individuals without THRT and in lowering AbTPO levels. They suggest Se doses above 100 μg/day may be most effective.

Focusing specifically on thyroid autoantibodies, Wichman et al. (66) conducted a systematic review and meta-analysis of 16 controlled trials (n=1494) to evaluate the effects of Se supplementation on thyroid autoantibody levels in adults with AITD. The review included trials comparing Se (with or without L-T4) to placebo and/or L-T4. In L-T4-treated patients, Se supplementation significantly reduced AbTPO levels at 3, 6, and 12 months. In newly diagnosed, L-T4-untreated patients, Se significantly lowered AbTPO only at 3 months. Regarding AbTg, L-T4-treated patients showed a significant decrease at 12 months, but not at 3 or 6 months. In L-T4-untreated patients, AbTg significantly decreased at 3 months, but not at 6 or 12 months. No correlation was found between AbTPO reduction and baseline AbTPO, baseline Se, age, or percentage of females. Subgroup analysis indicated that SeMet, but not sodium selenite, significantly reduced AbTPO at 3 months in L-T4-treated patients. While Se supplementation effectively reduced AbTPO and, to a lesser extent, AbTg levels, the authors concluded that routine Se supplementation for AITD is not warranted based solely on autoantibody reduction. Similarly, Kong et al. (67) conducted a meta-analysis to evaluate the clinical efficacy of Se supplementation in HT patients. Analysing data from 7 controlled trials (n=342), they found no evidence of publication bias. While significant heterogeneity existed between studies, appropriate statistical models were used. At 3 months, Se supplementation did not significantly alter AbTPO or AbTg levels. However, at 6 months, both AbTPO and AbTg levels significantly decreased. Higher baseline antibody levels correlated with greater reductions at 6 months. Subgroup analysis revealed significant reductions in both AbTPO and AbTg at both 3 and 6 months in patients with baseline antibody levels >1000 IU/mL. Patients with AbTPO <1000 IU/mL only showed a significant decrease in AbTPO at 6 months. The authors concluded that Se supplementation may reduce AbTPO and AbTg levels in HT

patients after 6 months, especially those with high baseline levels, but emphasize that these reductions don't necessarily translate to improved thyroid function, cautioning against routine supplementation without further research.

In contrast, Winther et al. (68) conducted a systematic review and meta-analysis of 9 trials (n=679) to assess the clinical efficacy of Se supplementation in HT. The review focused on changes in thyroid function, specifically subclinical hypothyroidism, TSH levels, and thyroid echogenicity. In L-T4-untreated patients, Se supplementation did not significantly reduce the development of subclinical hypothyroidism. Meta-analysis showed no significant changes in TSH levels in L-T4-untreated populations at 3, 6, or 12 months. Similarly, no significant improvements in thyroid echogenicity were observed at 6 or 12 months in L-T4-untreated individuals. The authors concluded that current evidence does not justify routine Se supplementation for AITD, emphasizing that while Se may have other health benefits, its use in AITD should be discouraged due to a lack of documented clinical efficacy.

3. Conclusion

In conclusion, the evidence regarding Se supplementation in HT presents a complex picture, yet some consistent trends emerge. Research, including meta-analyses, suggests that Se supplementation can effectively reduce thyroid autoantibody levels (AbTPO and, to a lesser extent, AbTg), particularly in individuals with high baseline antibody levels and those not receiving THRT. However, the clinical significance of these reductions remains a subject of debate, as some studies focusing on TSH and overall thyroid function have not demonstrated clear improvements. Large meta-analyses indicate potential benefits of Se in reducing TSH in specific subgroups and highlight the general safety of supplementation. While some individual trials have shown positive effects on thyroid hormone levels and even restoration of euthyroidism in subclinical hypothyroid patients, these findings require further confirmation. Therefore, while Se supplementation appears promising for modulating thyroid autoimmunity, particularly in certain subgroups, its routine use in HT cannot be recommended without more robust evidence. Future research should focus on determining the optimal dosage and form of Se, exploring its long-term clinical implications on disease progression and patient outcomes, and further elucidating the mechanisms by which Se influences thyroid autoimmunity and function.

References

1. McLeod, D.S.A., Cooper, D.S. The incidence and prevalence of thyroid autoimmunity. Endocrine 42, 252–265 (2012). https://doi.org/10.1007/s12020-012-9703-2
2. Caturegli, P., De Remigis, A., & Rose, N. R. (2014). Hashimoto thyroiditis: Clinical and diagnostic criteria. Autoimmunity Reviews, 13(4–5), 391–397. https://doi.org/10.1016/j.autrev.2014.01.007
3. Ragusa, F., Fallahi, P., Elia, G., Gonnella, D., Paparo, S. R., Giusti, C., Churilov, L. P., Ferrari, S. M., & Antonelli, A. (2019). Hashimoto's thyroiditis: Epidemiology,

pathogenesis, clinic and therapy. Best Practice & Research Clinical Endocrinology & Metabolism, 33(6), 101367. https://doi.org/10.1016/j.beem.2019.101367

4. Ralli, M., Angeletti, D., Fiore, M., D'Aguanno, V., Lambiase, A., Artico, M., De Vincentiis, M., & Greco, A. (2020). Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. Autoimmunity Reviews, 19(10), 102649. https://doi.org/10.1016/j.autrev.2020.102649
5. Osowiecka, K., & Myszkowska-Ryciak, J. (2023). the influence of nutritional intervention in the treatment of Hashimoto's thyroiditis-a systematic review. Nutrients, 15(4), 1041. https://doi.org/10.3390/nu15041041
6. Mikulska, A. A., Karaźniewicz-Łada, M., Filipowicz, D., Ruchała, M., & Główka, F. K. (2022). Metabolic characteristics of Hashimoto's thyroiditis patients and the role of microelements and diet in the disease management-an overview. International Journal of Molecular Sciences, 23(12), 6580. https://doi.org/10.3390/ijms23126580
7. Antonelli, A., Ferrari, S. M., Corrado, A., Di Domenicantonio, A., & Fallahi, P. (2014). Autoimmune thyroid disorders. Autoimmunity Reviews, 14(2), 174–180. https://doi.org/10.1016/j.autrev.2014.10.016
8. Iddah, M. A., & Macharia, B. N. (2013). Autoimmune thyroid disorders. ISRN Endocrinology, 2013, 1–9. https://doi.org/10.1155/2013/509764
9. Kust, D., & Matesa, N. (2018). The impact of familial predisposition on the development of Hashimoto's thyroiditis. Acta Clinica Belgica, 75(2), 104–108. https://doi.org/10.1080/17843286.2018.1555115
10. Brix, T. H., & Hegedüs, L. (2011). Twin studies as a model for exploring the aetiology of autoimmune thyroid disease. Clinical Endocrinology, 76(4), 457–464. https://doi.org/10.1111/j.1365-2265.2011.04318.x
11. Yin, X., Latif, R., Tomer, Y., & Davies, T. F. (2007). Thyroid epigenetics. Annals of the New York Academy of Sciences, 1110(1), 193–200. https://doi.org/10.1196/annals.1423.021
12. Brix, T. H., Hansen, P. S., Kyvik, K. O., & HegedüS, L. (2009). Aggregation of thyroid autoantibodies in twins from opposite-sex pairs suggests that microchimerism may play a role in the early stages of thyroid autoimmunity. The Journal of Clinical Endocrinology & Metabolism, 94(11), 4439–4443. https://doi.org/10.1210/jc.2009-0813
13. Lee, T., & Chiang, B. (2011). Sex differences in spontaneous versus induced animal models of autoimmunity. Autoimmunity Reviews, 11(6–7), A422–A429. https://doi.org/10.1016/j.autrev.2011.11.020
14. Brix, T. H., Kyvik, K. O., & Hegedüs, L. (2000). A population-based study of chronic autoimmune hypothyroidism in Danish twins. The Journal of Clinical Endocrinology & Metabolism, 85(2), 536–539. https://doi.org/10.1210/jcem.85.2.6385
15. McLachlan, S. M., & Rapoport, B. (2013). Breaking tolerance to thyroid antigens: Changing concepts in thyroid Autoimmunity. Endocrine Reviews, 35(1), 59–105. https://doi.org/10.1210/er.2013-1055
16. Smith, T. J., & Hegedüs, L. (2016). Grave's disease. New England Journal of Medicine, 375(16), 1552–1565. https://doi.org/10.1056/nejmra1510030

17. Antonelli, A., Ferri, C., Ferrari, S. M., Colaci, M., Sansonno, D., & Fallahi, P. (2008). Endocrine manifestations of hepatitis C virus infection. Nature Clinical Practice Endocrinology & Metabolism, 5(1), 26–34. https://doi.org/10.1038/ncpendmet1027

18. Tomer, Y., & Menconi, F. (2009). Interferon induced thyroiditis. Best Practice & Research Clinical Endocrinology & Metabolism, 23(6), 703–712. https://doi.org/10.1016/j.beem.2009.07.004

19. Walsh, J. P., Ward, L. C., Burke, V., Bhagat, C. I., Shiels, L., Henley, D., Gillett, M. J., Gilbert, R., Tanner, M., & Stuckey, B. G. A. (2006). Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: Results of a double-blind, randomized clinical trial. The Journal of Clinical Endocrinology & Metabolism, 91(7), 2624–2630. https://doi.org/10.1210/jc.2006-0099

20. Lombardi, F. A., Fiore, E., Tonacchera, M., Antonangeli, L., Rago, T., Frigeri, M., Provenzale, A. M., Montanelli, L., Grasso, L., Pinchera, A., & Vitti, P. (2013). The effect of voluntary iodine prophylaxis in a small rural community: The Pescopagano Survey 15 years later. The Journal of Clinical Endocrinology & Metabolism, 98(3), 1031–1039. https://doi.org/10.1210/jc.2012-2960

21. Luo, Y., Kawashima, A., Ishido, Y., Yoshihara, A., Oda, K., Hiroi, N., Ito, T., Ishii, N., & Suzuki, K. (2014). Iodine excess as an environmental risk factor for autoimmune thyroid disease. International Journal of Molecular Sciences, 15(7), 12895–12912. https://doi.org/10.3390/ijms150712895

22. Toulis, K. A., Anastasilakis, A. D., Tzellos, T. G., Goulis, D. G., & Kouvelas, D. (2010). Selenium supplementation in the treatment of Hashimoto's thyroiditis: A systematic review and a meta-analysis. Thyroid, 20(10), 1163–1173. https://doi.org/10.1089/thy.2009.0351

23. Wang, S., Wu, Y., Zuo, Z., Zhao, Y., & Wang, K. (2018). The effect of vitamin D supplementation on thyroid autoantibody levels in the treatment of autoimmune thyroiditis: A systematic review and a meta-analysis. Endocrine, 59(3), 499–505. https://doi.org/10.1007/s12020-018-1532-5

24. Fallahi, P., Ferrari, S. M., & Antonelli, A. (2016). In patients with subclinical hypothyroidism while in therapy with tablet L-T4, the liquid L-T4 Formulation is more effective in restoring euthyroidism. Endocrine Practice, 23(2), 170–174. https://doi.org/10.4158/ep161545.or

25. Duntas, L. H., & Benvenga, S. (2014). Selenium: An element for life. Endocrine, 48(3), 756–775. https://doi.org/10.1007/s12020-014-0477-6

26. Fairweather-Tait, S. J., Bao, Y., Broadley, M. R., Collings, R., Ford, D., Hesketh, J. E., & Hurst, R. (2010). Selenium in human health and disease. Antioxidants and Redox Signaling, 14(7), 1337–1383. https://doi.org/10.1089/ars.2010.3275

27. Rayman, M. P., Bode, P., & Redman, C. W. (2003). Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom. American Journal of Obstetrics and Gynecology, 189(5), 1343–1349. https://doi.org/10.1067/s0002-9378(03)00723-3

28. Ashton, K., Hooper, L., Harvey, L. J., Hurst, R., Casgrain, A., & Fairweather-Tait, S. J. (2009). Methods of assessment of selenium status in humans: A systematic review. American Journal of Clinical Nutrition, 89(6), 2025S-2039S. https://doi.org/10.3945/ajcn.2009.27230f

29. Rayman, M. P., Searle, E., Kelly, L., Johnsen, S., Bodman-Smith, K., Bath, S. C., Mao, J., & Redman, C. W. G. (2014). Effect of selenium on markers of risk of pre-eclampsia in UK pregnant women: A randomised, controlled pilot trial. British Journal of Nutrition, 112(1), 99–111. https://doi.org/10.1017/s0007114514000531

30. Vinceti, M., Crespi, C. M., Malagoli, C., Del Giovane, C., & Krogh, V. (2013). Friend or foe? The current epidemiologic evidence on selenium and human cancer risk. Journal of Environmental Science and Health Part C, 31(4), 305–341. https://doi.org/10.1080/10590501.2013.844757

31. Ventura, M., Melo, M., & Carrilho, F. (2017). Selenium and thyroid disease: From pathophysiology to treatment. International Journal of Endocrinology, 2017, 1–9. https://doi.org/10.1155/2017/1297658

32. Gorini, F., Sabatino, L., Pingitore, A., & Vassalle, C. (2021). Selenium: An element of life essential for thyroid function. Molecules, 26(23), 7084. https://doi.org/10.3390/molecules26237084

33. World Health Organization. Selenium in Drinking Water. 2011.

34. Filippini, T., Michalke, B., Wise, L. A., Malagoli, C., Malavolti, M., Vescovi, L., Salvia, C., Bargellini, A., Sieri, S., Krogh, V., Ferrante, M., & Vinceti, M. (2018). Diet composition and serum levels of selenium species: A cross-sectional study. Food and Chemical Toxicology, 115, 482–490. https://doi.org/10.1016/j.fct.2018.03.048

35. Rayman, M. P. (2012). Selenium and human health. The Lancet, 379(9822), 1256–1268. https://doi.org/10.1016/s0140-6736(11)61452-9

36. Thiry, C., Ruttens, A., Pussemier, L., & Schneider, Y. (2012). An *in vitro* investigation of species-dependent intestinal transport of selenium and the impact of this process on selenium bioavailability. British Journal of Nutrition, 109(12), 2126–2134. https://doi.org/10.1017/s0007114512004412

37. Goyens, P., Golstein, J., Nsombola, B., Vis, H., & Dumont, J. E. (1987). Selenium deficiency as a possible factor in the pathogenesis of myxoedematous endemic cretinism. European Journal of Endocrinology, 114(4), 497–502. https://doi.org/10.1530/acta.0.1140497

38. Dickson, R., & Tomlinson, R. (1967). Selenium in blood and human tissues. Clinica Chimica Acta, 16(2), 311–321. https://doi.org/10.1016/0009-8981(67)90197-0

39. Winther, K. H., Rayman, M. P., Bonnema, S. J., & Hegedüs, L. (2020). Selenium in thyroid disorders – essential knowledge for clinicians. Nature Reviews Endocrinology, 16(3), 165–176. https://doi.org/10.1038/s41574-019-0311-6

40. KöHrle, J., Jakob, F., Contempre, B., & Dumont, J. E. (2005). Selenium, the thyroid, and the endocrine system. Endocrine Reviews, 26(7), 944–984. https://doi.org/10.1210/er.2001-0034

41. Negro, R. (2008). Selenium and thyroid autoimmunity. Biologics, 265. https://doi.org/10.2147/btt.s2746

42. Lubos, E., Loscalzo, J., & Handy, D. E. (2010). Glutathione peroxidase-1 in health and disease: From molecular mechanisms to therapeutic opportunities. Antioxidants and Redox Signaling, 15(7), 1957–1997. https://doi.org/10.1089/ars.2010.3586

43. Labunskyy, V. M., Hatfield, D. L., & Gladyshev, V. N. (2014). Selenoproteins: Molecular pathways and physiological roles. Physiological Reviews, 94(3), 739–777. https://doi.org/10.1152/physrev.00039.2013

44. Kryukov, G. V., Castellano, S., Novoselov, S. V., Lobanov, A. V., Zehtab, O., Guigo, R., & Gladyshev, V. N. (2003). Characterization of mammalian selenoproteomes. Science, 300(5624), 1439–1443. https://doi.org/10.1126/science.1083516

45. Schweizer, U., Streckfuß, F., Pelt, P., Carlson, B. A., Hatfield, D. L., Köhrle, J., & Schomburg, L. (2005). Hepatically derived selenoprotein P is a key factor for kidney but not for brain selenium supply. Biochemical Journal, 386(2), 221–226. https://doi.org/10.1042/bj20041973

46. Santos, L. R., Neves, C., Melo, M., & Soares, P. (2018). Selenium and selenoproteins in immune mediated thyroid disorders. Diagnostics, 8(4), 70. https://doi.org/10.3390/diagnostics8040070

47. Wang, F., Li, C., Li, S., Cui, L., Zhao, J., & Liao, L. (2023). Selenium and thyroid diseases. Frontiers in Endocrinology, 14. https://doi.org/10.3389/fendo.2023.1133000

48. Institute of Medicine; Food and Nutrition Board; Panel on Dietary Antioxidants and Related Compounds; Subcommittee on Upper Reference Levels of Nutrients; Subcommittee on Interpretation and Uses of Dietary Reference Intakes; Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids; National Academies Press: Washington, DC, USA, 2000.

49. Winkel, L. H. E., Johnson, C. A., Lenz, M., Grundl, T., Leupin, O. X., Amini, M., & Charlet, L. (2011). Environmental selenium research: From microscopic processes to Global understanding. Environmental Science & Technology, 46(2), 571–579. https://doi.org/10.1021/es203434d

50. Kryczyk-Kozioł, J., Zagrodzki, P., Prochownik, E., Błażewska-Gruszczyk, A., Słowiaczek, M., Sun, Q., Schomburg, L., Ochab, E., & Bartyzel, M. (2021). Positive effects of selenium supplementation in women with newly diagnosed Hashimoto's thyroiditis in an area with low selenium status. International Journal of Clinical Practice, 75(9). https://doi.org/10.1111/ijcp.14484

51. Schomburg, L. (2021). Selenium deficiency due to diet, pregnancy, severe illness, or COVID–19–A preventable trigger for autoimmune disease. International Journal of Molecular Sciences, 22(16), 8532. https://doi.org/10.3390/ijms22168532

52. Hawkes, W. C., & Keim, N. L. (2003). Dietary selenium intake modulates thyroid hormone and energy metabolism in men. Journal of Nutrition, 133(11), 3443–3448. https://doi.org/10.1093/jn/133.11.3443

53. Duffield, A. J., Thomson, C. D., Hill, K. E., & Williams, S. (1999). An estimation of selenium requirements for New Zealanders. American Journal of Clinical Nutrition, 70(5), 896–903. https://doi.org/10.1093/ajcn/70.5.896

54. Duntas, L., Mantzou, E., & Koutras, D. (2003). Effects of a six month treatment with selenomethionine in patients with autoimmune thyroiditis. European Journal of Endocrinology, 148(4), 389–393. https://doi.org/10.1530/eje.0.1480389

55. Hurst, R., Armah, C. N., Dainty, J. R., Hart, D. J., Teucher, B., Goldson, A. J., Broadley, M. R., Motley, A. K., & Fairweather-Tait, S. J. (2010). Establishing optimal selenium status: Results of a randomized, double-blind, placebo-controlled trial. American Journal of Clinical Nutrition, 91(4), 923–931. https://doi.org/10.3945/ajcn.2009.28169

56. Winther, K. H., Bonnema, S. J., Cold, F., Debrabant, B., Nybo, M., Cold, S., & Hegedüs, L. (2015). Does selenium supplementation affect thyroid function? Results from a randomized, controlled, double-blinded trial in a Danish population. European Journal of Endocrinology, 172(6), 657–667. https://doi.org/10.1530/eje-15-0069

57. Esposito, D., Rotondi, M., Accardo, G., Vallone, G., Conzo, G., Docimo, G., Selvaggi, F., Cappelli, C., Chiovato, L., Giugliano, D., & Pasquali, D. (2016). Influence of short-term selenium supplementation on the natural course of Hashimoto's thyroiditis: Clinical results of a blinded placebo-controlled randomized prospective trial. Journal of Endocrinological Investigation, 40(1), 83–89. https://doi.org/10.1007/s40618-016-0535-4

58. Pirola I, Gandossi E, Agosti B, Delbarba A, Cappelli C. Selenium supplementation could restore euthyroidism in subclinical hypothyroid patients with autoimmune thyroiditis. Endokrynol Pol. 2016;67(6):567-571. doi: 10.5603/EP.2016.0064.

59. De Farias, C. R., Cardoso, B. R., De Oliveira, G. M. B., De Mello Guazzelli, I. C., Catarino, R. M., Chammas, M. C., Cozzolino, S. M. F., & Knobel, M. (2015). A randomized-controlled, double-blind study of the impact of selenium supplementation on thyroid autoimmunity and inflammation with focus on the GPx1 genotypes. Journal of Endocrinological Investigation, 38(10), 1065–1074. https://doi.org/10.1007/s40618-015-0285-8

60. Hu, Y., Feng, W., Chen, H., Shi, H., Jiang, L., Zheng, X., Liu, X., Zhang, W., Ge, Y., Liu, Y., & Cui, D. (2021). Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial. Clinical and Translational Science, 14(4), 1390–1402. https://doi.org/10.1111/cts.12993

61. Mantovani, G., Isidori, A. M., Moretti, C., Di Dato, C., Greco, E., Ciolli, P., Bonomi, M., Petrone, L., Fumarola, A., Campagna, G., Vannucchi, G., Di Sante, S., Pozza, C., Faggiano, A., Lenzi, A., & Giannetta, E. (2019). Selenium supplementation in the management of thyroid autoimmunity during pregnancy: results of the "SERENA study", a randomized, double-blind, placebo-controlled trial. Endocrine, 66(3), 542–550. https://doi.org/10.1007/s12020-019-01958-1

62. Rostami, R., Nourooz-Zadeh, S., Mohammadi, A., Khalkhali, H. R., Ferns, G., & Nourooz-Zadeh, J. (2020). Serum selenium status and its interrelationship with serum biomarkers of thyroid function and antioxidant defense in Hashimoto's thyroiditis. Antioxidants, 9(11), 1070. https://doi.org/10.3390/antiox9111070

63. Zheng, G., Cai, Y., Guo, Y., Song, F., Hu, Y., Li, L., & Zhu, L. (2022). The association between dietary selenium intake and Hashimoto's thyroiditis among US adults: National Health and Nutrition Examination Survey (NHANES), 2007–2012. Journal of Endocrinological Investigation, 46(7), 1385–1395. https://doi.org/10.1007/s40618-022-01987-0

64. Wu, Q., Wang, Y., Chen, P., Wei, J., Lv, H., Wang, S., Wu, Y., Zhao, X., Peng, X., Rijntjes, E., Wang, Y., Schomburg, L., & Shi, B. (2022). Increased incidence of Hashimoto thyroiditis in selenium deficiency: A Prospective 6-Year cohort study. The Journal of Clinical Endocrinology & Metabolism, 107(9), e3603–e3611. https://doi.org/10.1210/clinem/dgac410

65. Huwiler, V. V., Maissen-Abgottspon, S., Stanga, Z., Mühlebach, S., Trepp, R., Bally, L., & Bano, A. (2024). Selenium supplementation in patients with Hashimoto thyroiditis: A systematic review and meta-analysis of randomized clinical trials. Thyroid, 34(3), 295–313. https://doi.org/10.1089/thy.2023.0556

66. Wichman, J., Winther, K. H., Bonnema, S. J., & Hegedüs, L. (2016). Selenium supplementation significantly reduces thyroid autoantibody levels in patients with chronic autoimmune thyroiditis: A systematic review and meta-analysis. Thyroid, 26(12), 1681–1692. https://doi.org/10.1089/thy.2016.0256

67. Kong, X., Qiu, G., Yang, Z., Tan, Z., & Quan, X. (2023). Clinical efficacy of selenium supplementation in patients with Hashimoto thyroiditis: A systematic review and meta-analysis. Medicine, 102(20), e33791. https://doi.org/10.1097/md.0000000000033791

68. Winther, K. H., Wichman, J. E. M., Bonnema, S. J., & Hegedüs, L. (2016). Insufficient documentation for clinical efficacy of selenium supplementation in chronic autoimmune thyroiditis, based on a systematic review and meta-analysis. Endocrine, 55(2), 376–385. https://doi.org/10.1007/s12020-016-1098-z