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Causes of difficulties with adequate levothyroxine substitution — an immunoendocrine perspective

Magdalena Łukawska-Tatarczuk[1], *Edward Franek*[1, 2]

[1]*Department of Internal Diseases, Endocrinology, and Diabetology, National Medical Institute of the Ministry of the Interior and Administration, Warsaw, Poland*
[2]*Mossakowski Medical Research Institute PAS, Warsaw, Poland*

Abstract

Hypothyroidism is one of the most common endocrinopathies worldwide, the treatment of which is based on replacement therapy with levothyroxine. However, this seemingly simple treatment method is fraught with many difficulties and frequent dissatisfaction among patients. In fact, differences in response to levothyroxine probably depend on a complex interaction between individual, environmental, genetic, and epigenetic factors that are still not sufficiently understood. Immunological disturbances, underlying Hashimoto's disease, the most common cause of hypothyroidism, probably play a significant role in these relationships. Indeed, a growing number of studies indicate that autoimmunity through activation of low-grade inflammation can lead to impaired absorption, transport, metabolism, and action of thyroid hormones. This review provides an up-to-date overview of the causes responsible for both the difficulty in achieving target thyrotropin levels and persistence of nonspecific symptoms despite adequate hormone replacement from an immunoendocrine perspective. Understanding these mechanisms points to a new direction in the approach to hypothyroidism, indicating the need for new personalized treatment strategies. **(Endokrynol Pol 2024; 75 (4): 366–384)**

Key words: *hypothyroidism; Hashimoto's disease; levothyroxine; autoimmunity; persistent symptoms*

Introduction

Hypothyroidism is the most common endocrinopathy encountered in daily clinical practice, usually with irreversible and chronic nature, requiring lifelong replacement therapy. Its risk increases with age and female gender, and it is observed in 4 to 14% of the population, depending on the geographical area, mostly in the subclinical stage [1, 2]. In iodine-sufficient regions, the most common cause of primary thyroid dysfunction is Hashimoto's thyroiditis (HT) [2]. It is characterized by an autoimmune background, which is expressed by the presence of antithyroid antibodies and a typical ultrasound picture, which can coexist in the initial stage with euthyroidism, but often leads to hypothyroidism. Other causes of hypothyroidism include iodine deficiency, thyroidectomy, radioiodine therapy, medication, congenital, thyroid hormone resistance, infiltrative (Riedel's thyroiditis, amyloid, hemochromatosis, scleroderma), or secondary (hypothalamic or pituitary disease) [3]. For more than 40 years, synthetic thyroxine sodium has been used instead of animal thyroid extracts as the most stable, safe, and effective hormone replacement therapy [4]. All guidelines from major endocrine societies recommend levothyroxine (LT4) monotherapy as the therapy of choice for hypothyroidism [5]. However, its use poses clinical difficulties and is still a topic of lively debate.

According to data from the recent international survey: Treatment of Hypothyroidism in Europe by Specialists (THESIS), between 14.2% and 76.4% of respondents consider combination therapy with LT4 and liothyronine (LT3) in patients with persistent symptoms of hypothyroidism despite biochemical euthyroidism on LT4 treatment [6–11]. Importantly, LT3 should not be used during pregnancy. Moreover, there is no evidence that combination therapy is more beneficial than LT4, so it is not recommended [12]. Importantly, the most common persistent symptoms of hypothyroidism are nonspecific and can be caused by both individual and external factors [6, 13]. Therefore, a key question is whether the failures of LT4 monotherapy are because it is not an appropriate treatment for all patients or if it is due to errors made during its use. Solving this is essential because the data on patient dissatisfaction with LT4 monotherapy is alarming. In the latest survey conducted by the British Thyroid Foundation, as many as 77.6% of people taking LT4 assessed their quality of life as low and were dissatisfied with the therapy [14]. In turn, a meta-analysis of randomized clinical trials

Magdalena Łukawska-Tatarczuk, Department of Internal Diseases, Endocrinology, and Diabetology, National Medical Institute of the Ministry of the Interior and Administration, Warsaw, Poland, tel. +48 668 902 843; e-mail: lukawska.badanie@gmail.com

conducted by Feller et al. involving 2192 adult patients with subclinical hypothyroidism found that appropriate LT4 therapy was not associated with a benefit in terms of overall quality of life or reduction in thyroid symptoms [15]. Such results raise doubts about the validity of implementing hormone replacement in subclinical stages and prompt a revision of therapeutic goals.

Currently the LT4 dose is most often determined by thyroid-stymulating hormone (TSH) levels and depends on a number of factors, such as age, gender, cause of hypothyroidism, clinical picture, and comorbidities [16]. Individualization of LT4 treatment is important in specific groups of patients, which include pregnancy, pediatric populations, patients with differentiated thyroid cancer, elderly patients with cardiovascular disease or osteoporosis, and patients with severe medical conditions [4]. However, a growing body of data suggests that a better indicator of thyroid hormonal balance than TSH concentration is the assessment of free thyroid hormones: free triiodothyronine (FT3) and free thyroxine (FT4). A recent systematic review by Fitzgerald et al. found that FT4 is more strongly associated with clinical parameters than TSH levels [17]. Similarly, Cui et al. found that lower FT3 levels were associated with worsened quality of life in HT patients treated with LT4, regardless of TSH levels [18]. Moreover, the FT4/FT3 ratio was recently shown to be associated with coronary microvessel dysfunction in euthyroid patients, which may confirm its importance for organ damage [19]. Therefore, it seems that evaluation of free thyroid hormones in addition to TSH alone may become equally important in setting therapeutic targets for hypothyroidism, which requires further research.

Conversely, it is increasingly pointed out that the resolution of signs and symptoms associated with hypothyroidism is more important than biochemical tests in assessing the effectiveness of treatment [4]. An example is the assessment of the thyroid-related quality of life patient-reported outcome measure (ThyPRO) before and after the implementation of LT4 [20]. Importantly, differences in the clinical manifestation of hypothyroidism probably depend on the different local expression of proteins responsible for the transport of thyroid hormones into the cell, their metabolism, and action through receptors mediating genomic and non-genomic effects [21]. They depend on interactions between genetic, environmental, and epigenetic factors, the understanding of which may change the approach to hypothyroidism treatment toward personalization.

This review examines factors contributing to the difficulty in managing LT4, including both the problems in achieving normal thyroid biochemistry and the presence of persistent symptoms despite euthyroidism after LT4 replacement, particularly in HT. Our goal was to gain insight into their causes and develop suggestions for further management of hypothyroidism based on the latest reports. We hypothesize that a complex interaction between genetic susceptibility and environmental factors and epigenetic modifications may affect the absorption, transport, metabolism, and function of thyroid hormones through dysfunctions of the immune system (Fig. 1). Considering the increasing incidence of hypothyroidism and its impact on the quality of life, their analysis is necessary to develop optimal therapy that helps alleviate symptoms but also avoids overtreatment.

The importance of autoimmunity in the pathogenesis of signs and symptoms of HT

In chronic autoimmune thyroiditis, abnormalities in both cellular and humoral immunity are observed. Intensive research in recent years has shown that not only the predominance of Th1/Th2 lymphocytes, but also new subgroups of T cells, such as follicular helper T (Tfh) cells, T helper 17 (Th17), T helper 22 (Th22), and related cytokines, are involved in the pathogenesis of autoimmune thyroiditis [22, 23]. Moreover, excess pro-inflammatory cytokines originating from lymphocytic infiltration within thyroid tissue are detected in serum, which may have implications for the function of other systems and well-being [24–26]. Crucially, there is growing evidence that immune cells are involved in a bidirectional interaction with the balance of the hypothalamic-pituitary-thyroid axis [21]. On the one hand, various transporters for thyroid hormones, enzymes responsible for their conversion, and their receptors have been shown to be expressed in immune cells [27]. On the other hand, immune cells probably play a role in regulating thyroid hormone activity, independently of the pituitary gland [28]. Thus, immune dysfunction appears to be important for the effectiveness of hypothyroidism treatment.

The most characteristic sign of loss of tolerance to self-antigens in HT is the presence of autoantibodies against thyroglobulin (aTG, anti-thyroglobulin antibodies) and/or thyroid peroxidase (aTPO, thyroid peroxidase antibodies) [29]. In recent years, large systematic reviews of studies and meta-analyses have been conducted to assess their association with the persistence of non-specific symptoms despite euthyroidism. They suggest that the presence of anxiety and depression [30], as well as a general reduction in quality of life [31], are related to autoimmunity, regardless of thyroid hormone levels. Previous reports on a large cohort of euthyroid

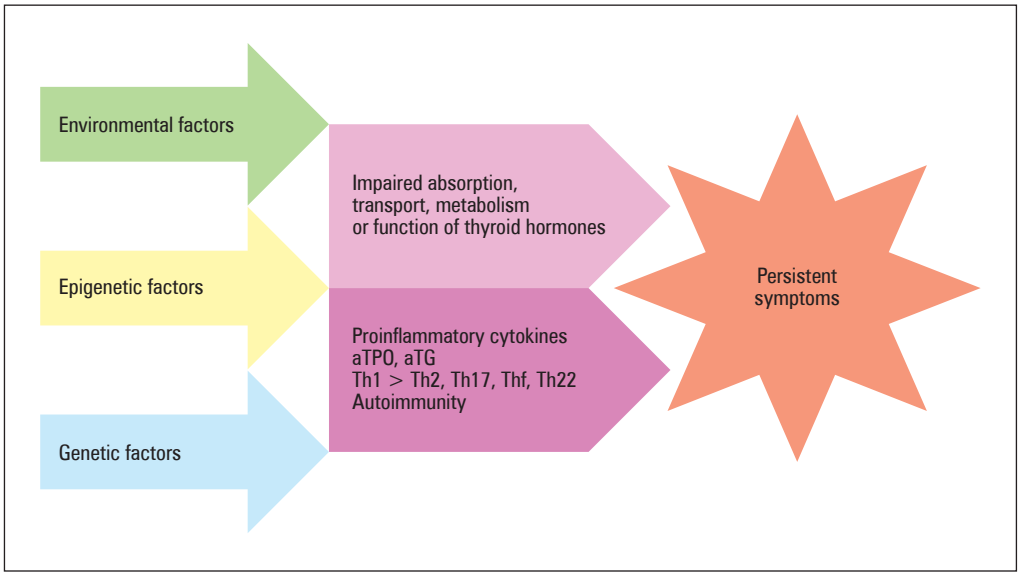

Figure 1. *Factors and mechanisms hypothesized to be responsible for persistent symptoms in patients with hypothyroidism. aTPO — thyroid paroxidase antibody; aTG — antithyroglobulin antibody; Th — T-helper*

adults also suggest an association of elevated thyroid antibody titers with hypertension [32] and even increased risk of mortality [33]. In fact, elevated aTPO titers have been correlated with atherosclerosis [34], myocardial dysfunction [35], and cardiovascular neuropathy [36]. However, the findings about the role of anti-thyroid antibodies are not consistent. For example, it was observed that community-dwelling older women seropositive for aTG and aTPO were less frail than seronegative women, regardless of thyroid function status [37]. Therefore, further studies are needed to find both the titer and duration of exposure to antithyroid antibodies and other markers of immune activity that may have a pathogenic effect.

Interestingly, Leyhle et al. showed that attention deficits in euthyroid patients with HT were associated with decreased gray matter density in the left inferior frontal gyrus, probably due to as yet unknown antibodies affecting the nervous system [38]. So far, isolated cases of Hashimoto's encephalopathy have been described, covering a wide spectrum of neurological symptoms (convulsions, psychiatric symptoms, focal neurological deficits, cerebellar ataxia) [39, 40]. It was observed in patients with chronic lymphocytic thyroiditis after exclusion of other possible causes of encephalopathy and resolved with high doses of corticosteroids [39]. However, the exact pathogenesis of neurological symptoms in HT patients is still unknown.

The above reports indicate a close relationship between HT-related immune dysfunction and the presence of signs and symptoms in general well-being, and the cardiovascular and nervous systems regardless of thyroid hormone levels. It is suspected that they may result from systemic inflammation and oxidative stress mediated by the excessive autoimmunity observed in HT patients [41]. Accordingly, in experimental studies immunomodulatory agents like transforming growth factor beta (TGF-β) [42], histone deacetylase-specific inhibitor 6, which inhibit Th17 [43], and the oxidative stress-reducing drug edaravone [44] are being explored as possible therapeutic options to reduce autoimmunity in thyroid disease. Although further research is needed, there are many indications that immune dysfunction may play a significant role both in the difficulty of achieving biochemical euthyroidism and the persistence of symptoms despite adequate replacement doses of LT4.

Factors contributing to difficulty in achieving TSH target levels

Difficulties with LT4 treatment include situations in which problems are observed in achieving normal thyroid biochemistry, when supra-physiological doses of the hormone are required (at a dose greater than 1.6–1.8 μg/kg per day), or thyroid hormone requirements suddenly increase [45].

Poor compliance with therapy

According to the CONTROL Surveillance Project study involving 925 hypothyroid patients, more than 20% of patients reported taking LT4 at breakfast or less than the recommended 30 minutes before eating. In addition, more than 50% of respondents admitted to using dietary supplements (mainly calcium and iron) or eating foods rich in fiber, iodine, or soy, which can

cause malabsorption of LT4 [45]. For those who experience problems following the recommendations related to taking LT4 in the morning, it has been shown that taking the hormone before bedtime can improve hormonal balance [46]. An alternative treatment option may also be the use of LT4 in the form of a soft gel or liquid, which may allow for a shorter interval between hormone administration and food intake, and may even improve quality of life [47, 48].

Absorption defects

Both a disturbance in pH in the stomach, where LT4 dissolves, or in the small intestine, where it is absorbed, may be associated with a decrease in the absorption of the hormone [49]. Among the most commonly reported conditions that could affect hormone absorption in hypothyroid patients on LT4, gastroesophageal reflux disease (33.8% of patients), irritable bowel syndrome (9.7%), and lactose intolerance (7.8%) were reported [45]. Others include conditions following gastric bypass or intestinal resection, *Helicobacter pylori* infection, inflammatory bowel disease, or gastroparesis [45]. The increased risk of autoimmune disorders in HT patients such as celiac disease or autoimmune atrophic gastritis is also associated with impaired absorption of LT4, as well as with micronutrient deficiencies, which may disrupt thyroid hormone function [45]. According to experts, in cases of malabsorption the liquid formulation of LT4 should be preferred because it is more effective than the tablet formulation [50]. LT4 absorption may also be improved by the addition of vitamin C [51].

Drugs that increase the need for thyroid hormones

There are many medications that can reduce the effectiveness of LT4. Table 1 shows the most common medications and mechanisms leading to increased demand for thyroid hormones. These include impaired absorption, increased concentrations of thyroid hormone binding proteins resulting in decreased concentrations of free thyroid hormones, increased microsomal enzyme activity leading to increased thyroxine catabolism, inhibition of thyroid hormone synthesis or release and increased autoimmune processes [52–54].

Noteworthy, the increasing use of immune checkpoint inhibitors — cytotoxic T cell antigen 4 antibodies (anti-CTLA-4), programmed death receptor 1 antibodies (anti-PD1) — can result in both hyperthyroidism and hypothyroidism. Their inclusion in patients with autoimmune thyroiditis may contribute to a change in LT4 dosage, conversion from HT to Graves-Basedow disease, or independently induce hypopituitarism [55]. Therefore, in these patients, vigilance and comprehensive evaluation are particularly important.

Misdiagnosis

If the clinical presentation is not consistent with the results of hormonal tests, the reason may also be a misdiagnosis before the implementation of LT4 or the appearance of a second condition independent of the first diagnosed hypothyroidism. In central hypothyroidism, TSH levels are reduced or normal, with low levels of FT4. The cause may be pituitary or hypothalamic dysfunction due to pituitary adenoma, head trauma, Sheehan's syndrome, surgery, radiation therapy, and genetic and infiltrative diseases [16]. Importantly, dysfunction of the hypothalamic-pituitary-thyroid axis has been described, resulting from direct pituitary or hypothalamic damage caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [56]. Therefore, the occurrence of this infection in a person with coexisting primary hypothyroidism may divert earlier LT4 requirements. In addition, it has been suggested that 2019 coronavirus disease (COVID-19) may cause direct infection of the thyroid gland and a storm of cytokines, which may exacerbate autoimmune disorders [57]. However, data on thyroid dysfunction after COVID-19 are still limited [57, 58]. Interestingly, a case of conversion from HT to Graves-Basedow's disease after COVID-19 vaccination in patients with type 1 diabetes has been described [59]. Such reports show the need for special alertness and monitoring of patients for progression of pre-existing thyroid disease or new thyroid disease in patients both after SARS-COV2 infection and after vaccination for COVID-19.

Another reason for inconsistent test results may be thyroid hormone resistance syndrome, which occurs in about 1:40,000 people and, as reports suggest, is more common in patients with autoimmune thyroiditis [60]. Elevated levels of free thyroid hormones with normal or elevated TSH levels and goiter may suggest a mutation within the gene encoding the thyroid hormone receptor beta (TRβ). In turn, with thyroid hormone receptor alfa (TRα) gene mutations, normal TSH levels, reduced FT4 levels, and increased FT3 levels are observed. The clinical picture may coexist with features of both hypothyroidism and hyperthyroidism, reflecting the different expression of individual thyroid receptor isoforms in the organs and the variability in type of genetic defect. Patients may require no treatment or the use of higher than physiological doses of LT4, LT3, or a thyroid hormone analogue, 3,3,5-triiodothyroacetic acid (Triac) [61–63]. Therefore, if the diagnosis is uncertain, pedigree analysis and genetic diagnosis may be indicated.

Laboratory interferences

If TSH levels are inadequate in relation to the clinical presentation, it is also worth considering the presence of factors that can interfere with immunoas-

Table 1. *Mechanisms and drugs responsible for increased demand for thyroid hormones [4, 52–54]*

Mechanisms responsible for the reduced effectiveness of LT4	Mechanism specific to drug group	Examples of drugs
Decrease in LT4 absorption in the gastrointestinal tract	Drugs that increase pH in the digestive tract	Proton pump inhibitors, histamine receptor blockers, antacids
	Drugs that form insoluble chelates with LT4	Cholestyramine, colestipol, sucralfate, aluminum, ferrous, calcium or magnesium salts, simethicone, orlistat
	Drugs that modify intestinal motility	Laxatives
Alteration in transport of thyroid hormones	Increase production of thyroid hormone-binding proteins, which is associated with a decrease in FT4 and an increase in TSH hormone levels	Oral contraception or oral estrogen replacement therapy, tamoxifen or other selective estrogen receptor modulators, clofibrate, methadone, mitotane, fluorouracil
Alteration in metabolism or excretion of thyroid hormones	Increase the activity of liver microsomal enzymes that is associated with increased catabolism of thyroxine	Carbamazepine, phenobarbital, phenytoin, valproate, rifampicin, antiretroviral drugs, sertraline
Inhibition of the synthesis and/ or release of thyroid hormones	Decrease in iodide transport, iodide oxidation and organification and thyroid vascularization	Iodine and iodine-containing drugs (amiodarone, contrast agents, radioiodine-based cancer therapies etc.)
	Increase intrathyroidal iodine, inhibits iodotyrosine coupling and blocks the release of thyroid hormones	Lithium Aminoglutethimide Sulfonamides Tolbutamide
	Blocking peroxidase activity in the coupling reaction	Tetracyclines
Immune dysfunction	Thyroid autoimmunity, disruption of thyroid vascularization, inhibition of iodine organification, inhibition of peroxidase, blocking iodine uptake	Tyrosine kinase inhibitors
	Stimulation of autoimmunity	Interleukin 2 Alemtuzumab Thalidomide analogues Interferon alpha
	Hypophysitis with central hypothyroidism and/or thyroiditis	Anti-CTLA-4 (ipilimumab) Anti-PD1 (pembrolizumab, nivolumab)

LT4 — levothyroxine; FT4 — free thyroxine; TSH — thyroid-stimulating hormone; CTLA-4 — cytotoxic T cell antigen 4; PD1 — programmed death receptor 1

says. The cause of falsely elevated TSH results can be the presence of macro TSH, heterophilic antibodies, including human animal antibodies, rheumatoid factor and heterophilic antibodies of unknown antigen exposure, and antibodies to ruthenium [64, 65]. The incidence of laboratory abnormalities associated with them is estimated to be around 0.4 to 0.5% [66]. Importantly, they can lead to both erroneously inflated and underestimated TSH levels. People with rheumatoid arthritis, undergoing immunotherapy, or exposed to animals for long periods of time are particularly susceptible to abnormalities in laboratory evaluation [67]. Therefore, if there are inconsistencies between the clinical picture and the test results, it is important to repeat them and inform the laboratory. Possible methods to eliminate the error are the use of different antibody pairs, incubation times, dilutions, or the use of polyethylene glycol (PEG) or the addition of blocking agents that remove the interfering antibody [68, 69].

An increasingly common, external cause of abnormal TSH determinations, as well as other hormones, may be biotin supplementation. Its use can lead to false positive or negative results. Therefore, to avoid this, it should be recommended, if possible, to stop biotin supplementation at least 48–72 hours before the blood test, or to use appropriate laboratory diagnostic methods [70, 71].

Causes of persistence of thyroid-related symptoms despite adequate LT4 substitution

Undiagnosed comorbidities

If nonspecific symptoms persist despite adequate LT4 dose and laboratory euthyroidism, it is important to

rule out other undiagnosed conditions that may cause them. According to data from a cross-sectional study by Sharma et al., the presence of a second autoimmune disease can occur in up to 27.8% of HT patients, with the most common being type 1 diabetes (9.5%), celiac disease (9.5%), and rheumatoid arthritis (2.8%) [72]. Importantly, if an increase in LT4 dose causes general fatigue, muscle aches, hypotension, or loss of appetite or weight, the cause may be adrenal insufficiency. Increasing the dose of the LT4 can exacerbate symptoms of hypocortisolemia, as it leads to increased breakdown of cortisol in the liver. Notably, patients undergoing anticancer treatment may be at higher risk for primary hypothyroidism and secondary adrenal insufficiency, which can occur even months after withdrawal of immune checkpoint inhibitors [73, 74]. Another cause of adrenal insufficiency, both secondary and primary in nature, may be infection with COVID-19 [75, 76]. It may have an autoimmune or iatrogenic basis resulting from withdrawal of long-term treatment with synthetic glucocorticoids [77].

Other diseases reported to be more common in patients with hypothyroidism are obstructive sleep apnea [78] and depression [79, 80]. They can similarly manifest as feelings of fatigue or impaired concentration and cause diagnostic difficulty. It has been proven that the severity of depression does not change despite the use of an adequate dose of LT4 in people with subclinical hypothyroidism [81]. In addition, awareness of chronic diagnosis may also cause low self-esteem of health in patients with hypothyroidism [82]. Therefore, accounting for psychological factors can also be significant in the search for the cause of persistent symptoms.

Similarly, polycystic ovary syndrome, which is closely related to insulin resistance, often occurs in hypothyroidism and causes nonspecific symptoms such as difficult weight loss or lethargy after meals [83]. Remarkably, in a prospective study, levothyroxine substitution in patients with overt or subclinical hypothyroidism did not lead to resolution of insulin resistance [84]. Moreover, another study found that insulin resistance impairs levothyroxine and hypothalamic-pituitary-thyroid axis activity [85]. This is another argument in favor of excluding undiagnosed diseases or, if detected, treating them first instead of escalating the LT4 dose.

Environmental factors

So far, many environmental factors have been described that can affect the effectiveness of LT4 substitution, presumably by affecting the severity of autoimmunity and the transport, metabolism, excretion, or action of thyroid hormones. As shown, even if TSH levels are normal, several factors can interfere with the metabolism of FT4 to FT3, directing conversion to inactive reverse T3 (rT3) [86]. These include exposure to chemical pollutants, chronic stress, malnutrition, or chronic inflammation [87].

Diet

An important factor affecting the balance within the hypothalamic–pituitary–thyroid axis is diet. To date, many studies have focused on evaluating the relationship between thyroid dysfunction and gluten consumption, which is likely based on a molecular mimicry mechanism between intestinal and thyroid tissue transglutaminase [88]. However, it has not been shown to be beneficial for gluten-tolerant people and may even be associated with the risk of nutritional deficiencies. Instead, it is suggested that patients with hypothyroidism should be recommended an anti-inflammatory diet, rich in vitamins, polyphenols, antioxidants, and omega-3 fatty acids and low in animal fats [89].

Gut microbiota

A growing number of reports indicate that changes in the gut microbiome affect thyroid function both by influencing the immune system and the absorption of micronutrients, which are essential for normal thyroid hormone metabolism and function [90–92]. The gut microbiota has been shown to differ in HT patients compared to controls, which is related to FT3 and FT4 concentrations [93]. Studies in animal models suggest that a healthy microbiome can prevent thyroid hormone fluctuations and even reduce the need for LT4 supplementation [91]. However, there is still no evidence supporting the routine use of probiotics, prebiotics, or synbiotics in patients with primary hypothyroidism [92, 94]. Therefore, further well-designed studies are needed to determine the importance of probiotics as adjunctive therapy in thyroid disease and their relevance in assessing quality of life.

Physical activity

In a large sample using the National Health and Nutrition Examination Survey (NHANES) data set, increased physical activity was associated with lower levels of inflammatory cytokines — C-reactive protein (CRP) and fibrinogen — and lower levels of FT4 and TSH among men and women [95]. Such results suggest that physical activity may suppress the hypothalamic-pituitary-thyroid axis. However, in a population-based cohort study, physical activity was not confirmed to affect endogenous TSH or FT4 secretion [96]. Nevertheless, it has been shown to have a positive effect on quality of life and reduce feelings of fatigue in patients during and after thyroid cancer treatment [97]. The probable cause is the impact of physical activity on reducing inflammation and oxidative stress [98]. In fact, a ran-

domized clinical trial conducted on a small group of 22 women with subclinical hypothyroidism showed that 16 weeks of aerobic exercise (lasting 60 minutes 3 times a week) significantly improved quality of life [99]. Therefore, it appears that its recommendation may be beneficial for patients with persistent symptoms despite adequate LT4 substitution.

Endocrine disruptors

A meta-analysis conducted by Kim et al. showed a significant relationship between diethylhexyl phthalate, a so-called plasticizer widely used in industrial products, and disruption of the hypothalamic-pituitary-thyroid axis [100]. In turn, in the Korean National Environmental Health Survey, increased urinary excretion of bisphenol A was significantly negatively correlated with serum FT3 and FT4 concentrations in overweight subjects [101]. Moreover, in a cross-sectional study, there was a correlation between increased urinary excretion of bisphenol C (a bisphenol A analog with a thyroxine-like structure) and decreased thyroid volume and elevated TSH levels (> 2.5) in young women without autoimmune thyroiditis [102]. The reason for the observed correlations is suspected to be the effect of bisphenol A analogs on both thyroxine-binding globulin (TBG) and thyroid hormone receptors (thyroid hormone receptors — TRα and TRβ) [103]. However, data on the relationship between exposure to endocrine disruptors and the persistence of complaints despite adequate LT4 dosing are still lacking. Therefore, further studies are needed to better understand these relationships.

Selenium

Selenium is a component of enzymes, selenoproteins, such as glutathione peroxidase and iodothyronine deiodinase, responsible for the production and conversion of thyroid hormones. Its deficiency can lead to oxidative stress leading to thyroid cell damage, autoimmunity, and activation of fibrotic processes [104]. A meta-analysis of studies by Wichman et al. showed that selenium supplementation was associated with a significant reduction in antithyroid antibody concentrations after just 3 months [105]. However, results to date are conflicting, and there is still insufficient evidence of clinical benefit from selenium supplementation in hypothyroidism [106, 107]. Nevertheless, a survey of European Thyroid Association members found that about half of physicians recommend selenium supplementation in HT to reduce circulating antithyroid autoantibodies, slow the rise in TSH levels, and improve quality of life [108].

Iron

Iron is a component of heme, essential for the activation of thyroid peroxidase, which is crucial in the iodination of thyroglobulin and the coupling of iodotyrosine molecules [91, 104]. A meta-analysis conducted by Luo et al. showed that iron deficiency in women of reproductive age significantly increases the risk of aTPO positivity, and in pregnant women it is associated with elevated TSH and reduced FT4 levels [109]. Similar conclusions were reached in a recent meta-analysis by Garofalo et al. in which iron-deficient, non-pregnant women showed significantly lower levels of FT4 and FT3 [110]. Importantly, iron deficiency can result from malabsorption due to autoimmune gastritis or celiac disease, non-celiac wheat sensitivity, and dysbiosis, the risk of which is higher in HT patients [91]. On the other hand, already latent anemia can cause nonspecific symptoms that are easily linked to hypothyroidism. Therefore, the relationship between iron deficiency and the presence of nonspecific symptoms in patients with hypothyroidism are bilateral [111].

Magnesium

Magnesium affects the maintenance of energy balance in the body and additionally regulates iodine uptake [112]. Wang et al. in a cross-sectional study involving 1257 patients showed that severely low serum magnesium levels (≤ 0.55 mmol/L) are associated with positive aTG antibodies and the presence of HT [113]. Magnesium deficiency can manifest as cognitive impairment, musculoskeletal complaints, or hair loss, which may correspond to non-specific symptoms associated with hypothyroidism [112]. It was postulated that biochemical abnormalities such as serum selenium levels below 80 ug/L, magnesium below 0.9 mmol/L, and coenzyme Q10 below 800 ug/L correlate with ultrasound features of autoimmune thyroiditis (hypoechogenicity and impaired perfusion), which can be reversed after 14–18 months of adequate supplementation [114]. However, the results of studies to date are not consistent, and there is a lack of evidence for the efficacy of such management.

Zinc

Zinc is a trace element that promotes the synthesis of hypothalamic thyrotropin-releasing hormone (TRH) and TSH, regulates the expression of thyroid hormones, is required for deiodinase to convert T4 to T3, and is an important component of the T3 receptor [115]. In hypothyroidism, lower serum zinc levels and higher phosphorus levels were observed [116]. A recently published systematic review of randomized controlled trials suggests that zinc supplementation in overweight or obese and hypothyroid patients increases FT3 levels [117]. The literature also reports normalization of TSH levels after 6 months of zinc supplementation in patients with Down syndrome, zinc deficiency, and subclini-

cal hypothyroidism [118]. However, due to the observed benefits only in selected groups of patients and the risk of overdose, routine zinc supplementation is not recommended in patients with hypothyroidism [115].

Vitamin D

Vitamin D deficiency has been shown to be more frequent in women with autoimmune thyroiditis and primary hypothyroidism than in the general population [119]. The likely mechanism responsible for this relationship is the effect of vitamin D deficiency on autoimmunity through activation of inflammation [120]. Importantly, a meta-analysis of previous studies has shown that vitamin D supplementation significantly reduces aTPO in patients with HT [121]. Given the pleiotropic beneficial effects of vitamin D on the functioning of many organs, its deficiency should be appropriately supplemented, especially in people with autoimmune diseases [122, 123].

Vitamin B12

The presence of HT is associated with a higher risk of other autoimmune diseases, including pernicious anemia and associated vitamin B12 deficiency, which may be associated with non-specific symptoms even on adequate LT4 substitution [124]. Vitamin B12 deficiency increases homocysteine levels, contributing to the comorbidity of vascular disease, cognitive decline, and increased risk of neuropsychiatric disease [125]. Moreover, vitamin B12 is essential for the normal function of the immune system, maintaining a normal CD4/CD8 ratio, or restoring the function of the complement system and enhancing humoral immunity by restoring immunoglobulin [126]. However, there is still a lack of data explaining the relationship between vitamin B12 deficiency and the persistence of complaints in HT patients despite euthyroidism.

Metformin

Subclinical hypothyroidism has been shown to increase insulin resistance in normoglycemic individuals [127], while positive aTPO antibodies have been associated with the presence of elevated fasting insulin levels [128] and higher homeostatic model assessment — insulin resistance (HOMA-IR) [129]. One recently published meta-analysis showed that metformin significantly reduces insulin resistance in patients with HT and subclinical hypothyroidism, as well as lowering the levels of aTPO, aTG, and TSH [130]. Therefore, the implementation of metformin in people with hypothyroidism and co-occurring insulin resistance most likely does not only eliminate the symptoms of insulin imbalance, but also reduces the risk of autoimmunity.

Myo-inositol

A growing body of evidence points to the beneficial effects of myo-inositol, a precursor of the phosphatidylinositol cycle, on thyroid function [131]. It probably increases the sensitivity of thyrocytes to TSH, affects iodination processes [132], and may be effective in protecting thyroid cells from the effects of pro-inflammatory cytokines [133]. Its deficiency may be associated with impairment of the inositol-dependent TSH signaling branch, resulting in thyrocyte resistance to TSH [132]. A randomized clinical trial involving 168 HT patients with TSH levels between 3 and 6 μIU/mL showed that administration of myo-inositol and selenium (at a dose of 600 mg myo-inositol and 83 μg selenium contained in 16.6 mg of L-selenomethionine) compared to the administration of selenium alone at a dose of 83 μg (contained in 16.6 mg of L-selenomethionine) for 6 months significantly reduced TSH levels and antithyroid antibody titers, and improved mood [134]. Similar results were obtained in a multicenter study involving 148 premenopausal women with subclinical hypothyroidism, in whom 6-month supplementation with myo-inositol 600 mg and selenium 83 ug was associated with significant reductions in TSH, aTPO, and aTG antibodies, total cholesterol, return of regular menstrual cycles, and fewer symptoms associated with hypothyroidism such as: feelings of fatigue, difficulty with weight loss, or feeling cold [135]. However, these data still need to be confirmed in studies conducted on larger groups of patients.

Ashwagandha [*Withania somnifera (L.) Dunal*]

In experimental studies in a rat model of hypothyroidism, ashwagandha restored T3 and T4 levels and prevented hypothyroidism complications in the nervous system, including oxidative stress and neuroinflammation [136]. A prospective, randomized, double-blind, single-center, placebo-controlled study conducted at Sudbhawana Hospital in Varanasi, India, showed that Ashwagandha root extract (600 mg daily) is beneficial in normalizing thyroid function in patients with subclinical hypothyroidism [137]. Other randomized studies, also carried out on small groups, have indicated efficacy in improving the quality of sleep in patients with insomnia [138], reducing stress and anxiety [139], sexual well-being, increasing serum testosterone levels in adult men [140], and improving female sexual health [141]. It probably relieves these conditions mainly through hypothalamic-pituitary-adrenal modulation as well as through GABAergic and serotonergic pathways [142]. However, there is still a lack of data on the safety of taking ashwagandha extract and its effectiveness in large-group clinical trials.

Genetic factors

A prospective observational study involving 353 patients showed that thyroid hormone conversion efficiency is individually variable, and LT4 dose escalation may have limited success in adequately raising FT3 [143]. Previous reports suggest an association with polymorphisms of genes such as proteins that transport thyroid hormones into the cell, i.e., monocarboxylate transporters (MCT8 or MCT10) [144], organic anion transporter polypeptide 1C1 (OATP1C1) [145], a protein that determines the conversion of the hormone FT4 to FT3, i.e. deiodinase type 2 (DIO2) [146], and the thyroid hormone receptor gene (THRα) [147]. Inherited defects in thyroid hormone metabolism include also selenocysteine insertion sequence-binding protein 2 (SECISBP2), sec-specific tRNA (TRU-TCA1-1), and deiodinase type-1 (DIO1) mutations [148, 149]. We can suspect them when we observe mostly low FT3, high rT3, high or normal FT4, and normal or elevated TSH [149]. Mutations, depending on the genetic variant, can be accompanied by complaints about skeletal structure and growth, muscle strength, and neurological or metabolic dysfunction [148]. An association between thyroglobulin (TG) [150] or thyroid peroxidase (TPO) [151] polymorphisms and HT severity and prognosis has also been shown. However, their link with the persistence of residual symptoms in patients with hypothyroidism despite LT4 treatment is not clear.

The best-studied polymorphism responsible for differences in response to LT4 is Thr92Ala DIO2 (rs225014). It occurs in up to one-third of the population and is associated with reduced amounts of active FT3 hormone, particularly in the central nervous system and skeletal muscle [152]. Meta-analyses of previous studies indicate its association with a higher risk of developing type 2 diabetes [153] and higher body weight [154]. In turn, a study in cellular and animal models indicates that the Thr92Ala D2 polymorphism is associated with endoplasmic reticulum stress, lower FT3 levels, and nervous system dysfunction. Importantly, its presence was associated with sluggishness in mice, which resolved after FT3 substitution [155]. A randomized, double-blind study of a small group of 45 patients showed that the presence of the Thr92Ala DIO2 polymorphism with an associated polymorphism in the gene for monocarboxylate transporters (MCT, rs17606253) was associated with a preference for FT3 and FT4 combination therapy [144]. However, the results are conflicting [156–158], and combination therapy has still not been proven to provide more benefit than LT4 alone, so it is not recommended [159].

It seems that a better understanding of the impact of genetic diversity on the treatment of hypothyroidism would make it possible to personalize therapy by isolating a group of patients in whom combination therapy would be effective in reducing persistent complaints. Thus, the American Thyroid Association (ATA), the British Thyroid Association (BTA), and the European Thyroid Association (ETA) issued a consensus indicating the need for well-designed studies with adequate power involving the effects of deiodinase and thyroid hormone transporter polymorphisms including patients dissatisfied with current therapy and requiring at least 1.2 μg/kg LT4 per day [160].

Epigenetic factors

Despite intensive exploration, the role of epigenetic mechanisms including histone modifications, DNA methylation, and non-coding RNA molecules (microRNAs, long non-coding RNAs and circular RNAs) in the pathogenesis and course of hypothyroidism is still not well enough understood [48]. The epigenome-wide association study (EWAS) recently published (2021 and 2023), which identified differential methylation of genes within Krueppel-like factor 9 (KLF9) and DOT1-like histone lysine methyltransferase (DOT1L), which correlated with FT3 and TSH levels [161, 162], suggesting the importance of these epigenetic factors in regulating the thyroid function. The transcription factor KLF9 has been shown to be a T3 target gene that regulates multiple stress-responsive and endocrine signaling pathways [163], while Dot1L acts as a T3 receptor coactivator [164]. However, these mechanisms are still not clear.

Data on the relationship between the persistence of residual symptoms despite euthyroidism in hypothyroid patients and epigenetic factors are limited. In a study conducted on a rat model, stress in early life was shown to have long-term effects in adults, manifested by changes in the pattern of DNA methylation in the thyroid hormone receptor (Thr) promoter [165]. Importantly, such disruption was more common in female individuals and was associated with energy imbalance [165]. In humans, there are reports indicating that polymorphisms in genes that regulate methylation, such as methionine synthase reductase (MTRR), have also been shown to correlate with levels of DNA hypomethylation and a more severe course of HT [166]. It has also been suggested that maternal exposure to persistent organic pollutants (i.e., pesticides, industrial chemical products) are associated with DNA methylation of genes related to thyroid hormone transport and metabolism in the placenta in a sex-dependent manner [167]. It appears that exposure to an adverse environmental factor can lead to long-term adverse changes in gene expression, even in subsequent generations. However, the role of epigenetic modifications in the persistence of

symptoms despite adequate LT4 substitution remains largely unknown.

Figure 2 illustrates the complexity of interactions between genetic, environmental, and epigenetic factors that can affect thyroid hormone function through immune system dysfunction.

Table 2 summarizes the factors affecting the efficacy of LT4 hormone replacement, the suspected mechanisms responsible for them, and the evidence from clinical trials conducted to date.

Suggestions for managing difficulties during hypothyroidism treatment

Table 3 summarizes the most common problems encountered during LT4 treatment discussed above

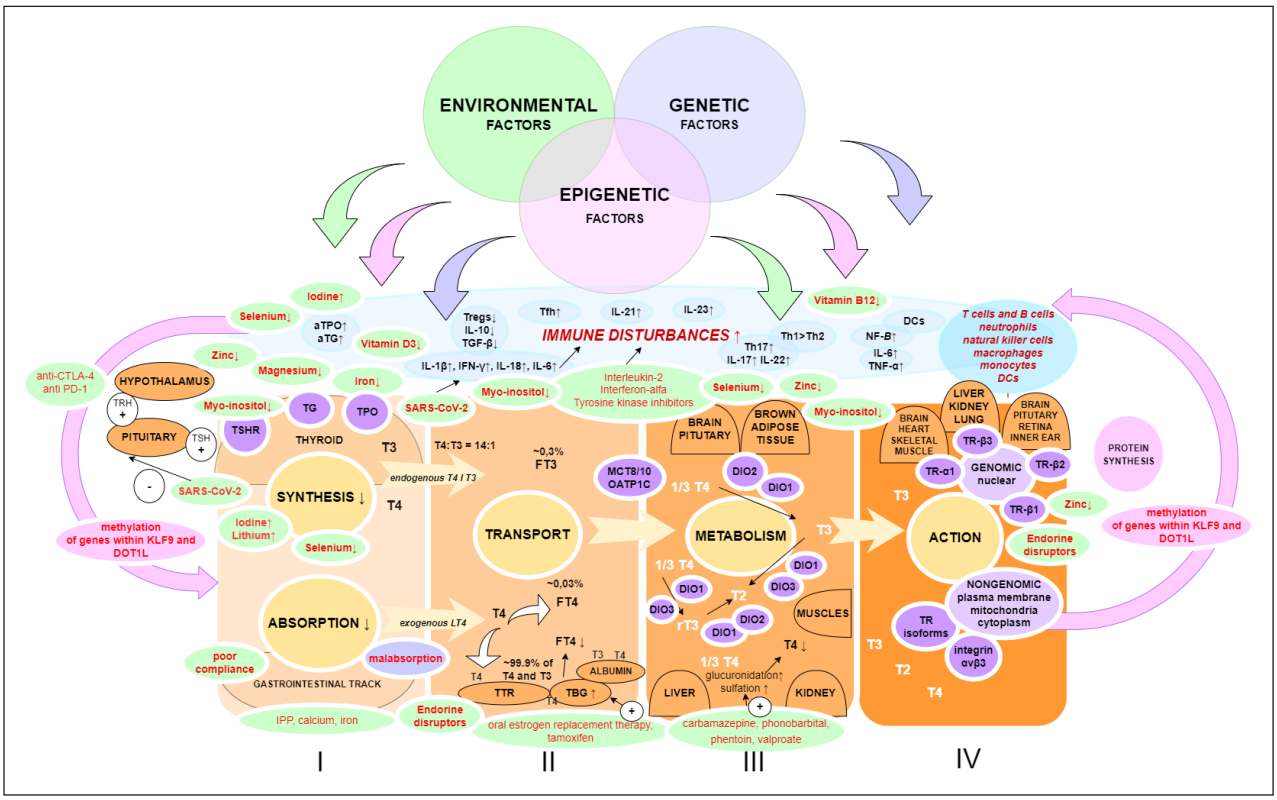

Figure 2. *The 4 structures in colors ranging from light orange to dark orange represent different stages of thyroid hormone transformation, on which depends the effectiveness of levothyroxine (LT4) substitution. I represents the source of thyroid hormones, which comes from the absorption of LT4 in the gastrointestinal tract and the synthesis of LT4 and LT3 in the thyroid gland (in a ratio of about 14:1). II shows the transport of thyroid hormones in peripheral blood in free form (about 0.3% T3 and 0.03% T4) and bound to proteins such as thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin (about 99.9% T3 and T4). The main transmembrane proteins that transport thyroid hormones through cells are monocarboxylate transporters (MCTs) and organic anion transporters (OATPs). III demonstrates the metabolism of thyroid hormones in cells of various organs using deiodases: about 1/3 of T4 is converted to active T3, 1/3 is converted to inactive rT3, and about 1/3 is eliminated by glucuronidation and sulfation. IV illustrates the action of thyroid hormones in target cells: through α and β receptors and genomic mechanisms in the nucleus and through αvβ3 integrin isoforms or other TRs and non-genomic mechanisms mediated by the cell membrane and/or mitochondrial binding sites. These processes can be disrupted by numerous factors, which are divided into environmental (shown in green), genetic (shown in purple), and epigenetic (shown in pink). An important mediator in these interactions is probably the immune system. Details of the impact of each factor are included in the body of the review [4, 21, 24, 27, 86, 104, 156, 167–170]. aTG — anti-thyroglobulin antibodies; aTPO — thyroid peroxidase antibodies; CTLA-4 — cytotoxic T lymphocyte-associated antigen; DCs — dendritic cells; DIO1 — type 1 deiodinase; DIO2 — type 2 deiodinase; DIO3 — type 3 deiodinase; DOT1L — disruptor of telomeric silencing 1-like; IFN-γ — interferon gamma; IL-1β — interleukin 1 beta; IL-6 — interleukin 6; IL-18 — interleukin 18; IL-21 — interleukin 21; IL-22 — interleukin 22; IL-23 — interleukin 23; KLF9 — Krueppel-like factor 9; MCT8 — monocarboxylate transporter 8; MCT10 — monocarboxylate transporter 10; NF-κB — nuclear factor kappa B; OATP1C — organic anion transporter polypeptide 1C1; PD-1 — programmed death receptor 1; rT3 — 3,3′,5′-triiodo-L-thyronine; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2; T2 — 3,5-diiodo-L-thyronine; T3 — 3,5,3′-triiodo-L-thyronine; T4 — thyroxine; TBG — thyroxine-binding globulin; Th1 — T helper 1; Th2 — T helper 2; Th17 — T helper 17; Th22 — T helper 22; THR — thyroid hormone receptor; TNF-α — tumor necrosis factor alpha; Tregs — regulatory T cells; TRs — thyroid hormone receptors; TRα — thyroid hormone receptor alpha; TRβ — thyroid hormone receptor beta; TRH — hypothalamic thyrotropin-releasing hormone; TTR — transthyretin*

Table 2. *Factors affecting the effectiveness of levothyroxine (LT4) hormone replacement*

Factor	Possible mechanism of action	Examples of evidence from clinical trials		
		Study design	Outcome	Author, date
Environmental				
Physical activity	Pleiotropic effect on systemic reduction of inflammation and oxidative stress	Randomized clinical trial of 22 women with subclinical hypothyroidism	After 16 weeks of aerobic exercise, there was a significant improvement in the quality of life	Werneck et al., 2018 [99]
Gut microbiome	Influence on the immune system and the absorption of micronutrients, which are necessary for the proper metabolism and function of thyroid hormones	Systematic review with meta-analysis of 136 hypothyroid participants	After 8 weeks of supplementation with mainly *Lactobacillus* and *Bifidobacterium* strains, there was a clinically and statistically insignificant decrease in TSH but no effect on FT3 levels	Zawadzka et al., 2023 [94]
Endocrine disruptors	Effects on thyroid hormone transport and signaling through binding to TBG and thyroid hormone receptors	Meta-analysis of date from 12,674 patients	A significant association was found between exposure to diethylhexyl phthalate metabolites and FT4 and TSH levels	Kim et al., 2019 [100]
		The cross-sectional study of 6478 adults	Inverse correlation between urinary bisphenol A and FT3 and FT4 levels in the group with higher BMI	Kwon et al., 2020 [101]
Selenium deficiency	Inactivation of glutathione peroxidase and increased oxidative stress leading to thyroid cell damage, autoimmunity and activation of fibrotic processes	Systematic review with meta-analysis of 16 controlled trials	Selenium supplementation reduced serum aTPO levels after 3, 6, and 12 months in an LT4-treated patients with chronic autoimmune thyroiditis and after 3 months in untreated patients with chronic autoimmune thyroiditis	Wichman et al., 2016 [105]
Iron deficiency	Decreased thyroid peroxidase activity and exacerbation of autoimmunity	Systematic review with meta-analysis of 8 cross-sectional studies	In women of reproductive age, iron deficiency significantly increases the risk of both positive aTPO and aTg, while in pregnant women it significantly increases serum TSH levels and decreases FT4 levels	Luo et al., 2021 [109]
		Systematic review with meta-analysis of 10 studies	In adults, iron deficiency significantly decreases FT4 and FT3 levels	Garofalo et al., 2023 [110]
Magnesium deficiency	Effect on energy balance and iodine uptake	The cross-sectional study of 1257 Chinese participants	Severely low serum magnesium levels were associated with an increased rate of aTG positivity, HT and hypothyroidism	Wang et al., 2018 [113]
Zinc deficiency	Effects on T lymphocyte activity and binding of T3 hormone to receptors	Systematic review of 13 randomized controlled trials	Zinc supplementation in people with overweight or obesity was associated with increase FT3 levels	Zavros et al., 2023 [117]

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Table 2. *Factors affecting the effectiveness of levothyroxine (LT4) hormone replacement*

Factor	Possible mechanism of action	Examples of evidence from clinical trials		
		Study design	Outcome	Author, date
Vitamin D3 deficiency	Increased inflammation and autoimmunity	Meta-analysis of 6 randomized controlled trials	Vitamin D supplementation significantly reduced the level of aTPO	Jiang et al., 2022 [121]
Vitamin B12 deficiency	Increased autoimmunity and dysfunction of metabolic cycles related to methylation, which is associated with an excess of homocysteine	The cross-sectional study of 100 hypothyroid patients	Vitamin B12 deficiency was found to be correlated with elevated serum levels of aTPO and aTG	Chatterjee et al., 2023 [124]
Metformin	Reduces autoimmunity	Systematic review and meta-analysis	Metformin significantly reduces aTPO and aTg levels in HT patients	Jia et al., 2020 [130]
Myo-inositol	Increased sensitivity of thyrocytes to TSH and effects on iodination processes	Randomised clinical trial of 168 patients with HT having TSH levels between 3 and 6 μIU/mL	Taking myo-inositol and selenium (at a dose of 600 mg myo-inositol and 83 μg selenium) compared to taking selenium alone (at a dose of 83 μg) for 6 months significantly reduced TSH levels, antithyroid antibody titres and improved mood	Nordio et al., 2017 [134]
		Prospective interventional multicentric study of 148 premenopausal women	6-month supplementation with myo-inositol 600 mg and selenium 83 ug was associated with significant reductions in TSH, aTPO, and aTG antibodies and fewer symptoms associated with hypothyroidism	Payer et al., 2022 [135]
Ashwagandha	Restored T3 and T4 levels and prevented complications of hypothyroidism in the nervous system, including oxidative stress and nervous system inflammation	Randomised clinical trial of 50 patients with subclinical hypothyroidsm	8 weeks of treatment with ashwagandha (600 mg daily) improved serum TSH, FT3, and FT4 levels significantly compared to placebo	Sharma et al., 2018 [137]
Genetic				
SNP in genes of transporters for thyroid hormones	Impaired transport of free thyroid hormones into the cell	Randomised clinical trial of 141 patients with HT	Both the OATP1C1-intron3C > T and the OATP1C1-C3035T polymorphism, were associated with symptoms of fatigue and depression, but not with preference for combined LT4-LT3 therapy	van der Deure et al., 2008 [145]
SNP in gene of *DIO2*	Decrease in the conversion of FT4 to FT3	Randomised clinical trial of 45 patients with HT	A combination of polymorphisms in DIO2 (rs225014) and MCT10 (rs17606253) is associated with the preference for combined LT4-LT3 therapy	Carlé et al., 2017 [144]

Table 2. *Factors affecting the effectiveness of levothyroxine (LT4) hormone replacement*

Factor	Possible mechanism of action	Examples of evidence from clinical trials		
		Study design	Outcome	Author, date
SNP in gene of *THR*a	Impaired action of thyroid hormones	The cross-sectional study of 228 patients with primary hypothyroidism	The THRa rs939348 polymorphism was associated with L-T4 replacement doses in hypothyroid patients and central obesity	Al-Azzam et al., 2014 [147]
SNP in gene of *TG*	Exacerbation of autoimmunity	The cross-sectional study of 137 patients with HT	The rs2076740 polymorphism correlated with the serum levels of aTg	Mizuma et al., 2017 [150]
SNP in gene of *TPO*	Exacerbation of autoimmunity	The cross-sectional study of 147 patients with HT	The TPO rs2071400 and rs2048722 polymorphisms were associated with the serum levels of aTPO	Tomari et al. 2017 [151]
SNP in gene of *MTRR*	Epigenetic modification, change in global DNA methylation levels	The cross-sectional study of 125 patients with HT	The MTRR+66AA genotype was observed to be more frequent in patients with severe HD than in those with mild HD	Arakawa et al., 2014 [166]
Epigenetic				
Environmental factors still not known	Differential methylation of genes within *KLF9* and *DOT1L* associated with the hypothalamic-pituitary-thyroid axis	Meta-analysis of EWAS of 7073 participants	*KLF9* DNA methylation was associated with thyroid hormone levels	Weihs et al., 2023 [161]
		Meta-analysis of EWAS of 563 participants	*KLF9* and *DOT1L* DNA methylation was associated with TSH and FT3 levels	Lafontaine et al., 2021 [162]
Maternal exposure to persistent organic pollutants (i.e., pesticides, industrial chemical products)	DNA methylation of genes related to thyroid hormone metabolism and transport in the placenta	The cross-sectional study of 106 Korean mothers at delivery	In utero exposure to persistent organic pollutants can affect DNA methylation of DIO3 and MCT8 genes in the placenta in a sexually dimorphic manner	Kim et al., 2019 [167]

TSH — thyroid stimulating hormone; FT3 — free triiodothyronine; TBG — thyroxine-binding globulin; FT4 — free thyroxine; TPO — thyroid peroxidase; BMI — body mass index; aTG — anti-thyroglobulin antibodies; SNP — single nucleotide polymorphism; HT — Hashimoto's thyroiditis; aTPO — thyroid peroxidase antibodies; OATP1C — organic anion transporter polypeptide 1C1; THRα — thyroid hormone receptor alpha; DIO3 — type 3 deiodinase; EWAS — epigenome-wide association study; MCT8 — monocarboxylate transporter 8; *KLF9* — Krueppel-like factor 9

Table 3. *Suggestions for managing difficulties in levothyroxine (LT4) substitution*

Problems encountered during treatment with LT4	Proposed diagnostics and question that we need to answear	Management suggestion
Supra-physiological doses of LT4 or problems with achieving euthyroidism	Does the patient follow the instructions for taking the drug (fasting minimum 30 minutes before meals and medications)?	Inform the patient how to take the drug and in case of non-adherence recomend taking LT4 taken before bed, rather than in the morning or offer LT4 in soft gel or liquid form
	Are there absorption disorders caused by gastrointestinal diseases, such as: gastroesophageal reflux disease, autoimmune atrophic gastritis, celiac disease, lactose intolerance, irritable bowel syndrome or others?	In case of malabsorption, propose LT4 in soft gel or liquid form and consider the addition of vitamin C
	Are there external factors, e.g., iron or calcium supplementation, or taking a proton pump inhibitor together with LT4, which may reduce its effectiveness?	Separating the administration of the hormone from consuming foods or medications that interfere with its absorption for 4–6 h
	Is there medication taken that may increase the need for thyroid hormones, e.g. estrogen, antiepileptic drugs, drugs that increase thyroid autoimmunity...?	Modify treatment if possible or increase LT4 dose sufficiently
Clinical presentation is not consistent with thyroid hormone test results	Laboratory interferences	Repeat the test, informing the laboratory of possible erroneous results so that other methods can be used If using biotin, discontinue its supplementation at least 48-72 hours before the blood test
	Revision of the causes of hypothyroidism (especially if there is a history of COVID-19 or treatment with immune control inhibitors)	Reassessment of thyroid panel with thyroid ultrasound examination
Weight gain despite euthyroidism	Assess whether the patient has insulin resistance (elevated serum insulin levels (fasting or during OGTT) and determination of HOMA-IR	Recommend increasing physical activity, low glycemic index diet, consider adding metformine or myo-inositol
Feelings of fatigue, impaired concentration, lowered mood	Does the patient have other previously undiagnosed diseases: e.g., depression, obstructive sleep apnea, celiac disease, atrophic gastritis (vitamin B12 deficiency), adrenal insufficiency?	Apply treatment appropriate to other co-morbidities with hypothyroidism
	Does the patient have latent iron deficiency (low ferritin levels), magnesium, vitamin D3 or others?	Implement supplementation to correct deficiencies
	Are the aTPO or aTG antibody titres very high?	If the levels of antithyroid antibodies are very high consider including selenium
	What is the FT4/FT3 ratio?	If low FT3 is observed, despite the exclusion of deficiencies or other causes that may be responsible for the presence of non-specific symptoms, consider combination therapy of T3 and T4

COVID-19 — 2019 coronavirus disease; OGTT — oral glucose tolerance test; HOMA-IR — homeostatic model assessment — insulin resistance; aTPO — thyroid peroxidase antibodies; aTG — anti-thyroglobulin antibodies; FT3 — free triiodothyronine; FT4 — free thyroxine

and suggests clinical questions and management depending on the cause.

Conclusion

Difficulties with LT4 treatment and the persistence of non-specific complaints despite adequate hormone replacement are common problems in clinical practice. To avoid them, a thorough analysis that takes into account personal factors, comorbid or undiagnosed diseases, drug interactions, and laboratory errors is essential. Optimizing the treatment of patients with hypothyroidism should ensure not only the restoration of biochemical euthyroidism, but most importantly the resolution of symptoms and signs of hypothyroidism. This is likely due to a complex interaction between individual, genetic, epigenetic, and environmental factors that result in disruption of the gut microbiome, associated micronutrient deficiencies, and immune dysfunction. It probably mediates impaired absorption or synthesis, transport, metabolism, and function of thyroid hormones. Therefore, therapies aimed at lowering autoimmunity are promising in resolving persistent symptoms but need to be confirmed in well-designed studies on larger groups of patients. Similarly, LT4 and LT3 combination therapy may be beneficial in selected groups of patients, probably with specific genetic predispositions that are still not well established. Thus, it is necessary

to better understand the pathogenetic basis of thyroid diseases and develop treatment strategies tailored to the patient's profile. It seems that developing a causal therapy based on knowledge of the pathogenesis of hypothyroidism as an immunoendocrine disorder may be the key to achieve the main goal of treatment, which is to improve quality of life.

Authors' contributions

All authors contributed to the study conception and design. The idea for the article, the literature search, data analysis, and writing the first draft of the manuscript were performed by M.Ł.T. E.F. participated in the planning process, and critically revised and commented on the draft manuscript. 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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REVIEW

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