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The effect of multiple nutritional factors on hypothyroidism - a systemic review

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ABSTRACT

Objective: The study aims to investigate the impact of various supplements, namely selenium, vitamin D, zinc, magnesium, vitamin A, iodine, L-carnitine, and proteolytic enzymes, on the management of hypothyroidism, with a particular focus on Hashimoto's thyroiditis.

Materials and Methods: The PubMed database was searched using the keywords „Hashimoto," „hypothyroidism," „sport," „physical activity," and „diet."

Results: Several studies show that supplements can help manage hypothyroidism. Vitamin D lowers TSH levels, with varying effects on thyroid hormones. Selenium reduces TPOAb, TGAb, and TSH levels, and boosts antioxidant activity, indicating potential immune benefits. Zinc is crucial for thyroid hormone synthesis, with supplementation improving fT3 levels. Magnesium and vitamin A together enhance thyroid function and reduce inflammation. Adequate iodine intake supports thyroid function, while both deficiency and excess can cause thyroid issues. L-carnitine reduces fatigue by enhancing energy metabolism, and proteolytic enzymes have anti-inflammatory effects, aiding autoimmune thyroid disease management.

Conclusions: The study highlights the potential benefits of supplementing mentioned nutrients in managing hypothyroidism by improving thyroid function, reducing inflammation, and better overall health in hypothyroid patients. Further large-scale, long-term studies are required to confirm these findings and determine optimal dosages and combinations for better effectiveness.

KEY WORDS: hypothyroidism, Hashimoto's disease, vitamin D, selenium, zinc, iodine,

INTRODUCTION

Hypothyroidism is a common chronic endocrine disease worldwide. Approximately 5% of the world's population has this diagnosis, and it is estimated that another 5% is undiagnosed.

More than 99% of those affected suffer from primary hypothyroidism, which is caused by a disorder of the thyroid gland itself, where it does not produce enough of its hormones (thyroxine- T4 and triiodothyronine- T3). Primary hypothyroidism is much more common in women than in men, with a prevalence that increases with age[1]. The female:male ratio varies across studies, ranging from 6 to 8-9[1,2]. Globally, the most common cause of hypothyroidism is iodine deficiency, but in areas with sufficient iodine levels Hashimoto's thyroiditis, an autoimmune disease, is the leading cause.

Autoimmune thyroiditis is more prevalent in populations with high dietary iodine intake[1,3]. The diagnosis of hypothyroidism is based on clinical symptoms and blood tests. These symptoms are nonspecific and can vary in severity, including mild to moderate weight gain, fatigue, concentration difficulties, mental slowness, depression, menstrual irregularities, infertility, constipation, cold, dry skin, hair loss, cold intolerance, hoarse voice, muscle stiffness and pain and bradycardia, among others[1–3]. Primary hypothyroidism can be overt/clinical, with more noticeable symptoms, elevated thyroid stimulating hormone (TSH) levels, and lower levels of thyroid hormones (free T4 in plasma). Several guidelines classify serum TSH levels of 5–10 mU/l as mild and levels above 10 mU/L as severe hypothyroidism[2]. It can also be subclinical, where TSH is above normal but thyroid hormones are within the normal range (free T4 in serum often close to the lower limit), and typical symptoms are usually absent. Subclinical hypothyroidism may present with low mood or depression, and auxiliary tests may show increased total cholesterol and plasma LDL.

In Hashimoto's thyroiditis, blood tests detect autoantibodies against thyroid peroxidase (anti-TPO) and often against thyroglobulin (anti-Tg). Anti-TPO antibodies can also be found in subclinical hypothyroidism, and their levels can help predict the likelihood of progression to overt hypothyroidism. Hashimoto's disease is also diagnosed through imaging studies such as ultrasound, where characteristic features include heterogeneity and hypoechogenicity of the thyroid parenchyma, which are observed in both goiter and thyroid atrophy. In the later stages of the disease, the vascularization of the thyroid is sparse. However, ultrasound is not decisive in the diagnosis. Levothyroxine (LT-4), a synthetic T4 hormone, is the preferred treatment for hypothyroidism, with most patients needing lifelong therapy[4].

A fair amount of nutrients impact the pathology, onset and course of thyroid diseases[5]. Vitamin D has shown positive effect on autoimmune system, reducing inflammation[6]. Thus it is believed that its deficiency may play a role in autoimmune thyroid diseases, such as Hashimoto’s thyroiditis and Graves-Basedow Disease. Selenium appears essential in thyroid hormone metabolism. Imbedded in selenoproteins, it has a role in antioxidant function and as an anti-inflammatory agent, as well as for active thyroid hormone production[7]. Iodine, an important substrate of thyroid hormone, is vital in maintaining proper thyroid activity. Both deficiency and excess may lead to either hypothyroidism or hyperthyroidism[8]. Zinc affects thyroid hormone metabolism in various ways. It is crucial for thyroid hormone synthesis and activation. It also contributes to immune system regulation[9]. Vitamin A influences thyroid

metabolism both peripherally and in the hypothalamo-pituitary-thyroid axis. It also acts as an antioxidant[10]. Magnesium is involved in DNA stabilization, immune system regulation and anti-inflammatory activity[11]. L-carnitine faces depletion in both hyper- and hypothyroidism. It is essential in fatty acids oxidation. Deficiency may result in increased fatigue[12,13]. Both protein kinases and bioflavonoids show anti-inflammatory effect[14,15].

MATERIALS AND METHODS

This study followed PRISMA search principles. The search used a medical database: Pubmed. The following keywords were used to find relevant articles: ((Hashimoto[Text Word]) OR (hypothyroidism)) AND ((sport) OR (physical activity) OR (diet)). The types of article included in the study were Clinical Trial, Observational Study, Randomized Controlled Trial. The publication period was restricted to the time period between 1st January 2005 and 29th June 2024. A total of 71 articles were found that met the criteria. After removing duplicate (n=1), three researchers reviewed the articles based on their titles and abstracts. Following additional analysis for relevance and quality, 23 articles were selected for the full text reading. Studies focusing on sport, physical activity, weight loss were excluded. Finally, 11 articles regarding impact of Vitamin D, Selenium, Iodine, Zinc, Magnesium, Vitamin A, L-carnitine and proteolytic enzymes were included in the research. The chosen studies were published during last ten years [16–25] with one published in 2012[26].

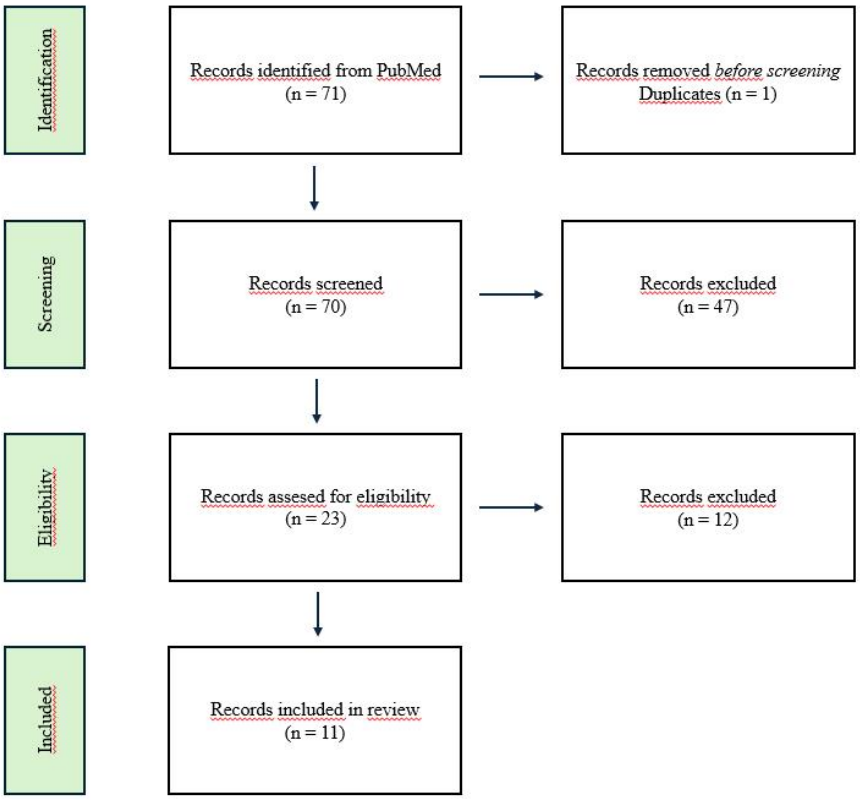

Figure 1
PRISMA flow diagram presenting summary of research and processing information.

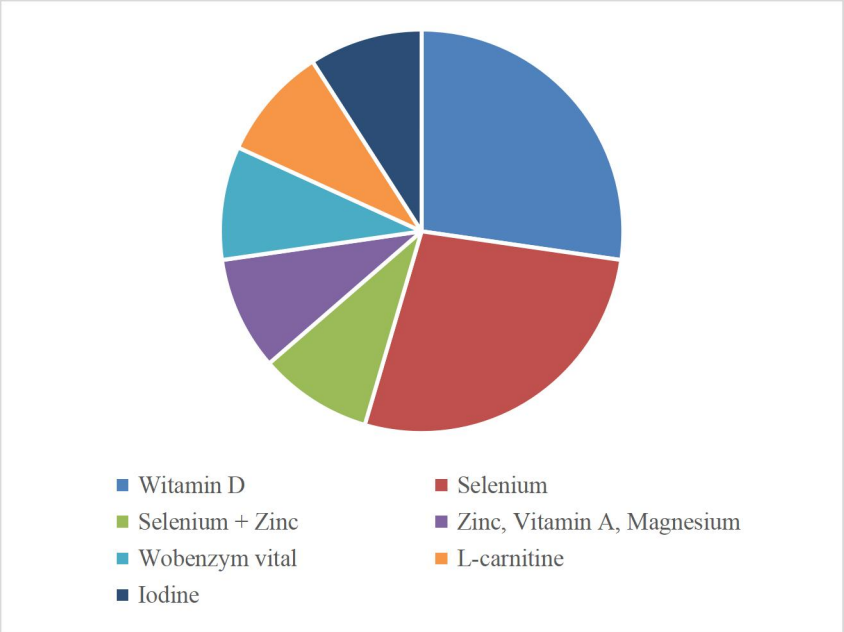

Figure 2
Distribution of nutrients in analyzed studies

RESULTS

Vitamin D

Safari et al.[24] examined the effects of vitamin D supplementation on thyroid hormones, lipid profiles, measures of obesity and serum irisin in women with subclinical hypothyroidism and obesity (BMI 25-37 kg/m2). 44 women were randomly allocated into two groups, 22 each. The control group received a placebo containing sunflower oil, while the experimental group received 50,000 IU of vitamin D for the span of 12 weeks, once a week. The study was completed by 41 participants: 21 in vitamin D and 20 in the placebo group. At the beginning of the trial, there were no significant differences in dietary energy, carbohydrate, fat and vitamin D intakes. However, there was a significant difference in protein intake between the two groups ($p = 0.018$). Participants were asked to maintain their eating habits, physical activity during the 12 weeks of the trial. Vitamin D supplementation led to an increase in 25(OH)D3 levels in patients ($p<0.001$), indicating improvement in vitamin D status. It also resulted in a reduction of TSH levels ($p<0.001$), suggesting a regulatory effect on thyroid function. There was a decrease significant in total cholesterol (TC) ($p<0.001$) and non-significant in LDL-C levels (p=0,119). The levels of irisin, a hormone associated with metabolic regulation, increased following vitamin D supplementation (p=0,054). The levels of thyroid hormones (T3, T4, and free thyroxine - fT4) remained stable (p-values 0,787, 0,082, 0,066 respectively). There were no notable changes in triglyceride (TG) (p= 0,219) and HDL-C (p=0,167) levels. At the end of the study, significant differences were observed between the two groups in fat mass (FM)% (decreased in vitamin D group)(p=0,024) and fat-free mass (FFM)% (increased in vitamin D group)(p=0,016) based on analysis of covariance adjusted for baseline values, physical activity and energy intake. Changes in weight, body mass index (BMI), and waist circumference (WC) were not significantly different between the groups. Within-group changes in all variables were not significant for either group.

Bhakat et al.[18] conducted a prospective study evaluating the role of cholecalciferol (vitamin D3) supplementation in reducing autoimmunity in patients with Hashimoto's Thyroiditis (HT).

The study lasted for over 12 months and included 100 newly diagnosed patients (male and female) with HT and vitamin D deficiency. Patients with other autoimmune diseases and chronic illnesses such as diabetes mellitus, chronic kidney or liver disease, malignancy were excluded from the trial. Participants were randomized into two groups. The first group (n=50) received 60,000 IU of cholecalciferol weekly for 8 weeks and the second group (n=50) received a placebo. The results showed a significant (p<0,05) 30,5% reduction in anti-thyroid peroxidase (anti-TPO) antibodies in the intervention group compared to a 16,5% reduction in the placebo group, indicating that vitamin D supplementation may be helpful in decreasing thyroid autoimmunity and improve thyroid function.

Mazokopakis et al.[21] studied the influence of vitamin D supplementation on patients from Crete with euthyroid Hashimoto disease. Among 218 participants, 186 had vitamin-D insufficiency (85,3%). Vitamin D deficient patients received supplementation ranging between 1 200 - 4 000 IU according to their needs for four months. High negative correlation was observed between serum 25(OH)D3 levels and anti-TPO, both in baseline findings concerning all patients (p<0,0001), and when comparing vitamin D sufficient and deficient patients before supplementation (p<0,0001). In the deficient group vitamin D supplementation resulted in significant reduction of anti-TPO levels (p<0,0001). BMI, anti-TG, TSH and fT4 showed no correlation with serum 25(OH)D3 at the beginning of the study both in the whole study population and in vitamin D sufficient/deficient groups comparison. After oral cholecalciferol supplementation in deficient group 25(OH)D3 levels rose significantly (P<0,0001). BMI, anti-TG and TSH levels have also improved, though those changes were not significant (respectively p=0,15, p=0,18 and p=0,54). No significant findings were noted in fT4, calcium and phosphorus levels and in sonographic tests.

Selenium

Hu et al.[19] randomized 90 patients with Hashimoto's Thyroiditis (HT) without levothyroxine treatment into two study groups: selenium (Se)-treated group (n=43), which received selenious yeast tablets (SYT) for 6 months and no treatment group (n=47) to assess the effects of selenium supplementation on HT. The participants were followed-up at 3 months and 6 months to evaluate thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) titers, thyroid hormone levels, serum Se and urinary iodine (UI) levels, Glutathione peroxidase3 (GPx3) and Selenoprotein P1 (SePP1) concentrations, regulatory T cell (Treg) numbers and function. Treatment compliance and the physical condition of participants were monitored monthly. The findings revealed that SYT treatment led to a significant reduction of TPOAb, TGAb, and TSH levels compared to the no-treatment group (all p=0,001). Selenium levels (p<0,001), as well as the antioxidant GPx3 (p = 0.028) and SePP1(p = 0.007), were increased in the Se-treated group. What's more, activated Tregs were more prevalent in intervention group, suggesting a potential immunomodulatory beneficial role of selenium in HT.

The aim of the study performed by Andrade et al.[17] was to investigate the relationship between dietary selenium intake and subclinical hypothyroidism. The sample included 14 283 adults aged 35-74, both male and female. Subclinical hypothyroidism was identified by elevated TSH levels (>4.0 IU/mL) with normal T4 levels, excluding those on thyroid medication. Selenium intake was assessed via a validated food frequency questionnaire. The main results showed that 5.4% of the sample had subclinical hypothyroidism. (p<0.05). Moreover, higher Se intake was associated with lower likelihood of subclinical hypothyroidism. When compared to the lowest tertile of Se intake, the odds ratios (ORs) for

subclinical hypothyroidism were 0.79 (p<0.05, 0.65-0.96%) for the second tertile and 0.72 (p<0.05, 0.58-0.90%) for the third tertile, demonstrating a significant inverse correlation.

Wu et al.[25] conducted a cross-sectional observational study to determine if the prevalence of thyroid disease varied between two areas that were alike, except for significantly different soil and crop selenium levels. 6152 participants (3038 from an adequate-Se county and 3114 from a low-Se county) completed demographic and dietary questionnaires, and underwent physical and thyroid ultrasound examinations (measurement of thyroid gland volume). Serum samples were analyzed for thyroid function parameters, including TSH, T3, T4, TPO antibodies, and selenium concentration. 1499 participants (24.4%) had some form of thyroid disease. In the adequate-Se county, 548 (18,0%) had thyroid disease, compared to 951 (30,5%) in the low-Se county (p < 0,001). The highest prevalence was for subclinical hypothyroidism (16,6%) and the lowest for Graves' disease (0,6%). Subclinical hypothyroidism was significantly lower in the adequate-Se county (p < 0,001), as was overt hypothyroidism (p < 0,001) and autoimmune thyroiditis (p = 0,007). Enlarged thyroids were less common in the adequate-Se county (p = 0,001). No significant differences were found in the prevalence of hyperthyroidism, Graves' disease, or thyroid nodules. Subclinical hyperthyroidism was lower in the low-Se county than in the adequate-Se county (p = 0,003). Participants from both counties were also grouped into five categories based on their serum selenium levels. The lowest serum Se group (<47 μg/L) had the highest rates of overt hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis, and enlarged thyroid. As serum Se levels increased up to the third quintile (69–90.99 μg/L), the prevalence of these conditions decreased, but then either reversed or leveled off above this range. Enlarged thyroid prevalence was lowest in the highest serum Se group (≥120 μg/L). Additionally, individuals with subclinical hypothyroidism and enlarged thyroid had significantly lower serum Se levels (p < 0,05) compared to those without these conditions.

Selenium with Zinc

Mahmoodianfard et al.[20] investigated the effects of zinc and selenium supplementation on thyroid function in overweight or obese women with hypothyroidism in a double-blind, randomized controlled trial. Sixty-eight women were randomly allocated to one of the 4 supplementation groups receiving Zn + Se, Zn + placebo, Se + placebo, or placebo + placebo for 12 weeks. Serum Zn, Se, fT3, tT3, fT4, tT4, TSH, and anthropometric parameters were measured. There were no significant changes in zinc and selenium concentrations between groups. Mean serum fT3 levels increased significantly in both the ZS (zinc and selenium) and ZP (zinc and placebo) groups (p < 0.05). No significant changes in fT3 levels were detected in the SP (selenium and placebo) and PP (placebo and placebo) groups. Mean serum fT4 levels increased significantly in the ZS group (p < 0.05). TSH levels decreased significantly in the ZS group (p < 0.05) but not in the Zn or Se groups alone. Serum tT3 and tT4 levels decreased in all groups, but the decrease was significant only in the SP group. No notable changes in BMI and weight were observed.

Zinc, Vitamin A and Magnesium

A randomized controlled trial was conducted by Rabbani et al.[23] to evaluate the combined effects of co-supplementing Zn, Mg, and vitamin A on thyroid function, oxidative stress, and inflammatory markers in patients with hypothyroidism. The study involved 88 patients who were 20-65 years old and had BMI <=35kg/m2 from Iran University of Medical Sciences. They were divided into intervention and placebo groups. The intervention group (n=43) received supplements of Zn (one tablet of 30 mg zinc gluconate per day), Mg (one tablet of 250 mg magnesium oxide per day), and vitamin A (25 000 IU twice per week) for 10 weeks,

while the placebo group (n=44) received similar-looking placebos. Participants were instructed to stick to their usual diets and physical activity routine and to avoid supplements containing Zn, Mg, or vitamin A throughout the experiment. Adherence to the guidelines was monitored through weekly phone check-ins and by counting the number of tablets returned at the conclusion of the study. The results showed that the intervention group had a significant increase in serum fT4 levels and a significant reduction in serum high sensitivity C-reactive protein (hs-CRP) levels compared to the placebo group ($p<0,05$). There were no significant differences in other thyroid hormones (fT3, TSH, and tT4). The study concluded that Zn, Mg, and vitamin A co-supplementation can improve thyroid function and reduce inflammation in hypothyroid patients. This trial is the first to examine the combined effects of these micronutrients on thyroid function and related health markers.

Iodine

A different approach was made by Zhongha et al.[26], in a study seeking out the highest safe daily iodine intake. 256 Chinese students, aged 19 to 25 years, with no thyroid dysfunction, antibodies associated with thyroid inflammation and no low iodine urinary concentration at baseline were divided into 11 groups of different iodine supplementation, ranging from 100 to 2000 μg I/d and one placebo group. When considering iodine intake from food and salt total iodine intake ranged from 351 μg/d to 2375 μg/d. No statistical differences were found in baseline TSH, fT3, fT4 and median urinary iodine concentration (MUIC) levels. MUIC increased significantly in subjects with at least 200 μg/d supplementation after 4 weeks of experiment ($p<0,05$). Both fT3 and fT4 serum levels faced a significant increase in groups with higher iodine supplementation (from 500 μg/d and 200 μg/d respectively, $p<0,05$), nonetheless all remained in normal range. Elevated TSH levels were observed in all groups ($p<0,05$), though abnormal ranges were seen only in groups of 300 μg/d and higher iodine supplementation. Subclinical hypothyroidism prevailed in 5-10% of subjects from higher dose groups (500 – 2000 μg/d) one month after experiment. Furthermore, an ultrasonography revealed reduced thyroid size in 1500, 1750, and 2000 μg/d groups ($p < 0.05$).

L-carnitine

An et al.[16] conducted a double blind, randomized, placebo-controlled study on patients affected by hypothyroidism (chronic autoimmune thyroiditis or iatrogenic after total thyroidectomy) and suffering from fatigue despite adequate hormone supplementation. Participants were divided into two groups, The first received L-carnitine supplementation in the span of 12 weeks, with the other receiving placebo treatment. Serum total and acyl-carnitine levels increased significantly in the L-carnitine group (all $p<0,05$) with no significant change in placebo group. Fatigue Severity Scale's (FSS) and Wessely and Powell Scale's (consisting of Physical Fatigue Score (PFS) and Mental Fatigue Score (MFS)) changes after 12-weeks were compared between groups. The differences in decrease were significant only in MFS ($p<0,01$), though statistically insignificant differences could also be seen in PFS and FFS ($p>0,05$). Improvements in FFS, PFS and MFS scores could be seen in 75,0%, 53,6%, and 50,0% of the L-carnitine group respectively, with only 20,0%, 24,0%, and 24,0% in the placebo group (all $p<0,05$). In subgroup analyses, when comparing differences in changes in fatigue scores between groups, $p<0,05$ was reached in PFS and MFS in patients younger than 50 years, and those with $fT3 \geq 4.0$ pg/mL, and in MFS in patients whose serum total carnitine level was ≥ 60.9 μmol/L and after total thyroidectomy. Subgroups divided by body fat mass (BFM), BMI, free TSH/fT4, cholesterol levels or alanine transaminase (ALT) did not show significant differences. Furthermore, there were no statistical differences when dividing L-carnitine treated patients into improved and non-improved groups in their baseline

characteristics. No significant changes were observed in BMI, WC, BFM, serum liver, lipid and glycemic profiles and thyroid function in either group (all p>0,05).

Proteolytic enzymes with bioflavonoids

In a study by Nordio et al.[22] patients suffering from autoimmune chronic thyroiditis were divided into three groups; receiving Wobenzym vital (Wob) alone (a food supplement containing proteolytic enzymes - bromelain, papain, trypsin, chino trypsin and bioflavonoids, vitamin C, vitamin D, vitamin E), Wobenzym vital with thyroid hormones (Wob+L-thyr) and thyroid hormones alone (L-thyr). A questionnaire regarding the subjective symptoms of thyroid inflammation showed significant (p<0,05) improvement after 3 months of Wobenzym vital treatment (with or without thyroid hormones supplementation) compared with significant improvement only after 6 months of only hormone supplementation. There were no significant differences in the General Health Questionnaire – 28. Significant reduction in inhomogeneity level in USG was reached only in Wob+L-thyr group (p<0,05). Inferior thyroid artery speed velocity showed reduction in groups treated with Wobenzym vital (p<0,05), while TSH levels were improved only in groups treated with L-thyroxine (p<0,05). In antibodies assessments, significant decrease (p<0,05) was reached in human thyroglobulin (hTG) after Wobenzym vital treatment (with or without L-thyroxine) and TGAb after Wobenzym and L-thyroxine. No changes were noted in TPOAb levels. CRP levels were reduced in all groups, with statistical significance reached only in groups treated with Wobenzym vital (p<0,05).

Authors, Year, Country	**Participants**	**Groups**	**Supplemented ingredient**	**Duration**
Safari et al., 2023, Iran	41 women with subclinical hypothyroidism and overweight/obesity:	21 in a vitamin D group, 20 in a placebo group	Vitamin D	12 weeks
Bhakat et al., 2023, India	100 participants of both sexes with Hashimoto Thyroiditis	50 in a vitamin group 50 in a placebo group	vitamin D	8 weeks
Mazokopakis et al., 2015, Greece	218 euthyroid HT patients from Crete	186 vit. D-deficient patients 30 vit. D-sufficient	vitamin D	4 months
Hu et al., 2021, China	90 patients with Hashimoto Thyroiditis without levothyroxine treatment	43 in Se-treated group 47 in placebo group	Selenium	6 months

Andrade et al., 2018, Brazil	14283 patients	3 groups a 4761 each - different tertile of Se consumption	Selenium	12-months
Wu et al., 2015, China	6152 from two counties in China	-3038 adequate-selenium participants and 3114 low-selenium participants -5 groups by the serum Se level	Selenium (in soil; serum Se)	
Mahmoodianfard et al., 2015, Iran	58 women with hypothyroidism and overweight/obesity:	16 Zinc+Selenium, 12 Zinc+Placebo, 14 Selenium+Placebo, 16 Placebo+Placebo	Zinc and/or Selenium	12 weeks
Rabbani et al., 2021, Iran	88 patients with hypothyroidism	43 Zinc +Magnesium + Vitamin A 44 placebo	Zinc, Magensium, Vitamin A	10 weeks
Nordio et al., 2014, Italy	45 patients with Hashimoto thyroiditis	15 Wobenzym vital, 15 Wobenzym vital + thyroid hormones, 15 thyroid hormones	Wobenzym vital: proteases (bromelain, papain, trypsin, chino trypsin) and bioflavonoids with vitamins C, D, E	6 months
An et al., 2016, South Korea	60 patients with hypothyroidism with euthyreosis and fatigue	30 L-carnitine, 30 placebo	L-carnitine	12 weeks
Sang et al., 2011, China	256 Chinese healthy individuals of age 19-25	12 intervention groups with iodine supplementation ranging from 0 to 2 000 μg/d	Iodine	4 week

Table 1
Articles included in this study

DISCUSSION

Regardless of small number of collected studies, their analysis brings the conclusion of multiple nutritional factors having an effect on the onset, progress and management of thyroid diseases, one of the best studied being vitamin D and selenium. Cholecalciferol is synthetized in our skin with exposure to sunlight[5,6]. Due to relatively short periods of sun exposure in some countries during winter months resulting in common insufficiency vitamin D supplementation is recommended. It plays a role in moderating immune system, by decreasing T cell activation, encouraging the shift from Th1, Th17 phenotype to Th2, changing immune status from pro-inflammatory to more tolerogenic and taking part in B cell inhibition. As such, 25(OH)D3 deficiency seems to take part in pathogenesis of autoimmune thyroid disorders, including Hashimoto's disease and Graves' disease. A high negative correlation of anti-TPO levels compared to 25(OH)D3 serum levels in baseline findings[21] and a significant reduction of anti-TPO after cholecalciferol supplementation[18,21] suggests potential benefits in reducing thyroid autoimmunity and that vitamin D deficiency may be a significant risk factor for Hashimoto's thyroiditis. Nonetheless, a decrease in anti-TPO is not sufficient to prove this correlation and histopathological evidence is needed. Reduction of TSH after supplementation[18,24], though not significant in every study[21] proposes positive effect on thyroid function. Another observed beneficial effects were lowering of total cholesterol levels and increasing irisin levels, though it did not significantly impact lipid markers[24]. The authors suggest that the increased irisin, which is an enzyme that, among other functions, increases thermogenesis by stimulating browning in white adipose tissue, might have influenced body composition and that a longer vitamin D supplementation period might be needed to improve obesity markers. In a study by Mazokopakis et al.[21] BMI dropped insignificantly, at least partly due to lack of dietary changes, short period of observation (4 months) and relatively low percentage of obese and overweight patients. Thyroid hormones were also nor significantly affected by 25(OH)D3 supplementation[21,24].However, several limitations restrict analyzed data. In a study by Bhakat et al.[18] vitamin D status was not measured at the end of treatment, limiting the ability to determine the optimal level of vitamin D needed to improve the progression of HT. What's more, cholecalciferol was used in the study, with authors suggesting that the active form – calcitriol might be more beneficial. It's also important to note that only patients with vitamin D deficiency were included in the trial, meaning that the findings can't improve the beneficial effects of vitamin D supplementation in HT patients with adequate vitamin D levels. Conclusions from Safari et al.[24] are limited by the small sample size, the inclusion of only women, and the short duration. Future research should include other doses of vitamin D, a more diverse population, including men, individuals with normal body weight, and those with different thyroid disorders, to obtain more generalizable results. The impact on thyroid hormones should also be studied in broader populations, as the current study focused on individuals with subclinical hypothyroidism, where hormone levels are within the normal range. Mazokopakis et al.[21] conducted a study during sunny spring and summer season involving people affected by HT working and living on Crete, an island with high sun exposure. Though findings suggest a role 25(OH)D3 insufficiency in thyroid diseases, no comparison between vitamin D levels in healthy and unhealthy subjects was made due to a lack of control group of healthy individuals.

Selenium is a microelement with its highest concentration in thyroid gland[27,28]. The population's dietary characteristics and their geographical location (mainly soil composition) affect selenium levels[7]. It is a part of selenoproteins, such as glutathione peroxidases (GPXs), thioredoxin reductases (TRs) and deiodinases[29]. GPXs and TRs have an antioxidant function with TRs also contributing to gene expression, while deiodinases play a role in thyroid

hormone metabolism. The latter are responsible for conversion from T4 to T3, inhibition of T4 activation and T3 inactivation. In one of the studies, selenium supplementation reduced thyroid antibodies and TSH levels in patients with HT and enhanced regulatory T cells in subjects. As such, selenium supplementation could be a valuable treatment approach for managing HT. Despite these outcomes, the study has several limitations. It was an open-label, single-center study with a small sample size and did not include a placebo control group[19]. An inverse association, independent of energy and other nutrient intakes, was found between selenium intake and the likelihood of subclinical hypothyroidism[17]. However, the study used a Food Frequency Questionnaire (FFQ) for estimating Se intake, which can overestimate dietary intake and lacks accuracy. Interpretation was also obstructed by the cross-sectional design of the study and the variability of Se levels in foods due to soil differences. In another study, higher selenium levels (both in the soil and in the serum) were correlated with lower prevalence of subclinical and overt hypothyroidism, autoimmune thyroiditis, and enlarged thyroids and a higher prevalence of subclinical hyperthyroidism[25]. Higher serum Se levels were associated with consumption of meat, eggs, and green tea. Those results were hindered by gender imbalance (7:3 ratio favoring women), indirect measurement of Se levels by questionnaires, lack of consideration for other factors, such as genetic predispositions, diet, and environment.

Zinc is involved in thyroid hormone metabolism by affecting their synthesis[9,30]. Both thyrotropin releasing hormone's and thyroid stimulating hormone's synthesis relies on this microelement. It is also essential for receptor activity of thyroid hormones (mostly T3). Zinc appears crucial for T4 to T3 conversion, as in its absence the activity of type I-5' deiodinase is constricted, though high zinc concentrations may also show adverse effects on type I deiodinase. By increasing the production of thyroid-binding protein it affects T4 levels. Mahmoodianfard et al. on zinc and selenium proved that zinc supplementation increases fT3 levels and improves the fT3:fT4 ratio. Selenium supplementation resulted in decreased tT3 and tT4 levels with no significant changes in thyroid function markers. The combination of zinc and selenium supplementation increased fT4 levels and decreased TSH, suggesting a synergistic effect on thyroid function of hypothyroid female patients. Zinc and selenium serum levels were not increased. A bigger sample size, extended intervention period and control for diet, physical activity, and sun exposure are needed.
Vitamin A acts as an antioxidant, lowering the risk of autoimmune diseases[10,31]. Iodine status affects its effect on thyroid metabolism. Thyroid hormone intake and thyroglobulin synthesis are impaired in vitamin A deficient rats. Vitamin A deficiency (VAD) may suppress TSH production by inhibiting TSHβ gene by 9-*cis*-retinoic acid-activated retinoid X receptor (RXR). Free and total thyroid hormone is also increased in VAD, Magnesium stabilizes nucleic acids structure and possibly takes part in DNA replication, transcription and repair, suggesting its connection to the development of tumors, including thyroid gland cancer[11,32]. It is also involved in immune system regulation, participating in lymphocyte T and B activation. Serum levels of magnesium are inversely related with levels of inflammatory factors, including interleukin-6 and C-reactive protein. The effects of multi-nutrient therapy (zinc, magnesium and vitamin A) on thyroid function and inflammation in patients with hypothyroidism were studied by Mahmoodianfard[20]. The findings include a significant increase in serum fT4 levels and a decrease in high-sensitivity hs-CRP levels after supplementation. However, no significant changes were found in serum TSH, fT3, tT4, and malondialdehyde (MDA) levels. Zinc and magnesium might help reduce inflammation by down-regulating NF-kB and through Mg's role in ATP synthesis, which is essential for iodine uptake. Additionally, vitamin A might help in reducing weight and BMI by potentially

decreasing leptin gene expression. Overall, the findings suggest that a multi-nutrient therapy including Zn, Mg, and vitamin A can improve thyroid function and reduce inflammation and oxidative stress markers in hypothyroid patients. Although promising results, the research has limitations. The 10-week duration may have been too short to observe significant changes in some thyroid and metabolic parameters, such as TSH and fT3 levels. Furthermore, the relatively small sample size of 43 participants per group might limit the generalizability of the findings and reduce the statistical power to detect subtle changes. Therefore, further research is necessary to fully understand the mechanisms and long-term effects of these nutrient interventions on thyroid health and overall metabolic function.

Thyroid hormones, triiodothyronine and thyroxine, contain iodine[8,33]. Both iodine deficiency and excess may led to the development of thyroid diseases. Insufficient iodine intake during pregnancy and in children remains the most common cause for preventable mental retardation worldwide. Deficiency may also led to toxic goiter and thus hyperthyroidism in adults. Exposure to high iodine levels causes inflammation of thyroid gland leading to Hashimoto thyroiditis. Wolff-Chaikoff effext is a permanent or temporary inhibition of thyroid hormone synthesis following excess iodine intake. Sang et al.[26] studied the highest safe iodine intake, supplementation ranging from 100 to 2 000 μg I/d. Since maximum iodine intake varies depending on population, this study has focused on Chinese individuals. While fT3 and fT4 increased with higher doses, they remained in normal ranges. In groups with supplementation higher than 300 μg I/d subclinical hypothyroidism was observed. Moreover, it has prevailed one month after the end of supplementation in participants with doses of 500 μg I/d or higher and in 5 % of participants with 400 μg I/d dose 3 months after experiment, indicating possible adverse effect of supplementation lower than 500 μg I/d. The authors have proposed highest daily iodine intake of 800 μg, though more studies are needed. The study detriments were relatively short exposure time (4 weeks) and subjects being mostly young, healthy and well-educated, indicating possible lower maximum doses for children, elderly and less healthy individuals.

L-carnitine plays a role in fatty acids metabolism and energy production[12]. Free fatty acids, converted into acyl-coenzyme A, need L-carnitine in order to penetrate the outer mitochondrial membrane. Thus carnitine depletion impedes their oxidation possible only on inner mitochondria membrane. As this process is T3 dependent, hyperthyroidism may cause increased oxidation and L-carnitine deficiency. Thyroid hormone promotes synthesis of L-carnitine, thus hypothyroidism may lead to insufficiency[13]. As such, both hypothyroidism and hyperthyroidism may be responsible for L-carnitine deficiency. Since skeletal and cardiac muscles depend on fatty acids as main source of energy, L-carnitine low levels are linked with increased fatigue[34]. In a study conducted on patients with hypothyroidism supplementations of L-carnitine resulted in a significant decrease in MFS, with an insignificant decrease in both FFS and PFS[16]. Hence, L-carnitine shows promising effects on lowering fatigue in euthyroid patients. FFS and PFS scales not reaching statistical significance may be due to relatively small groups (30 people each), thus further studies are needed. Moreover, people under 50 years old, with high T3 levels and after post cancer thyroidectomy (receiving high doses of T4 for TSH suppression) are more prone to L-carnitine positive effects on fatigue thanks to their greater metabolic activity. As patients with higher L-carnitine levels showed better results there is a possibility of sub-optimal dosage of L-carnitine in this study. It has to be noted, that since fatigue is subjective and vague it proves difficult to assess even with various objective scores. Most patients were women with the mean age of 50 years old, meaning the results may have been confounded due to varying perimenopausal estrogen levels. Consequently,

more large-scale studies considering additional variables affecting fatigue such as estrogen levels are needed. In addition, there was no positive effect on metabolic parameters, possibly resulting from short treatment duration (12 weeks) and small groups.

Wobenzym vital is a dietary supplement containing proteolytic enzymes (bromelain, chymotrypsin, trypsin and papain), bioflavonoids and vitamins C, D and E. Proteases are believed to take part in both the inflammation process and the control of inflammation, possibly by clearing the inflammatory debris. An anti–inflammatory effect by protease-induced catecholamine release is also plausible, though requires further investigations[15]. Flavonoids are known antioxidants capable of scavenging free radicals. Their anti-inflammatory effect is also shown in inhibition of transcription factors, protein kinases and phosphodiesterases. Lastly, they regulate immune system, preferring more tolerogenic phenotype[14]. In a study by Nordio te al.[22] Wobenzym vital showed promising results in reducing inflammation thus improving the management of autoimmune thyroid disease. In patients treated with Wobenzym vital a faster subjective symptoms lessening was observed. It showed a promising effect on antibodies concentration, though insufficient possibly due to small groups. Lower effect on TSH indicated that thyroid function improvement stems from its anti-inflammatory activity. Notably, relatively small groups (15 people each) and impossibility to ascertain the compliance are this study shortcomings.

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REFERENCES:

1. Chiovato L, Magri F, Carlé A. Hypothyroidism in Context: Where We've Been and Where We're Going. *Adv Ther*. 2019;36(Suppl 2):47-58. doi:10.1007/s12325-019-01080-8

2. Nygaard B. Hypothyroidism (primary). *BMJ Clin Evid*. 2014;2014:0605. Accessed July 23, 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3931439/

3. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet Lond Engl*. 2017;390(10101):1550-1562. doi:10.1016/S0140-6736(17)30703-1

4. Dalugodage SS, Bowatte G, Antonypillai C, Rajapakse S, Tennakoon TMIUK. Association of pharmacogenomic, clinical and behavioural factors with oral levothyroxine (LT-4) dose of hypothyroid patients in Sri Lanka: a matched case control study. *BMC Med Genomics*. 2024;17:79. doi:10.1186/s12920-024-01849-z

5. Danailova Y, Velikova T, Nikolaev G, et al. Nutritional Management of Thyroiditis of Hashimoto. *Int J Mol Sci*. 2022;23(9):5144. doi:10.3390/ijms23095144

6. Kim D. The Role of Vitamin D in Thyroid Diseases. *Int J Mol Sci*. 2017;18(9):1949. doi:10.3390/ijms18091949

7. Ventura M, Melo M, Carrilho F. Selenium and Thyroid Disease: From Pathophysiology to Treatment. *Int J Endocrinol*. 2017;2017:1297658. doi:10.1155/2017/1297658

8. Osowiecka K, Myszkowska-Ryciak J. The Influence of Nutritional Intervention in the Treatment of Hashimoto's Thyroiditis—A Systematic Review. *Nutrients*. 2023;15(4):1041. doi:10.3390/nu15041041

9. Baltaci AK, Mogulkoc R, Baltaci SB. Review: The role of zinc in the endocrine system. *Pak J Pharm Sci*. 2019;32(1):231-239. Accessed Juny 23 2024. https://www.pjps.pk/uploads/pdfs/32/1/Paper-33.pdf

10. Rubab G, Hassan S, Sanaullah A, Basharat D, Arshad M, Shahid M. Influence of Zinc, Vitamin A and Magnesium supplementation on Hypothyroidism. Published online November 12, 2023. Accessed July 23, 2024. https://www.isisn.org/BR-20-3-2023/895-903-20(3)2023BR23-184.pdf

11. Zhou Q, Xue S, Zhang L, Chen G. Trace elements and the thyroid. *Front Endocrinol*. 2022;13:904889. doi:10.3389/fendo.2022.904889

12. Flanagan JL, Simmons PA, Vehige J, Willcox MD, Garrett Q. Role of carnitine in disease. *Nutr Metab*. 2010;7:30. doi:10.1186/1743-7075-7-30

13. Galland S, Georges B, Le Borgne F, Conductier G, Dias JV, Demarquoy J. Thyroid hormone controls carnitine status through modifications of gamma-butyrobetaine hydroxylase activity and gene expression. *Cell Mol Life Sci CMLS*. 2002;59(3):540-545. doi:10.1007/s00018-002-8445-3

14. Maleki SJ, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. *Food Chem*. 2019;299:125124. doi:10.1016/j.foodchem.2019.125124

15. Viswanatha Swamy AHM, Patil PA. Effect of Some Clinically Used Proteolytic Enzymes on Inflammation in Rats. *Indian J Pharm Sci*. 2008;70(1):114-117. doi:10.4103/0250-474X.40347

16. An JH, Kim YJ, Kim KJ, et al. L-carnitine supplementation for the management of fatigue in patients with hypothyroidism on levothyroxine treatment: a randomized, double-blind, placebo-controlled trial. *Endocr J*. 2016;63(10):885-895. doi:10.1507/endocrj.EJ16-0109

17. Andrade GRG, Gorgulho B, Lotufo PA, Bensenor IM, Marchioni DM. Dietary Selenium Intake and Subclinical Hypothyroidism: A Cross-Sectional Analysis of the ELSA-Brasil Study. *Nutrients*. 2018;10(6):693. doi:10.3390/nu10060693

18. Bhakat B, Pal J, Das S, et al. A Prospective Study to Evaluate the Possible Role of Cholecalciferol Supplementation on Autoimmunity in Hashimoto's Thyroiditis. *J Assoc Physicians India*. 2023;71(1):1. Accessed July 23, 2024. https://journal-api.s3.ap-south-1.amazonaws.com/issues/January2023.pdf

19. Hu Y, Feng W, Chen H, et al. Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial. *Clin Transl Sci*. 2021;14(4):1390-1402. doi:10.1111/cts.12993

20. Mahmoodianfard S, Vafa M, Golgiri F, et al. Effects of Zinc and Selenium Supplementation on Thyroid Function in Overweight and Obese Hypothyroid Female Patients: A Randomized Double-Blind Controlled Trial. *J Am Coll Nutr*. 2015;34(5):391-399. doi:10.1080/07315724.2014.926161

21. Mazokopakis EE, Papadomanolaki MG, Tsekouras KC, Evangelopoulos AD, Kotsiris DA, Tzortzinis AA. Is vitamin D related to pathogenesis and treatment of Hashimoto's

thyroiditis? *Hell J Nucl Med*. 2015;18(3):222-227. Accessed July 23, 2024. https://www.nuclmed.gr/wp-content/uploads/2017/03/07.pdf

22. Nordio M, Basciani S. Efficacy of a food supplement in patients with hashimoto thyroiditis. *J Biol Regul Homeost Agents*. 2015;29(1):93-102. Accessed July 23, 2024. https://www.biolifesas.org/EN/Y2015/V29/I1/93

23. Rabbani E, Golgiri F, Janani L, et al. Randomized Study of the Effects of Zinc, Vitamin A, and Magnesium Co-supplementation on Thyroid Function, Oxidative Stress, and hs-CRP in Patients with Hypothyroidism. *Biol Trace Elem Res*. 2021;199(11):4074-4083. doi:10.1007/s12011-020-02548-3

24. Safari S, Rafraf M, Malekian M, Molani-Gol R, Asghari-Jafarabadi M, Mobasseri M. Effects of vitamin D supplementation on metabolic parameters, serum irisin and obesity values in women with subclinical hypothyroidism: a double-blind randomized controlled trial. *Front Endocrinol*. 2023;14:1306470. doi:10.3389/fendo.2023.1306470

25. Wu Q, Rayman MP, Lv H, et al. Low Population Selenium Status Is Associated With Increased Prevalence of Thyroid Disease. *J Clin Endocrinol Metab*. 2015;100(11):4037-4047. doi:10.1210/jc.2015-2222

26. Sang Z, Wang PP, Yao Z, et al. Exploration of the safe upper level of iodine intake in euthyroid Chinese adults: a randomized double-blind trial. *Am J Clin Nutr*. 2012;95(2):367-373. doi:10.3945/ajcn.111.028001

27. Błażewicz A, Wiśniewska P, Skórzyńska-Dziduszko K. Selected Essential and Toxic Chemical Elements in Hypothyroidism—A Literature Review (2001–2021). *Int J Mol Sci*. 2021;22(18):10147. doi:10.3390/ijms221810147

28. Köhrle J, Jakob F, Contempré B, Dumont JE. Selenium, the thyroid, and the endocrine system. *Endocr Rev*. 2005;26(7):944-984. doi:10.1210/er.2001-0034

29. Schomburg L. Selenium, selenoproteins and the thyroid gland: interactions in health and disease. *Nat Rev Endocrinol*. 2011;8(3):160-171. doi:10.1038/nrendo.2011.174

30. Severo JS, Morais JBS, de Freitas TEC, et al. The Role of Zinc in Thyroid Hormones Metabolism. *Int J Vitam Nutr Res Int Z Vitam- Ernahrungsforschung J Int Vitaminol Nutr*. 2019;89(1-2):80-88. doi:10.1024/0300-9831/a000262

31. Biebinger R, Arnold M, Langhans W, Hurrell RF, Zimmermann MB. Vitamin A Repletion in Rats with Concurrent Vitamin A and Iodine Deficiency Affects Pituitary TSHβ Gene Expression and Reduces Thyroid Hyperstimulation and Thyroid Size1. *J Nutr*. 2007;137(3):573-577. doi:10.1093/jn/137.3.573

32. Wang K, Wei H, Zhang W, et al. Severely low serum magnesium is associated with increased risks of positive anti-thyroglobulin antibody and hypothyroidism: A cross-sectional study. *Sci Rep*. 2018;8:9904. doi:10.1038/s41598-018-28362-5

33. Chung HR. Iodine and thyroid function. *Ann Pediatr Endocrinol Metab*. 2014;19(1):8-12. doi:10.6065/apem.2014.19.1.8

34. Matsui H, Einama T, Shichi S, et al. L-Carnitine supplementation reduces the general fatigue of cancer patients during chemotherapy. *Mol Clin Oncol*. 2018;8(3):413-416. doi:10.3892/mco.2018.1557