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Mini-Review

Thyroid, Diet, and Alternative Approaches

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Abstract

Background: Increasingly, patients are asking their physicians about the benefits of dietary and alternative approaches to manage their diseases, including thyroid disease. We seek to review the evidence behind several of the vitamins, minerals, complementary medicines, and elimination diets that patients are most commonly using for the treatment of thyroid disorders.

Summary: Several trace elements are essential to normal thyroid function, and their supplementation has been studied in various capacities. Iodine supplementation has been implemented on national scales through universal salt iodization with great success in preventing severe thyroid disease, but can conversely cause thyroid disorders when given in excess. Selenium and zinc supplementation has been found to be beneficial in specific populations with otherwise limited generalizability. Other minerals, such as vitamin B12, low-dose naltrexone, and ashwagandha root extract, have little to no evidence of any impact on thyroid disorders. Avoidance of gluten and dairy has positive impacts only in patients with concomitant sensitivities to those substances, likely by improving absorption of levothyroxine. Avoidance of cruciferous vegetables and soy has little proven benefit in patients with thyroid disorders.

Conclusion: While many patients are seeking to avoid conventional therapy and instead turn to alternative and dietary approaches to thyroid disease management, many of the most popular approaches have no proven benefit or have not been well studied. It is our responsibility to educate our patients about the evidence for or against benefit, potential harms, or dearth of knowledge behind these strategies.

Key Words: complementary medicine, lifestyle interventions, iodine, ashwagandha, naltrexone

Abbreviations: AITD, autoimmune thyroid disease; ARE, ashwagandha root extract; PA, pernicious anemia; rT3, reverse triiodothyronine; T3, triiodothyronine; T4, thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; USI, universal salt iodization.

Increasingly, patients are asking their physicians about the benefits of dietary and alternative approaches to manage their diseases, including thyroid disease. According to the most recent National Health Statistics Report on the topic, 38.3% of US adults use some form of complementary health approach and spend $12 billion out-of-pocket annually on natural product supplements alone (1). Data on many of the alternative and dietary approaches used by patients are not widely known or reported in guidelines (2), and physicians should be aware of the literature when treating patients who are taking these approaches. We seek to review the evidence behind several of the vitamins, minerals, complementary medicines, and elimination diets that patients are most commonly using for the treatment of thyroid disorders.

Vitamins and Minerals

Iodine

Iodine is a trace element vital to thyroid physiology and the synthesis of thyroxine (T4) and triiodothyronine (T3). Dietary iodine is dependent on the presence of iodine in the soil in which food is grown, which varies throughout the world (3). According to the World Health Organization, iodine deficiency is the single most important preventable cause of brain impairment (3). Severe iodine deficiency can cause endemic goiter, cretinism, and intellectual disabilities among children of iodine-deficient mothers. Daily consumption of 150 µg of iodine is recommended for the prevention of iodine deficiency in nonpregnant adults (4). Universal salt iodization (USI) is the strategy endorsed by UNICEF and the World Health Organization for safe, cost-effective, and sustainable supplementation of iodine to ensure sufficient intake by all individuals (3). It is now well recognized that USI is the most effective way to eliminate iodine deficiency, which has been virtually eradicated in the countries in which it has been successfully implemented.

Additional iodine supplementation is recommended for women who are pregnant or nursing. Maternal iodine needs surge as maternal thyroid hormone synthesis increases, fetal thyroid hormone synthesis increases, and maternal glomerular filtration rate increases (5). As a result, it is recommended that pregnant and lactating women take in 250 µg of iodine daily for the prevention of fetal iodine deficiency (3).

While there is clear evidence for the supplementation of iodine in patients with deficiency and mothers who are pregnant or nursing, supplemental iodine may be deleterious in patients with iodine sufficiency or excess. Patients with underlying thyroid disease may develop hyperthyroidism or hypothyroidism when exposed to supplemental iodine. First described centuries ago, patients with endemic goiter

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may develop hyperthyroidism after iodine supplementation, known as the Jod–Basedow phenomenon (6). A similar condition has also been described in patients with multinodular goiter (6). More recent data have studied the adverse effects of iodine supplementation on a population level after the introduction of USI policies. Two separate population-based studies spanning close to 20 years (1997-2016 and 1997-2017) were conducted in Denmark to look at the incidence of hypothyroidism (7) and thyrotoxicosis (8), respectively, after the introduction of iodine fortification in subjects with mild to moderate iodine deficiency. Whereas the first study measured a sustained increase in the incidence of hypothyroidism among young and middle-aged subjects, the second study only noted an increase in the incidence of hyperthyroidism in the initial years after introduction of fortification. This rate subsequently declined to baseline (in areas of initially mild deficiency) or below that (in areas of initially moderate deficiency) within 4 to 8 years. A separate trial (9) for determining the safe upper limit of daily iodine intake in the Chinese population saw the development of subclinical hypothyroidism in the participants who took approximately 800 µg per day of iodine as supplementation. Additionally, a prospective cohort study of communities in China with mild iodine deficiency, more than adequate iodine intake, and iodine excess (as determined by urinary iodine levels) found higher cumulative incidence of autoimmune thyroiditis in patients from the more than adequate iodine intake and iodine excess communities than in those from the mild iodine deficiency community over the 5-year follow-up period (10).

The mechanism by which hypothyroidism occurs after iodine exposure is not well described; however, some data point to induction of autoimmunity as a possible culprit. There have been a few studies to postulate the development of thyroid autoantibodies upon iodine supplementation in patients with endemic goiter from iodine-deficient areas (11) and the development of thyroid autoantibodies as well as lymphocytic infiltration in the thyroid of some of the patients with nontoxic goiter from iodine-replete areas after administration of iodized oil (12).

Currently, iodine supplementation is indicated in pregnancy and lactation, as well as in iodine-deficient individuals found in certain geographic regions. Outside of these scenarios, the evidence does not support additional supplementation of iodine in the diet, with known potential harm.

Selenium

Selenium (Se) is a trace mineral found in Brazil nuts, organ meat, and muscle meat essential to the function of the thyroid. The recommended daily allowance of Se is 55 µg for nonpregnant adults (4). Many thyroidal enzymes are selenoproteins, such as the deiodinases that metabolize T4 to T3 and reverse triiodothyronine (rT3) (13), and the glutathione peroxidases that help to manage oxidative stress in the thyrocyte (14). Se deficiency is associated with autoimmune thyroid disease and increased risk of mortality (14). As a result, some have hypothesized that supplementing Se in Se-sufficient populations may improve or reduce the risk of developing autoimmune thyroid disease. Several meta-analyses have investigated the effect of Se supplementation on autoimmune thyroiditis, demonstrating reduced thyroid peroxidase antibody titers but no changes in thyroid-stimulating hormone (TSH) or levothyroxine dosing (15-18). Other studies have shown improved mood and wellbeing after supplementation with Se (15).

The European Group on Graves' Orbitopathy published a randomized, double-blind, placebo-controlled study of 159 patients with thyroid eye disease in which those given sodium selenite 200 µg daily had statistically significantly greater improvement in Clinical Activity Score than patients given placebo, as well as improved quality of life and overall ophthalmic score—a composite evaluation of eyelid aperture, soft-tissue involvement, proptosis, and eye muscle motility (19).

The strongest evidence for Se supplementation in Hashimoto's thyroiditis comes from a study by Negro et al that demonstrated a 20% absolute risk reduction of hypothyroidism ($P < .01$) in euthyroid thyroid peroxidase (TPO) antibody–positive pregnant women who were given 200 µg of selenomethionine after the twelfth week of gestation and continued through 1 year postpartum (20). Another, smaller study in the UK was unable to replicate these results using a lower dose of 60 µg of Se per day (21). However, a 2019 study of 49 TPO-positive patients randomized to receive 83 µg of selenomethionine per day or placebo during pregnancy and 1 year postpartum did show similar reduction in TPO antibody titers at the postpartum measurement compared with placebo (22). Given these conflicting data, the American Thyroid Association does not currently recommend Se supplementation in euthyroid TPO antibody–positive women planning for pregnancy (23).

Excess Se supplementation does have some negative consequences. Toxicities include alopecia and dermatitis, and may include an increased risk of type 2 diabetes (24, 25). The recommended maximum daily intake by the US National Academy of Sciences, inclusive of food and supplementation, is 400 µg per day and supplementation is not recommended in Se-sufficient patients (14).

Zinc

Taken by many patients to "boost immunity" during cold and flu season, zinc (Zn) is also used by some for thyroid health. An essential mineral, the recommended daily allowance of Zn is 8 to 11 mg for nonpregnant adults (4). Zn has a crucial role in modulating the synthesis and functioning of thyroid hormones (26). Zn participates in the synthesis of thyrotropin-releasing hormone as well as its action on the pituitary gland, contributing to the synthesis of TSH. Zn also moderates the function of deiodinases, thus regulating the synthesis and concentration of T3 and T4. T3 nuclear receptors also contain Zn ions (27). As a result, there has been much interest in the effect of Zn supplementation on thyroid function, especially in patients with other underlying risk factors.

Several groups have investigated the role of Zn in thyroid dysfunction in patients with trisomy 21, who have relatively higher rates of subclinical hypothyroidism but lower rates of antithyroid autoantibodies than the general population. According to one comparative study, levels of TSH were found to be higher and levels of rT3 were found to be decreased in children with Down syndrome than in controls, and both were successfully restored following supplementation with zinc sulfate (28). Another study with a similar design first identified subjects with hypozincemia prior to initiating Zn supplementation and similarly observed that Zn normalized the initially higher TSH levels in these children (29). As a

result, it was recommended by the study authors to assess Zn status in patients with Down syndrome who have subclinical hypothyroidism and supplement those with hypozincemia as treatment for their thyroid disorder.

Another population of interest for Zn supplementation is patients in developing countries, who may be at higher risk for nutritional deficiencies. A study by Kandhro et al in Pakistan comparing serum Zn concentrations in patients with endemic goiter and normal controls found higher rates of hypozincemia in the goitrous patients (30). After providing Zn supplementation for 6 months, serum Zn level improvement corresponded to lower serum TSH concentrations.

A double-blind, randomized controlled trial conducted to investigate the effects of Zn and Se cosupplementation on the thyroid function of overweight or obese women with hypothyroidism observed an increase in mean free serum T4 and decrease in TSH ($P < .05$) in the Zn–Se group and a significant increase in free serum T3 in both the Zn–Se and Zn–placebo groups ($P < .05$) (31). The relationship between thyroid hormones and Zn is bidirectional since thyroid hormones are essential to the absorption of Zn as much as Zn is indispensable to the functioning of thyroid. This may have influenced results in these studies (27).

Zn supplementation appears to be beneficial in specific populations, but there remains a need for a well-designed study to analyze the role of supplementation in the general population given these results.

Vitamin B12

Vitamin B12 is also taken by many patients for thyroid health. The recommended daily allowance of vitamin B12 is 2.4 µg for nonpregnant adults (4). There is a known, frequent coexistence of vitamin B12 deficiency in patients with autoimmune thyroid disease (AITD) secondary to pernicious anemia (PA). A study by Ness-Abramof et al (32) found the prevalence of PA to be 31% when evaluated by high fasting serum gastrin levels in patients of AITD with low vitamin B12 levels. Another longitudinal study (33) spanning 2010-2017 accorded with the continual ties between PA and AITD going as far as to recommend that all patients with PA be assessed for occult thyroid disease, especially those with weight loss, diabetes mellitus, or gastric autoantibodies. Yet another study found an approximate 40% prevalence of vitamin B12 deficiency in patients of hypothyroidism (34).

The multitude of autoimmune conditions in one individual increases the likelihood of both AITD and PA. Velarde-Mayol et al concluded that when there was a third autoimmune disease, the likelihood of AITD and PA increased 4-fold (35). While replacement of vitamin B12 leads to improvement of symptoms associated with the deficiency, there is likely no impact on thyroid function as the placebo effect cannot be ruled out (34) nor can anything be said about the improvement in the symptoms of the primary thyroid pathology with supplementation of B12. A study by Ottesen et al (36) found no systematic effect on thyroid function after treatment with cyanocobalamin even in patients with decreased plasma cobalamin levels but simultaneously recommended routine screening for thyroid function and thyroid autoantibodies in patients with latent or overt PA.

So far, there exists no substantial evidence supporting the improvement in thyroid function as a result of vitamin B12 augmentation despite the frequent coexistence of autoimmune thyroid disease and pernicious anemia.

Other Minerals

While not commonly supplemented by patients for the purposes of thyroid health, there are other minerals worth briefly mentioning that may affect thyroid function.

Fluoride is a mineral essential for the prevention of dental carries. It has been added to municipal water systems in many communities for this purpose, drawing concerns from some in the public and environmental health communities for potential adverse effects, including thyroid dysfunction (37). Several observational studies have been conducted with variable outcomes. A systematic analysis by Chaitanya et al found a positive correlation between excess fluoride exposure and hypothyroidism, though few randomized controlled trials were included in the analysis (38). Another study in Chinese school children determined fluoride exposure to have an inverse relationship with levels of free and total T4 while noticing a positive trend in the levels of TSH with the exposure. This same study also observed low intelligence quotient scores in these children, which the authors suggested may be related to hypothyroidism (39). Additionally, a large observational study based in England determined a higher prevalence of hypothyroidism in fluoridated areas and found higher fluoride levels in drinking water to be useful in predicting the prevalence of hypothyroidism (40). In contrast, a Canadian study found fluoride exposure to have no correlation to thyroid dysfunction and no differences in TSH levels were noted. The same study also concluded that while high urinary fluoride levels had no association with TSH levels, individuals with moderate to severe iodine deficiency who had higher urinary fluoride levels were also more likely to have higher TSH levels and therefore at increased risk of hypothyroidism (41). Other reports include the same caveat that iodine deficiency may not be appropriately controlled for in studies suggestive of a relationship between hypothyroidism and fluoride supplementation (37). In conclusion, while there are certainly negative effects from excessive exposure to fluoride in the form of dental and skeletal fluorosis, it is yet undetermined if there is any significant independent risk of hypothyroidism from chronic exposure to community water fluoridation.

Several cross-sectional studies have noted a correlation between elevated thyroid hormone levels and copper (Cu) levels. Most notably, Jain analyzed the data from National Health and Nutrition Examination Survey (2011-2012) and found the Cu levels to be associated with elevated levels of thyroid hormones (42). A study in Korea also found increased thyroxine levels associated with increased Cu levels (43). One prospective study of pregnant women noticed that women with overt hyperthyroidism had the highest plasma Cu levels and found Cu levels to positively correlate with free T4 levels whereas an inverse relationship to TSH levels was observed (44). More prospective, longitudinal studies are needed to fully elucidate this apparent association between Cu and elevated thyroid hormone levels.

Magnesium (Mg) is thought to have anti-inflammatory effects and deficiency in Mg is proposed to be linked to autoimmune thyroid disorders. Several studies have noted a correlation between Mg intake and a reduction in markers of inflammation (45, 46). One cross-sectional study in China

found that patients with severe Mg deficiency (≤0.55 mmol/L) were 4 to 5 times more likely to have subclinical or overt hypothyroidism compared with those with a normal Mg level (47). Similarly, another study by Klatka et al observed that Mg levels are lower in Graves' disease patients than euthyroid controls and higher Mg level at time of diagnosis was associated with long remission in the Graves' disease group. Patients treated with methimazole who achieved euthyroidism had post-treatment Mg levels indistinguishable from the healthy controls (48). It appears there is a suggested association between Mg deficiency and autoimmune thyroid disease which would need to be further investigated.

Complementary Medicines

Low-dose Naltrexone

Naltrexone, an opioid receptor antagonist, has been proposed as an alternative treatment for several autoimmune disorders, including Hashimoto's thyroiditis, when prescribed at doses an order of magnitude less than those used in the management of substance use disorders. The idea for the use of low-dose naltrexone stems from work in neuroblastoma mice models which showed a reduction in tumor growth when opioid receptors were partially occupied by lower doses of naltrexone and increased rate of tumor growth when opioid receptors were fully occupied by higher doses of naltrexone when compared with controls (49). Since then, low-dose naltrexone has been studied as an immunomodulator and has reported efficacy in multiple sclerosis, inflammatory bowel disorders, fibromyalgia, and AIDS (50). Some have extrapolated this data and used low-dose naltrexone as alternative therapy to thyroid hormone replacement in the treatment of Hashimoto's thyroiditis. A group in Norway extracted data from the national prescribing database and compared doses of thyroid hormone replacement prescribed to patients before and after being prescribed low-dose naltrexone (51). They found no significant difference.

To date, there are no studies demonstrating the efficacy of low-dose naltrexone in autoimmune thyroid disorders and there is no evidence to support its use.

Ashwagandha

Ashwagandha (*Withania somnifera*) is a popular herb used in Ayurveda, a traditional medicine system originating from India, to improve energy levels and memory. It has been found to have several effects on thyroid function. A 1998 animal study found an increase in T3 and T4 levels after administering ashwagandha root extract (ARE) to adult mice (52). Similarly, there is an example case report of thyrotoxicosis in a 32-year-old woman who had been consuming ashwagandha for chronic fatigue. Upon cessation of the herb, her symptoms resolved, and her laboratory values normalized (53). A prospective, randomized, double-blind study looked at 50 patients with subclinical hypothyroidism, 25 of whom were randomized to 600 mg daily of ARE and the other 25 were given placebo. This study found statistically significant normalization of TSH ($P < .001$) as well as T3 and T4 levels within 8 weeks in the group treated with ashwagandha (54).

Abdel-Wahhab et al (55) studied effect of ashwagandha methanolic extract in propylthiouracil-induced hypothyroid rats and found that ashwagandha methanolic extract remarkably mitigated the changes induced in thyroid tests and improved histological picture of thyroid gland. A similar rat model study concurred with these findings and concluded that ARE reduced complications of thyroid dysfunction on the nervous system, including oxidative stress and neuroinflammation (56).

Of concern, a systematic review of human trials examining the modulation of the hypothalamic–pituitary–adrenal axis by plants and phytonutrients published by Lopresti et al showed that ashwagandha lowered morning cortisol levels in multiple randomized, double-blind, placebo-controlled trials. It was the single, most consistent evidence of any phytonutrient's effect on the hypothalamic–pituitary–adrenal axis seen in this systematic review (57).

It seems that ARE has an impact on increasing thyroid hormone production, seen in rat models and a few human subjects, at least in the short term. We currently lack strong evidence that would suggest that supplementing with ARE is of benefit in the long-term management of hypothyroidism and we certainly have concerns regarding its potential to cause adrenal insufficiency.

Dysbiosis and Elimination Diets

The concept of dysbiosis and its role in the pathogenesis of autoimmune pathologies, including autoimmune thyroid disease, has been garnering a lot of attention. Dysbiosis is the disruption of gut microbiome and alteration of the normal commensal bacterial population. This is thought to disrupt the intestinal epithelial barrier, increase intestinal permeability and, therefore, increase translocation of bacteria and bacterial products across the gut (58, 59). This translocation is referred to as a "leaky gut". Through small studies, an association has been suggested between "leaky gut" and autoimmune thyroid diseases, both Graves' disease and Hashimoto's thyroiditis (60-62). While most studies indicate the coexistence of autoimmune thyroid disease and changes in intestinal flora, one study of 91 patients showed that the severity of Graves' disease correlated with circulating levels of leaky gut biomarkers (60). In addition to the utilization of probiotics to restore normal gut flora, several elimination diets—in which a particular food group is avoided for health reasons—have been proposed as treatment for autoimmune thyroid disease. The minimally described effects of these interventions on thyroid function and disease management are outlined below.

Dairy-free Diet

Many patients seek elimination diets to avoid foods which may be considered to be proinflammatory. Milk products are one such category of food which has mixed evidence regarding benefits and ill-health effects (63). In Seventh Day Adventists who exclude all animal products from their diet (veganism), the prevalence of hyperthyroidism is 50% that of omnivorous Seventh Day Adventists (64). Those who consume milk products but avoid meat (lacto-ovo vegetarianism) also have reduced odds of having hyperthyroidism, which may point to meat rather than milk products as the implicated substance. Studying the same group regarding the prevalence of hypothyroidism showed no significant difference compared with omnivores (65). Consuming dairy products is not associated with increased risk of thyroid cancer (66). Though little evidence points to avoiding dairy for the promotion of thyroid health in all-comers, lactose intolerance in patients with thyroid disease does deserve increased attention.

Lactose intolerance is a common condition with varying prevalence throughout the world. Taken on average, two-thirds of the world population has hypolactasia (67), though symptomatology is widely variable based on degree of hypolactasia, frequency and amount of lactose consumed, and differences in gut flora (68). One case–control study in a group of Caucasian Central Europeans found that lactose intolerance, as measured by hydrogen breath tests, was twice as frequent in patients with Hashimoto's thyroiditis compared with normal controls (42.2% vs 21.1%, $P = .04$) (68). Patients with concomitant Hashimoto's thyroiditis and lactose intolerance need larger doses of levothyroxine in order to achieve euthyroidism, likely due to malabsorption (69). Lactose restriction effectively lowers TSH levels in patients with both conditions on levothyroxine replacement therapy (70) and liquid formulations of levothyroxine are more effective in the same setting (71).

Some patients without lactose intolerance avoid dairy in the hopes of improving the symptoms of their thyroid disorder. There are no studies showing that the elimination of dairy in patients with autoimmune thyroid disease who do not have lactose intolerance is of any clinical benefit. It may be worthwhile to pursue hydrogen breath testing in patients with Hashimoto's thyroiditis with significant gastrointestinal symptoms given the overall frequency of the condition.

Gluten-free Diet

Another elimination diet which is often implemented by patients with thyroid disease is a gluten-free diet. Again, the idea is to avoid a food considered by some to be proinflammatory. It has been shown that patients with autoimmune thyroid disease are more likely to have celiac disease. One study in Italy found the incidence of celiac disease to be 10 times higher in patients with autoimmune thyroid disease than in the general population (3.0% vs 0.33%) (72). There is little and conflicting evidence on whether a gluten-free diet improves thyroid function in patients with celiac disease (73, 74). A study of 2 patients in Italy did not show a decrease in thyroid antibody levels or change in TSH levels after 6 months of a gluten-free diet (74). A larger study of 34 patients in Poland found reduction in thyroid antibody levels in the group randomized to a gluten-free diet, but no difference in TSH levels (72).

In a group of patients taking levothyroxine who were screened for celiac disease, those who had positive tissue transglutaminase antibodies were more likely to not have thyrotropin levels at goal and required a median levothyroxine dose per kilogram 49% higher than patients without celiac disease when not adherent to a gluten-free diet (75). When these patients were adherent to a gluten-free diet, this difference in levothyroxine dose required to obtain goal thyrotropin level was eliminated.

Patients with Hashimoto's thyroiditis and concomitant celiac disease do benefit from a gluten-free diet, particularly in reducing the mean levothyroxine dose. A gluten-free diet in patients without celiac disease has not been shown as an effective intervention in changing the natural course of Hashimoto's thyroiditis or improving thyroid function.

Cruciferous Vegetables Elimination

Cruciferous or brassica vegetables are common components of our diet. These vegetables include broccoli, cauliflower, brussels sprouts, cabbage, kale, and others that are a common part of our patients' diets. Due mostly to animal model and in vitro data, it is believed that these vegetables contain goitrogenic compounds, namely goitrin, thiocyanates, and isothiocyanates, that are capable of producing hypothyroidism (76-79). In addition, there is a case report of an 88-year-old woman who presented in myxedema coma after months of consuming up to 3 lb of raw bok choy daily, without a previous history of thyroid disease (80).

In contrast, the only randomized trial to evaluate this effect in humans failed to show any effect on thyroid hormone levels or thyroid autoimmunity (81). In this study, 137 individuals received a broccoli sprout beverage for 12 weeks while 130 subjects received placebo. TSH, free T4, thyroglobulin, TPO, and antithyroglobulin levels remained the same for both groups from their baseline. Additionally, 2 other small, nonrandomized studies reported by Kim et al showed that the consumption of 15.2 oz (431 grams) of kale juice had no effect on TSH and free T4, despite increases in serum and urinary thiocyanate concentration as well as transient changes in I-123 uptake (82).

In summary, the ordinary consumption of cruciferous vegetables is unlikely to cause hypothyroidism or autoimmune thyroid disease in humans.

Soy Elimination

Soy, commonly found in Asian cuisines and alternative meat and dairy products, has also been investigated for its potential effect on thyroid function. Isoflavones (such as genistein, daidzein, and glycitein) are the polyphenolic compounds found in soy that are used in various dietary supplements. Prior to the advent of USI in the United States, there were cases reported of goiter in infants consuming soy-based formulas (83, 84). Later studies suggested the development of clinical hypothyroidism only in people consuming soy products who had inadequate iodine intake or those with subclinical hypothyroidism (85). A study of 60 patients by Sathyapalan et al evaluated the effect of soy phytoestrogen supplementation on patients with subclinical hypothyroidism and found a 3-fold increase in risk of progression to overt hypothyroidism in the high-dose supplementation group. This group was given 16 mg of phytoestrogens (54% genistein, 35% daidzein, and 12% glycitein), which is the equivalent of the daily average intake of vegan patients. Of note, these patients demonstrated iodine sufficiency with 24-hour urine iodine excretion estimation of 262 ± 18 µg/day (86). Mechanistically, it has been observed that soy isoflavones inhibit the enzyme TPO, which is essential for the synthesis of T3 and T4, leading to hypothyroidism (87, 88). However, a meta-analysis conducted by Otun et al found no correlation between soy supplementation and thyroid hormones except for only a modest increase in TSH levels, the clinical relevance for which could not be established (89). As with many other vitamins and supplements, there have been reports of reduced absorption of levothyroxine when consuming soy protein supplements in close temporal relationship to levothyroxine (90).

Several studies have shown no effect of soy products in euthyroid people with replete iodine stores (85, 91-93). A study of patients in early pregnancy also found no difference in the thyroid function of patients stratified by frequency of soy consumption, despite significantly higher levels of urinary isoflavones in the high-frequency consumption group (94). In

Table 1. Summary of effects of dietary and alternative approaches on thyroid health

Supplement or diet	Recommended dietary allowance	Effects on thyroid health
Iodine	Recommended daily intake of 150 µg of iodine for nonpregnant adults, usually obtained in diet/iodized salt in iodine sufficient populations Additional supplementation of iodine up to 220-290 µg daily is encouraged in pregnancy and lactation	Deficiency is associated with neurological underdevelopment, goiter, and hypothyroidism Excess is associated with both hyperthyroidism and hypothyroidism
Selenium	The current recommended dietary allowance in adults is 55 µg/day Studies looking at effects on thyroid disease include dosing of 80-200 µg daily of selenium	Deficiency is associated with higher prevalence of benign thyroid disease, including goiter, particularly in populations with nutritional deficiencies Supplementation may reduce circulating antibody levels in chronic autoimmune thyroiditis with no known clinical benefit Possible benefit in improving thyroid eye disease
Zinc	The recommended daily intake of zinc is 8 mg for women and 11 mg for adult men Studies looking at effects on thyroid disease include dosing of 30 mg daily of zinc	No strong evidence for or against zinc supplementation in thyroid disease
Magnesium	The recommended daily intake of magnesium is 310-320 mg for women and 400-420 mg for adult men.	Inconclusive data, some showing that magnesium deficiency may be associated with hypothyroidism, other data showing that increased magnesium levels are associated with better disease control of Graves'
Copper	The recommended daily intake of copper is 900 mg	High levels of Cu may be associated with increased thyroid hormone levels
Fluoride	The recommended daily intake of fluoride is 2-9 mg	Can be associated with hypothyroidism in the setting of coexisting iodine deficiency
Vitamin B12	The recommended daily intake of vitamin B12 for adults is 2.4 µg	No studies show any impact of B12 supplementation on thyroid disease
Low-dose naltrexone	N/A	No benefit of supplementation in thyroid disease and no difference in thyroid hormone requirement compared with controls
Ashwagandha	N/A	Possible impact on altering thyroid function by increasing thyroid hormone production in the short term No evidence that supports ashwagandha is of benefit in the long-term management of thyroid disease
Probiotics	N/A	Conclusive effect of supplementation on thyroid health has not been determined
Dairy-free diet	N/A	Beneficial for improved levothyroxine absorption in patients who have lactose intolerance
Gluten-free diet	N/A	Beneficial for improved levothyroxine absorption in patients who have celiac disease
Cruciferous vegetables	N/A	One randomized trial shows no impact of the consumption of cruciferous vegetables on thyroid health
Soy products	N/A	Increased consumption may be associated with hypothyroidism in the setting of coexisting iodine deficiency

an animal study by Doerge et al involving rats that were fed a genistein-fortified diet, it was found that although genistein caused a dose-dependent inactivation of both human and rat TPO in vitro, other thyroid parameters such as T3, T4, TSH, thyroid weight, and histopathology were normal, suggesting that a second hit, such as iodine deficiency, may be necessary for this isoflavone to have a clinically relevant effect (95, 96). In conclusion, there may be an effect of isoflavones to reduce the activity of TPO, but clinically significant hypothyroidism was not found in all but 1 study of iodine-replete patients.

Conclusion

Lifestyle and dietary interventions for health and wellbeing are an important aspect of medical care for many disease states. Frequently, patients seek alternative treatment modalities that would minimize their need for standard therapy. Patients have increasing access to books and articles which promote the effects of these interventions as an alternative solution to their thyroid conditions. It is our responsibility to educate our patients about the evidence for or against benefit, potential harms, or dearth of knowledge behind these strategies. A summary of these findings may be found in Table 1.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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