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Autoimmune thyroiditis: an update on treatment possibilities

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Abstract

Autoimmune thyroiditis (AIT) is due to an autoimmune process that destroys thyrocytes, leading to hormonal disorders. AIT is more common in women, and the aetiology is multifactorial. The destruction of thyroid cells may release free thyroid hormones into the bloodstream, causing hyperthyroid symptoms. With further destruction of thyroid cells, patients develop euthyroidism and eventually chronic hypothyroidism. The diagnosis of AIT is based on clinical symptoms, positive anti-thyroid antibodies, ultrasound, and histological features. The main goal of treatment is correcting hormonal disorders and achieving euthyroidism. Treatment of AIT involves replacing thyroid hormone deficiency with the use of synthetic hormones. Prophylactic levothyroxine (L-T4) treatment of euthyroid patients with AIT may reduce both serological and cellular markers of autoimmunisation. Attention should be paid to the starting dose of L-T4, potential drug interactions, and drug formulation. A follow-up should be planned to determine the optimal dose. The authors highlighted that a healthy lifestyle and supplementing selected vitamins and microelements appropriately are essential. In selected clinical conditions, thyroidectomy should be considered. There are also alternative therapeutic strategies, such as herbal medicine and acupuncture, but their effectiveness has yet to be conclusively confirmed in research studies. Monitoring the thyroid gland enlargement and the possibility of developing nodular goitre is integral to patient care over AIT patients.

In conclusion, treating AIT is complex, involving thyroid hormone replacement therapy, taking care of a healthy diet and lifestyle, and proper supplementation. It requires an individual approach. Regular follow-up is necessary to control the disease and minimise its effects. **(Endokrynol Pol 2024; 75 (5): 461–472)**

Keywords: *autoimmune thyroiditis; thyroid; hypothyroidism; autoimmune disease; levothyroxine; TSH; thyroidectomy; acupuncture; radioactive iodine; herbal medicine*

Introduction

Autoimmune thyroiditis (AIT) is the most common type of autoimmune thyroid disorder (AITD). AIT is a frequent cause of hypothyroidism in adults in developed countries. It is estimated to affect 0.3–1.5 cases per 1000 people [1, 2].

AIT is chronic, most often leading to permanent hypothyroidism [3]. The most popular laboratory findings demonstrate an elevated thyroid-stimulating hormone (TSH) and low levels of free thyroxine (fT4), coupled with increased titres of antithyroid autoantibodies [4]. This article aims to present an update on AIT treatment and summarise the effectiveness of alternative therapy strategies.

Aetiology of autoimmune thyroiditis

AIT is an autoimmune disease, meaning the immune system attacks and destroys the body's healthy cells. Immunological tolerance is disturbed by genetic susceptibility and environmental triggers. In effect, excessively stimulated cytokines and chemokines attack the thyroid tissue [4, 5]. The histological hallmark of AIT is lympho-plasmacytic infiltration (especially TCD 4+ cells) and follicular destruction, which lead to atrophy and fibrosis [6, 7]. Current research has indicated the important role of recently discovered cells such as Th17 (CD4+IL-17+) or T regulatory cells (CD4+CD25+[high]FoxP3+) in the initiation of autoimmune disorders [8]. An increased infiltration of proinflammatory cytokines — interleukins: 1beta (IL-1β), 2 (IL-2), 12 (IL-12); tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and cluster of differentiation 154 (CD40L) in AIT was confirmed. It leads to the activation of macrophages and thyroid cell apoptosis. Cytokines may also stimulate the production of nitric oxide (NO) and prostaglandin (PG), increasing the inflammatory response in AIT [9]. The classic

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form of AIT generally presents in the fifth decade of life, and approximately 75% of patients are euthyroid at diagnosis. The thyroid gland becomes larger, has a rubbery texture, and sometimes feels lumpy. A few variants of AIT have been identified based on clinical and histological features, such as fibrous, juvenile, and painless (or silent) thyroiditis [3, 10–12]. Another rare form of AIT with lymphoplasmacytic sclerosing changes and increased numbers of immunoglobulin G4 (IgG4)-positive plasma cells may be closely suggested to IgG4-related disease [13]. Rarely, transient clinical signs of hyperthyroidism (*hashitoxicosis*), caused by the release of excessive amounts of thyroid hormones from destroyed thyrocytes, may occur [14, 15].

Risk and protective factors

Genetic and existential factors

Several factors are worth mentioning in the genetic backdrop of AIT. First of all, polymorphisms in human leukocyte antigen (HLA), T lymphocyte-associated 4 (CTLA-4), protein tyrosine phosphatase, non-receptor type 22 (PTPN22) genes, the interleukin 2 receptor (IL2R), estrogen receptors, adhesion molecules (CD14, CD40), and the promoter region of selenoprotein S. In addition, chromosome X inactivation patterns may be necessary [4]. AIT prevalence increases in patients suffering from other autoimmune diseases, e.g. myasthenia gravis (MG), systemic lupus erythematosus (SLE), or celiac disease (CD), and also in some genetic syndromes, e.g. Down syndrome (DS) and Turner syndrome (TS) [16–19]. Rarely, AIT may be a part of autoimmune polyendocrine syndromes (APS) type 1 or 2, and also immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) syndrome [20, 21].

AIT prevalence increases with age (the case peak is between 45 and 65). In adults, the female-to-male predominance is around 4–10 times [10, 22]. In childhood and adolescence, the AIT is the most common cause of acquired hypothyroidism. The prevalence of AIT in children reaches a peak at early to mid-puberty. Female predominance has been reported, with a female-to-male ratio 3.4:1 [23].

Environmental and nutritional factors

Several different bacterial and viral infections may play a significant role. Components of several viruses, such as hepatitis C virus (HCV), human parvovirus B19 (HPV B19), or Epstein-Barr virus (EBV), were detected in thyroid tissues [24–26]. A possible mechanism that leads to autoimmune reaction may result from molecular mimicry between some peptides of viruses and thyroid cells [27]. Chiuri et al. showed that *Bartonella henselae* can trigger AIT's clinical syndromes. Infections may be responsible for AIT by a direct inflammatory process or a "molecular mimicry" that triggers the autoimmune response [28]. Still, it may also be reversible if the pathogenetic factor is eliminated early in the disease [29]. *Helicobacter pylori* (*H. pylori*) infection remains a controversial trigger of AIT. One study showed that *H. pylori* eradication reduced anti-thyroid peroxidase antibodies (TPO-Abs) and anti-thyroglobulin antibodies (Tg-Abs). Other studies suggest that *H. pylori* infection may enhance the progression of AIT. One meta-analysis proved that the incidence of *H. pylori* is higher in patients with AIT than in people without AIT [30]. Another randomised study showed *H. pylori* has nothing to do with AIT [31].

The role of smoking in AIT development has not been confirmed so far. Some research results suggest that cigarette smoking may protect against AIT by decreasing TPO-Abs titre [32]. On the other hand, smoking may increase the risk of hypothyroidism in patients with AIT [33].

Alcohol intake was proposed to decrease the risk for AIT [34]. One prospective study reported a significant protective role of alcohol (modest to high alcohol consumption of 1–20 units/week) in preventing autoimmune overt hypothyroidism [35].

Patients suffering from AITD may have a deficiency of minerals such as iodine, iron, zinc, copper, magnesium, potassium, and vitamins A, C, D, and B group vitamins [36, 37]. Low 25-hydroxy vitamin D (25[OH] D3) concentrations (below 30 ng/mL) and low selenium intake (consumption below 40 μg/day or selenium concentration in blood below 60 μg/L) are suggested to be risk factors for AIT development. However, the role of these factors in AIT needs to be confirmed [38, 39]. Also, high iodine intake (median urinary iodine concentration $\geq$ 300 μg/L), particularly in areas with appropriate iodine supply, is one of the most well-known factors that increase the incidence of AIT [40]. Too much iodine may stimulate apoptotic processes, increase the production of free radicals, and, in effect, lead to destruction and tissue atrophy [41].

Microbiota dysbiosis, which stimulates autoimmune processes, is observed in patients with AIT. Harmful microbiome composition containing *Bacteroides fragilis* significantly increased in AIT compared to control individuals without autoimmunity [42, 43].

Other potential triggers include maternal-foetal microchimerism, exposure to flame retardants and phthalates, radiation exposure, living in almost sterile conditions, or increased levels of oxidative stress [44–47]. The increased risk of AIT may also result from adverse effects (AEs) of some medications, e.g. IFN or monoclonal antibodies for cancer treatment [48–50].

Radiation exposure is associated with an increased risk of hypothyroidism. However, it is still unclear if

antibody production after presenting antigenic material from necrotic thyrocytes induces the AIT. Thyroid dysfunction is more likely to occur with high-dose irradiation (> 50 Gy) [51].

Diagnosis of autoimmune thyroiditis

The diagnosis of AIT is based on clinical symptoms like goitre, positive anti-thyroid antibodies, ultrasound, and histological features. AIT is marked by elevated titres of autoantibodies like TPO-Abs and/or Tg-Abs. Serum TPO-Abs are present in about 95% of patients, with positive Tg-Abs in 60–80%. However, seronegative AIT can be seen in 5–10% of cases [12, 52]. TPO-Abs are also present in 12–16% of euthyroid patients, and in other autoimmune diseases, e.g. type 1 diabetes mellitus, Addison's disease, rheumatoid arthritis, systemic lupus erythematosus or Sjögren's syndrome [9]. They can derive from any class of IgG, but most of them are IgG1 and IgG4 [53]. TPO-Abs can induce the complement system and cellular cytotoxicity [9]. Tg-Abs belong mainly to the IgG4 class, do not fix complement, and do not cause thyroid cell destruction. Low levels of IgA antibodies have also been described. Tg-Abs may also occur in healthy subjects [53, 54]. Both antibodies mentioned above can cross the placenta barrier to a changeable range. The effect on the neonate is unclear, but the potential negative impact on cognitive development in children has not been confirmed. TPO-Abs and Tg-Abs levels cannot be diminished and can remain pathologically increased upon therapy [55].

Anti-TSH receptor antibodies (TRAbs) are the hallmark of GBD, where TRAbs occurrence is estimated at 90–95%. In subjects with AIT, the prevalence of TRAbs is 10–20%. Therefore, TRAbs detection is a valuable tool in the differential diagnosis of patients with hyperthyroidism [56]. It must be undertaken that laboratory testing for TRAbs estimates the concentration, not the functionality, stimulation *vs.* blocking. Although the dominant kind of TRABs is stimulation antibodies, the occurrence of the blocking type observed in AIT may change the clinical symptoms and signs of the disease. TSH receptor (TSHR)-blocking autoantibodies bind to the TSHR and neither activate the cyclic adenosine monophosphate (AMP) pathway nor stimulate thyroid hormone synthesis, but act as TSHR antagonists and can cause the hypothyroidism of AIT [57].

In an ultrasound examination, features of AIT include heterogeneity, hypoechogenic pattern, and increased vascularity. Rarer hypoechoic micronodules with echogenic rims occur, but the findings are not specific [58, 59]. In turn, in transient *hashitoxicosis*, limited thyroid gland radioiodine uptake may help differentiate from Graves-Basedow disease (GBD) [15].

Elevated TSH levels in hypothyroidism and AIT presence were defined as independent risk factors for thyroid carcinoma (TC) [60, 61]. In iodine-sufficient areas, the coexistence of AIT with papillary thyroid carcinoma (PTC), in particular, is not rare [62]. Moreover, the vast majority of patients with PTC exhibit AIT, so AIT does not play a so-called "protective role". The question arises as to whether AIT has any influence on cancer formation or whether thyroid cancer is immunogenic for autoimmunity activation. Since patients in the AIT group are at risk of developing thyroid neoplasia in the future, long-term follow-up is essential, especially in areas with a relatively high intake of iodine in the diet [63]. AIT is less commonly associated with follicular thyroid carcinoma (FTC) than PTC. Among PTC, AIT may be strongly associated with the diffuse sclerosing variant [64]. With a risk of about 60 times higher than in the general population, non-Hodgkin primary thyroid lymphoma was strongly associated with AIT [3].

In diagnosing, evaluating, and managing AIT, ultrasonography (or sonography) is an essential noninvasive tool to help physicians make clinical decisions. Patients should be followed carefully, particularly those with initially enlarged thyroids and elevated TSH levels [62]. Hypoechogenicity, pseudonodules, heterogeneous parenchyma, "Giraffe pattern", and the presence of small cysts are the basis of the ultrasonographic signs of AIT. Various vascularity types, including hypervascularity, marked internal flow, and "focal thyroid inferno" may be observed on colour Doppler ultrasonography of the thyroid [4, 65]. EU-TIRADS should be considered an accurate way of stratifying the risk of malignancy of thyroid nodules in ultrasonography. When ultrasonography fails to differentiate AIT from other thyroid conditions, ultrasound-guided fine-needle aspiration cytology can provide valuable assistance [66].

Treatment of autoimmune thyroiditis

Established methods commonly used in autoimmune thyroiditis therapy

Levothyroxine

The main point of AIT treatment is the stabilisation of hormonal parameters and achieving euthyroidism. Despite overt hypothyroidism, L-T4 has approval for subclinical hypothyroidism (SCH) with TSH > 10 mIU/L due to reduced risk of progression to overt hypothyroidism, heart failure, cardiovascular events, and ischaemic heart disease-associated mortality. In the case of SCH with TSH ≤ 10 mIU/L, consider L-T4 when positive TPO-Abs, multiple symptoms of hypothyroidism, hyperlipidaemia, progressively increasing TSH levels, planning pregnancy, and diffuse/nodular goitre pres-

ence, especially for patients under 65 years of age [67]. Individualise the treatment approach in older patients with SCH [4, 67]. Moreover, L-T4 therapy in hypothyroidism that develops by the AIT can decrease oxidant status and decline serum TPO-Abs [68, 69].

Therefore, in the treatment of overt hypothyroidism, oral administration of a synthetic hormone, L-T4, at a dosage of 1.6–1.8 μg/kg of actual body weight (BW) is recommended [70]. However, the risk of cardiac ischaemia decompensation and arrhythmias such as atrial fibrillation (AF) increases in older adults [71].

Several factors may affect the absorption of thyroxine, including food intake, medical conditions, and drugs. Therefore, it is recommended to delay food intake by at least 60 minutes following traditional tablet formulation of L-T4 ingestion and separate administration from ingestion of interfering drugs by 4–6 hours [72–74].

Several studies have shown that vitamin C (ascorbic acid) in a dose of 1 g/day possibly enhances the effect on the absorption of L-T4 [75-76]. Jubiz et al. proved that vitamin C improves the circulating concentrations of thyroid hormones and TSH in patients with hypothyroidism and gastritis [75]. This approach may be helpful in the management of these patients. The suggested dose of vitamin C is between 500 mg and 1 g [75–76]. Only one randomised controlled trial was conducted. There was no significant difference in levels of TSH and Tg-Abs between vitamin C and the control group ($p > 0.05$). Still, the authors found that TPO-Abs significantly decreased after treatment with vitamin C. This emphasises the antioxidant benefit of vitamin C on antibodies specific to the thyroid [77].

New levothyroxine formulations

It is estimated that L-T4 therapy may be either suboptimal or excessive in about 32–45% of patients [78]. Some comorbidities, patient non-compliance, infections, or interactions influence the bioavailability of the L-T4 tablet form and may mandate repeated dose adjustments. Therefore, innovative L-T4 formulations, including soft gel (L-T4soft) and liquid (L-T4liq) gel, have been developed [74]. L-T4liq has faster pharmacokinetics than the tablet form and might lead to more efficient L-T4 absorption. The main indication of new formulations is AIT fluctuations and intermittent therapy due to other interfering medications. It may reduce frequent dose adjustments and office visits [74, 79]. Some patients with AIT may not tolerate the tablet form of L-T4 and may feel much better after L-T4liq introduction. Other of them were satisfied due to the possibility of L-T4 administration without regard to food with simultaneous normalisation of TSH levels [79]. Therefore, new levothyroxine formulations may be considered for AIT treatment, when tablet form is insufficient.

Figure 1 summarises L-T4 use according to the clinical condition [4, 12, 67, 80, 81].

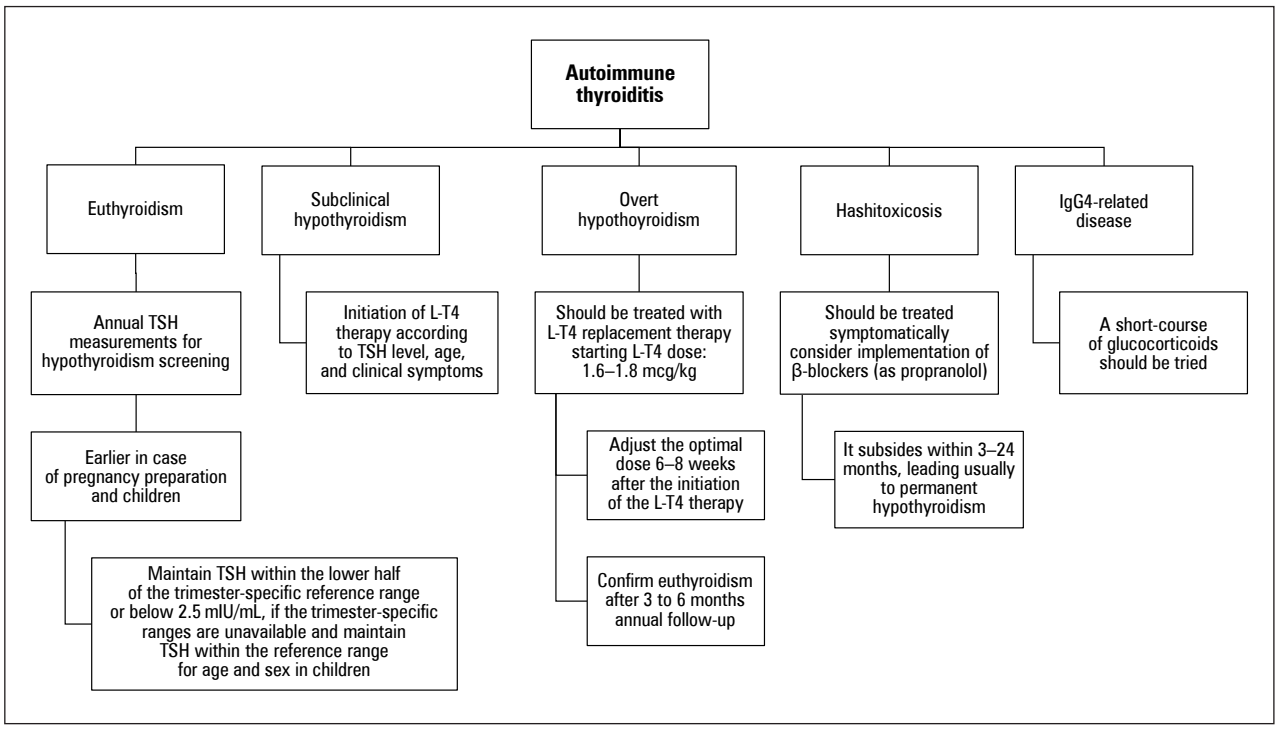

Figure 1. *Levothyroxine (L-T4) using according to the clinical condition in autoimmune thyroiditis. IgG4 — immunoglobulin G4; TSH — thyroid-stimulating hormone*

Diet and lifestyle

AIT is an autoimmune disease, and a healthy lifestyle and normalisation of body weight play a vital role. The role of an anti-inflammatory diet (including natural antioxidants like vitamins A, C, and E), proper protein intake, dietary fibre and unsaturated fatty acids, and various micronutrients and vitamins has been indicated [35, 82]. Supplementing selected vitamins and microelements appropriately is extremely important in treating AIT. Serum levels of iodine, selenium (Se), iron, and vitamins D and B12 in AIT patients are essential, and a careful supplementation in case of deficiency of these agents is recommended [83]. It is worth noting that patients without coeliac disease (CD) or other forms of gluten intolerance should not be proposed to follow a gluten-free diet [37, 84]. Also, lactose intolerance is often diagnosed in patients with AIT; therefore, a lactose tolerance test and elimination should be considered [84, 85]. Table 1 summarises the recommendations relevant to AIT therapy.

Figure 2 presents infrequent but possible alternatives in autoimmune thyroiditis treatment.

Alternative methods used in autoimmune thyroiditis therapy

Thyroidectomy

In AIT, the standard treatment approach is hormone supplementation. However, there are several subsets of patients when thyroidectomy is indicated [102]. Thyroidectomy is performed when a thyroid nodule with potential neoplastic transformation occurs, and physicians do not know whether the patient has only AIT or AIT and thyroid cancer simultaneously [103]. Shih et al. showed that cancer is common in patients who have a thyroidectomy for AIT, even when not suspected preoperatively. More than half had thyroid cancer at the final histological examination [104]. The second indication is the occurrence of symptoms such as dysphagia and dyspnoea due to severe compression of the substernal goitre on the local structures [103]. The critical point is the fact that there is no algorithm for patients' treatment suffering from AIT with persistent symptoms despite biochemical euthyroidism. Thyroidectomy may also be considered in the case

REVIEW

Table 1. *Selected vitamin and microelement supplementation in autoimmune thyroiditis (AIT) — summary*

Selected vitamin or microelement	Recommendation summary
Iodine	Excessive iodine supplementation in AIT should be discouraged. Pregnant and breast-feeding women should consume 250 μg of iodine per day, while children over 12 years of age and adults — 150 μg, as recommended by the WHO [82, 83, 86]
Iron	Iron deficiency is diagnosed in up to 60% of patients with hypothyroidism. Anaemia may increase the risk of thyroid dysfunction [87, 88]
Vitamin B12	Vitamin B12 deficiency is associated with AITD. TPO-Abs were significantly elevated in patients with low vitamin B12 [89, 90]. Therefore, physicians should detect iron and/or vitamin B12 deficiency and initiate appropriate treatment
Magnesium	The association between magnesium deficiency and AIT is still unclear. One research revealed that low serum magnesium increases the risk of HT prevalence and Tg-Abs positivity but without correlation with TPO-Abs [84, 91]
Selenium	Some research showed an increased risk of AIT caused by selenium deficiency [92]. Another study showed that selenium supplementation is associated with TSH normalization or TPO-Abs/Tg-Abs decreased [93, 94]. Wichman et al. suggested that it supports the treatment with L-T4 [93]. Larsen et al. revealed that TPO-Abs after 12 months of daily supplementation with 200 μg selenium was lower than in the placebo group, but it did not influence L-T4 dosage or free triiodothyronine–free thyroxine ratio. No differences in quality-of-life improvement in both groups have been shown [95]. However further studies are needed to confirm beneficial selenium supplementation effects, and the ETA/ATA do not recommend routine selenium supplementation in AIT
Zinc	Zinc deficiency may lead to thyroid hormone levels disorders and an increase in antibody titres, and it may manifest in hypothyroidism as intense hair loss [36, 96, 97]. Zinc insufficiency is frequently detected in patients with Down syndrome [98]. Physicians should detect a possible deficiency of this microelement and implement supplementation
Vitamin D	Patients with AIT may have a 2-fold lower level of vitamin D in the blood compared to healthy people [83]. One study implied that higher serum 25(OH)D3 levels were associated with decreased risk of developing hypothyroidism in AIT [99]. The lower level of vitamin D can be associated with a higher level of TSH [100]. Hahn et al. found that vitamin D supplementation (cholecalciferol; 2000 IU/day) for 5 years reduced autoimmune disease by 22%, while marine omega-3 fatty acids supplementation (1 g/day containing 460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid) reduced this rate by 15%. Two years after trial termination, the protective effects of 1 g/day of omega-3 fatty acids were sustained [101]. However, vitamin D supplementation should be carried out by WHO recommendations

WHO — World Health Organization; AITD — autoimmune thyroid disorder; TPO-Ab — anti-thyroid peroxidase antibody; AIT — autoimmune thyroiditis; Tg-Abs — anti-thyroglobulin antibodies; TSH — thyroid-stimulating hormone; L-T4 — levothyroxine; ETA — European Thyroid Association; ATA — American Thyroid Association

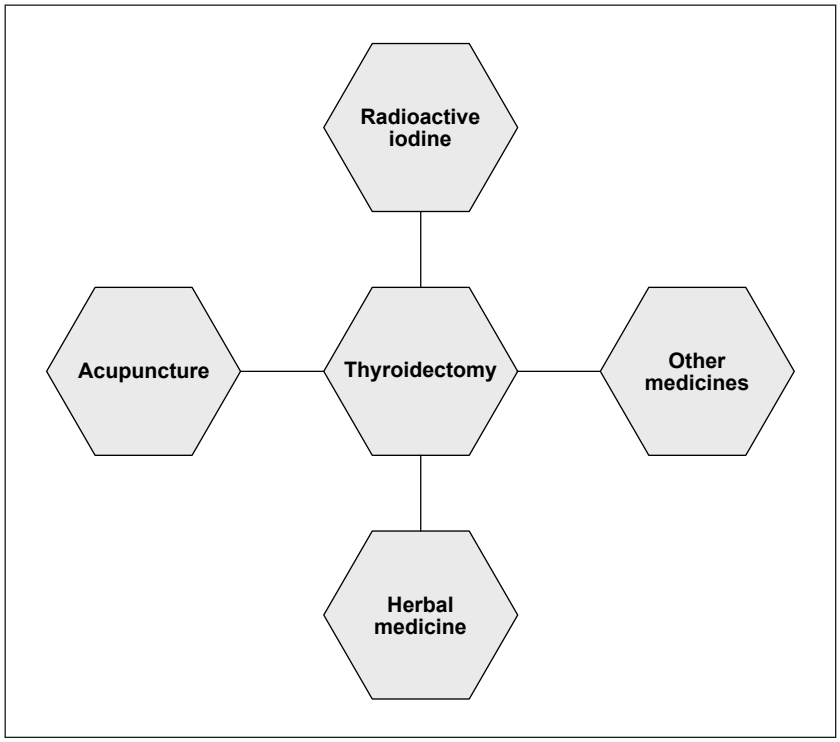

Figure 2. *Possible alternatives in autoimmune thyroiditis treatment*

of benign thyroid nodules and/or goitre or upon the patient's request for cosmetic reasons [103, 104]. Last clinical data have shown that thyroidectomy may be a helpful option in patients with highly raised TPO-Abs titre and/or with persistent symptoms such as neck pain in painful AIT, hoarseness, and hormonal fluctuations, which lead to quality of life decreased [105–107]. Interestingly, one study found that greater preoperative TPO-Abs titer correlated significantly with lower postoperative energy levels and a lower sense of emotional prosperity [108].

However, prospective studies are required because it is impossible to ignore the possible transient and permanent complications associated with thyroidectomy. Among them, the most common are postoperative hypocalcaemia, transient and permanent, hoarseness due to recurrent laryngeal nerve (RLN) injury, and postoperative neck haematoma [104, 109]. McMannus et al. presented an association between significantly higher rates of postoperative transient hypothyroidism in patients undergoing thyroidectomy because of AIT compared to patients without AIT [109]. Surgery may not be suitable, especially for elderly patients, because of comorbidities such as heart or liver disease. Therefore, an individual approach to the patient should be applied, and possible thyroidectomy should be considered after analysing the indications for this procedure and the risk of permanent surgical complications.

Radioactive iodine

Radioactive iodine (RAI) is the primary treatment for GD with a toxic nodule or toxic multinodular goitre and is also an integral part of the differentiated thyroid cancer (DTC) treatment [110, 111]. RAI is also effective against nontoxic multinodular goitre [112]. Tajiri et al. have proven the effectiveness of RAI in AIT with a large goitre. Thirteen mCi of ^{131}I were administered two to six times at an interval of 1–6 months [113]. The average weight of the thyroid gland significantly decreased after the last RAI and the percent reduction from baseline was 58.7 ± 14.2%. Antibody titer after RAI did not statistically decrease significantly. However, in this retrospective cohort study, a small group of patients (n = 13) may suggest limited data [113].

Interestingly, AIT may disturb the treatment efficacy of RAIT in low- to intermediate-risk DTC, reducing the successful rate of excellent response [114]. Furthermore, RAI therapy is not a perfect treatment – it is associated with acute and long-term adverse reactions. Acute risks include nausea and vomiting, ageusia (loss of taste), dry eye, bone marrow suppression, and radiation thyroiditis/pneumonitis [115]. Longer-term complications include, among others, sialadenitis, mouth pain, dental caries, gonadal damage, pulmonary fibrosis, and secondary cancers, including bone, salivary gland, and leukaemia [115, 116].

There are no universal recommendations on the use of this method in the treatment of AIT. The indications

for RAI therapy in AIT should be limited to elderly patients with large goitre whose thyroiditis is refractory to TSH suppression therapy and who decline surgical treatment. Future studies should confirm the efficacy of thus treatment.

Acupuncture

Acupuncture is an integral part of traditional Chinese medicine (TCM). It is a nonpharmacological treatment option and comprises the insertion of sterile needles into one or more acupoints (specific stimulation points) [117]. The combined neuro-immune function is a general mechanism of acupuncture. Acupuncture alleviates some clinical symptoms such as fatigue, neck pressure, and mood swings and scarcely has AEs. Some studies showed the numerous anti-inflammation and anti-oxidation effects [118, 119]. Decrease in plasma of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 after electroacupuncture (EA) management have been detected [120]. EA downregulates the infiltration of CD4+ T cells and the expressions of transcription factors of Th1 and Th17 cells in the experimental autoimmune encephalomyelitis (EAE) model [121]. This suggests enhancing the immune system and the potential therapeutic value of acupuncture for AIT.

More high-quality studies and evidence on acupuncture for AIT need to be conducted. Some researchers are underway to assess the feasibility and effectiveness of acupuncture in treating AIT [118, 122]. Li et al. [122] will evaluate acupuncture therapy in a child-bearing period female with AIT. They suggest that acupuncture can stop or delay AIT advancement and improve fertility in child-bearing period females.

It is postulated that acupuncture may reduce the titer of antibodies and thus enable the reduction of L-T4 dose in the treatment of symptoms of hypothyroidism. In addition, it may improve patients' quality of life [118, 123]. Ka et al. showed a significant decrease in TSH and TPO-Abs after 20 thirty-minute acupuncture sessions in 20 patients with AITD [123]. They detected no changes in free thyroid hormone (fT4) or Tg-Abs. Acupuncture sessions may significantly increase serum triiodothyronine (T3) and thyroxine (T4) levels in patients suffering from AIT coupled with hypothyroidism [124]. As mentioned earlier, acupuncture carries negligible side effects and may be involved with bleeding, haematoma, fainting, and subjective experience of pain [118]. Still, the amount and content of the research on treating AIT with acupuncture therapies is limited.

Treatment with herbal medication

Despite considerable enthusiasm on the Internet about the role of herbs in treating AIT, there needs to be more evidence documenting its effectiveness. Table 2 concludes the species of herbs with a confirmed or presumed effect in treating hypothyroidism. It is postulated that other plants may positively affect the course of AIT. Some of them, due to their anti-inflammatory and antioxidant action, are motherwort (*Leonurus cardiaca*) and turmeric (*Curcuma longa*) [125, 126]. On the other hand, another species - Lemon balm (*Melissa officinalis*) - may be associated with improvements in mood and/or cognitive performance, which may

Table 2. *Herbal treatment for hypothyroidism — summary*

Herbal drug	Extract	Action on body	Dosage	References
Ashwagandha *[Withania somnifera (L.) Dunal]*	Root extract	Significant increase in serum T4 and T3 levels Serum TSH levels decreased significantly	300 mg × 2/day	[128]
Bladder wrack *[Fucus vesiculosus]*	Seaweed	An excellent source of iodine and selenium Anti-inflammatory effect	4–8 drops × 3/day	[129, 130]
Gum guggul *[Commiphora mukul]*	Dubbed guggulipid	Helps to increase the uptake of iodine by the thyroid gland Increases the conversion of T4 to T3 Helps to elevate the activity of the thyroid peroxidase enzyme Hypolipidemic effect	25 mg × 3/day	[129, 130]
Blue flag root *[Iris versicolor L.]*	Liquid of fresh rhizome	Promotes T3 production by thyroid Anti-inflammatory effect This has a special effect on the enlargement of the thyroid and goitre	1–2 ml × 3/day	[129, 130]
Black cumin *[Nigella sativa L.]*	Milled black seeds (powder)	Improves thyroid status, reducing VEGF and body weight in patients with AIT	2 g, × 1/day	[131]

T3 — triiodothyronine; T4 — thyroxine; TSH — thyroid-stimulating hormone; VEGF — vascular endothelial growth factor; AIT — autoimmune thyroiditis

support patients with AIT treatment [127]. The severity of AEs during treatment with herbal medicine was mild and temporary. They included headache, fever, cough, gastrointestinal disorders, and allergic reactions [125–131]. Research describing AIT treatment with herbal medication has a low quality of evidence. Only two studies were randomised [128, 131]. Further study is needed to determine the benefits and safety of herbal remedies for patients with AIT

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Painful AIT is a rare diagnosis, and optimal treatment remains still unclear. Most cases are empirically treated as subacute thyroiditis (SAT) with corticosteroids, L-T4, or nonsteroidal anti-inflammatory drugs (NSAIDs). As first-line treatment for patients with painful AIT, low-dose oral prednisone, less than 25 mg/day, for up to 3 months should be considered. Other treatment options include intrathyroidal steroid injection of 40 mg triamcinolone acetate or total thyroidectomy. The surgery treatment yields 100% sustained pain resolution [132, 133].

Metformin

Metformin, the most widely prescribed oral hypoglycaemic drug, has been considered a worldwide milestone in the treatment of type 2 diabetes for the last few years. Metformin improves peripheral insulin sensitivity [134]. In addition, metformin has immunomodulatory properties. One study showed that metformin had a therapeutic effect on mice with AIT, primarily by reducing Tg-Abs and lymphocyte infiltration in thyroid cells. Metformin restrained the number and function of Th17 cells and M1 macrophage polarisation in AIT mice [135]. Jia et al. conducted a meta-analysis. They found that metformin significantly reduced the level of TPO-Abs, which was more pronounced in the AIT group than in the subclinical hypothyroidism (SH) group. In addition, patients with AIT also showed a significant decrease in Tg-Abs [136]. Metformin therapy can reduce TSH levels in hypothyroid individuals. By influencing the IRS1 phosphorylation pattern, metformin may sensitise the TSH receptor (TSHR) to TSH, thus explaining the findings of clinical studies [137]. Further studies are needed to assess the metformin's effectiveness in treating AIT.

Myoinositol plus selenium

Myoinositol (Myo) is an isoform of inositol, a cyclic polyol with 6 hydroxyl groups. Myo regulates iodine organification and thyroid hormone biosynthesis by forming hydrogen peroxide (H2O2) in thyrocytes [138]. Research suggests that Myo has a positive effect on AIT therapy. One study included women with SH treated for six months with a daily dose of 600 mg myo-Ins plus 83 mcg Se. After six months of treatment, the titer of TPO-Abs and Tg-Abs significantly decreased in more than 60% of patients [139]. Myo plus Se therapy, in the same doses as above, may also considerably reduce TSH. However, other studies showed no significant variation in the TSH after Myo and Se treatment [138].

Microbiome and its derivatives

Patients with AIT suffer from dysbiosis. Beneficial bacteria (such as *Lactobacillus* and *Bifidobacterium*) in the intestines of patients with AIT decrease, and harmful microbiota (such as *Bacteroides fragilis*) increase significantly [140]. It should be remembered that *Lactobacillus* species may be higher in patients without thyroid hormone replacement compared with those who use oral L-T4 [141]. On the other hand, some microbiota, such as *Lactobacillus*, *Bifidobacterium*, and *Helicobacter pylori*, can induce thyroid autoimmunity through molecular mimicry. The restoration of intestinal homeostasis should be individualised. Physicians should select different antibiotics according to the changes in the microbial composition of AIT patients and combine probiotics and other biological agents to eliminate pathogenic bacteria while restoring normal flora, which maintains an ingenious balance [140, 141].

Mesenchymal stem cell and thyroid gland transplantation

Mesenchymal stem cells (MSCs) are a type of multipotent stem cell that exists in a wide range of tissues. MSCs are believed to have immunomodulatory or regenerative effects. One study presents MSCs reduced TPO-Abs and Tg-Abs levels in a rat AIT model, decreasing associated thyroid tissue damage [142]. The thyroid transplantation (TT) literature is heterogeneous and generally controversial. More actual studies on TT and AIT need to be conducted.

AIT is usually an irreversible process. The potential reversibility of AIT was described when underlying environmental factors such as infections or drugs were involved [27, 47, 48].

Summary

AIT is a common autoimmune disease in the world. Over the years, various methods of AIT therapy have been postulated, both drug and eastern herbal medicine. We know that AIT's first-line treatment is weight optimisation, proper diet, and substitution treatment of hypothyroidism with L-T4 preparations. Innovative L-T4 preparations, such as L-T4soft and L-T4liq, gain an advantage. Surgery and radioiodine treatment remain reserved in specific clinical situations. Treatment of

AIT may require comprehensive cooperation between a physician and a clinical dietician. More research is needed to determine the safety and effectiveness of acupuncture and herbal medicine in AIT therapy.

Author contributions

Conceptualization: K.D.; methodology: K.D., M.O.M., M.N.; software: K.D., M.O.M., M.N.; validation: K.D., M.O.M., M.N.; formal analysis: K.D., M.O.M., M.N.; investigation: K.D., M.O.M., M.N.; resources: M.N.; data curation: K.D., M.O.M., M.N.; writing — original draft preparation: K.D., M.O.M.; writing — review and editing: K.D., M.O.M., M.N.; visualization: K.D.; supervision: K.D.; project administration: K.D.; funding acquisition: M.N. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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