REVIEW PAPERS

Factors associated with quality of life in patients with chronic lymphocytic thyroiditis-a review of literature.

Czynniki wpływające na jakość życia pacjentów z przewlekłym limfocytarnym zapaleniem tarczycy- praca poglądowa.

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KEY WORDS:

- Health-related quality of life
- questionnaire
- Hashimoto's thyroiditis
- euthyreosis
- autoimmune disease.

ABSTRACT

Hashimoto's thyroiditis (HT) represents the most common organ-specific autoimmune disorder, characterized by chronic lymphocytic infiltration of the thyroid parenchyma and the presence of circulating antithyroid autoantibodies, predominantly antibodies against thyroid peroxidase (TPO Ab) and antibodies against thyroglobulin (Tg Ab). The pathogenesis of HT involves a complex interplay between genetic predisposition and environmental factors, culminating in the loss of immune tolerance and progressive destruction of thyroid tissue. Although HT remains the principal etiology of hypothyroidism in developed countries, accumulating evidence indicates that patients may exhibit systemic manifestations and reduced health-related quality of life (HRQoL) even in the euthyroid state. These clinical features are mediated by ongoing autoimmune activity, chronic inflammation, and the pathogenic effects of autoantibodies, contributing to structural and functional alterations within the thyroid gland. Furthermore, HT is frequently associated with a spectrum of comorbidities, including other autoimmune disorders, metabolic syndrome, cardiovascular diseases, psychiatric conditions, and neoplasms, which collectively exacerbate morbidity. Optimal management of HT necessitates a multidisciplinary approach that extends beyond thyroid hormone replacement to include comprehensive evaluation of psychological status and screening for concomitant diseases. This review delineates the multifactorial determinants of HRQoL impairment in HT and underscores the imperative for integrative, patient-centered therapeutic strategies. Continued research on the immunopathogenesis, novel biomarkers, and targeted interventions is essential to improve clinical outcomes and quality of life in affected individuals.

SŁOWA KLUCZOWE:

- jakość życia związana ze zdrowiem
- kwestionariusz
- zapalenie tarczycy typu Hashimoto
- eutyreoza
- choroba autoimmunologiczna

STRESZCZENIE

Choroba Hashimoto (HT) stanowi najczęstsze narządowo swoiste schorzenie autoimmunologiczne, charakteryzujące się przewlekłym naciekiem limfocytarnym miąższu tarczycy oraz obecnością krążących autoprzeciwciał przeciwtarczycowych, głównie przeciwko peroksydazie tarczycowej (TPO Ab) i tyreoglobulinie (Tg Ab). Patogeneza HT obejmuje złożoną interakcję pomiędzy predyspozycją genetyczną a czynnikami środowiskowymi, prowadzącą do utraty tolerancji immunologicznej i postępującego uszkodzenia tkanki tarczycowej.

Chociaż HT pozostaje główną przyczyną niedoczynności tarczycy w krajach rozwiniętych, narastająca liczba danych wskazuje, że pacjenci mogą wykazywać objawy ogólnoustrojowe oraz obniżoną jakość życia związaną ze zdrowiem (HRQoL) nawet w stanie eutyreozy. Objawy te

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wynikają z utrzymującej się aktywności autoimmunologicznej, przewlekłego stanu zapalnego oraz patogennych efektów autoprzeciwciał, które przyczyniają się do zmian strukturalnych i czynnościowych w obrębie gruczołu tarczowego.

Ponadto HT często współistnieje z szerokim spektrum chorób współistniejących, w tym z innymi chorobami autoimmunologicznymi, zespołem metabolicznym, chorobami sercowo-naczyniowymi, zaburzeniami psychicznymi oraz nowotworami, które łącznie nasilają chorobowość. Optymalne postępowanie w HT wymaga podejścia wielodyscyplinarnego, wykraczającego poza samą substytucję hormonów tarczycy i obejmującego kompleksową ocenę stanu psychicznego oraz badania przesiewowe w kierunku chorób współistniejących.

Niniejszy przegląd przedstawia wieloczynnikowe uwarunkowania pogorszenia jakości życia związanej ze zdrowiem u pacjentów z HT oraz podkreśla konieczność wdrażania zintegrowanych, zorientowanych na pacjenta strategii terapeutycznych. Dalsze badania nad immunopatogenezą, nowymi biomarkerami i ukierunkowanymi interwencjami są kluczowe dla poprawy wyników klinicznych oraz jakości życia chorych.

Shortcuts

ASI	- antibody synthesis intrathecal
BP	- bipolar disorder
CSF	- cerebrospinal fluid
HE	- Hashimoto's encephalopathy
HRQOL	- Health-Related Quality of Life
HT	- Hasimoto' thyroiditis
MAAS	- Mindful Attention Awareness Scale
PCOS	- Polycystic Ovary Syndrome
PLR	- Platelet-to-Lymphocyte Ratio
SDQ	- questionnaire of strengths and difficulties
SPECT	- Single Photon Emission Computed Tomography
Tg Ab	- antibodies against thyroglobulin
ThyPRO	- Thyroid disease-specific quality of life questionnaires
ThyPROpl	- Thyroid disease-specific quality of life questionnaires, Polish version
TPO Ab	- antibodies against thyroid peroxidase
TSHR Ab	- antibodies agains thyroid stimulating hormone
US	- ultrasound

Introduction

Hashimoto's thyroiditis (HT), otherwise known as chronic lymphocytic thyroiditis or chronic autoimmune thyroiditis is the most frequent autoimmune disease and at the same time the most common cause of hypothyroidism in the developed countries, including Poland [1]. HT was first described in 1912 by a Japanesee physician Hakaru Hashimo. He presented 4 cases of lymphocytic goiter, in which there was intense lymphocytic infiltration with the formation of lymph nodules in the thyroid parenchyma [2].

The incidence of HT has been rising rapidly in recent decades, and now affects about 5% of the population with a 10-fold predominance of women over men. The incidence increases with age, but the peak of diagnosis occurs between 45 and 55 years of age. A higher incidence of the disease has also been observed among whites than blacks [3].

To establish a diagnosis of HT, two out of three features must be confirmed: hypothyroidism, typical image of HT on thyroid ultrasound (US), and the presence of antibodies against thyroid peroxidase (TPO Ab) and/or antibodies against thyroglobulin (Tg Ab). In about 10% of cases, seronegative forms of HT are observed, that is, without positive anti-thyroid antibodies. Features of HT on US include hypoechogenicity, parenchymal heterogeneity or the presence of cysts [4].

Patients with HT may have different thyroid hormonal function at different stages of the disease. Initially, HT is often asymptomatic or causes mild symptoms, typically occurring with euthyroidism or subclinical hypothyroidism. The disease progresses to overt hypothyroidism in patients: 2.6% per year in those without antibodies to 4.3% per year in those with antibodies. It has been established that this chronic disease can negatively impact the patients' quality of life, affecting both physical and mental health. The reduced quality of life is often related to the instability of the disease and the different course at different stages of the disease. It should be noted, however, that some clinical symptoms may manifest irrespective of thyroid hormonal status, and can be present even in patients with biochemically confirmed euthyroidism. [5]. The autoimmune background of the disease influences many symptoms, which is why we observe them even in euthyroid patients. It has been established that patients with HT report symptom distress more often than those with non-autoimmune thyroid disorders.

Pathogenesis of HT

HT is a multifactorial disease, the development of which is affected by genetic predisposition as well as various environmental factors [2]. The environmental factors include, but are not limited to, excess iodine intake, selenium deficiency, cytokine therapy, smoking, severe stress, a history of bacterial and viral infections, and pregnancy [6].

The inflammation observed in HT results from both humoral and cellular immune response. The activity of HT is primarily dependent on the titer of antithyroid antibodies and the intensity of the autoreactive T cell response, which is triggered by the formation of antigen-antibody complexes [7].

TPO Ab are present in approximately 90% of patients with HT. Tg Ab are found less frequently (in about 60-80% of cases) and exhibit lower sensitivity and specificity compared to TPO Ab, although they are more commonly detected in the early stages of the disease. Approximately 15% of HT patients have TSH receptor antibodies (TSHR Ab), primarily of the blocking type, with the stimulating type being much

rarer. It is worth noting that TPO Ab and Tg Ab may also be present in individuals without overt thyroid disease [8].

In HT, there is an increase in both macrophages and T and B lymphocytes, which leads to an elevated secretion of pro-inflammatory cytokines, such as interleukin-1, interleukin-6, tumor necrosis factor-alpha, and interferon-gamma, as well as chemokines like interferon-inducible protein 10 and chemokine ligand 2. These immune responses contribute to the chronic inflammatory process and direct damage to thyrocytes. The resulting oxidative stress further exacerbates structural damage to the thyroid gland, potentially progressing to thyroid fibrosis [9].

Research on the pathogenesis of HT has led to the creation of various models of the disease. Mathematical models and animal models of HT have been created to further understand the mechanisms involved in the immune imbalance and to develop new causal treatments for HT. Salazar et al. have developed a mathematical model of HT. This is the first report that, by studying the pathogenesis of HT, allows the simulation of various interactions between thyroid cells, the thyroid immune system and the gut microbiota. Such models may help medical decision-making in the future [10].

New markers of inflammation are being sought to diagnose HT. One of them may be the platelet-to-lymphocyte ratio (PLR). Erge et al. showed that PLR is higher in patients with HT. In addition, other increased inflammatory markers such as C-reactive protein and high-sensitivity C-reactive protein are also more frequently observed [11].

Health-related quality of life in HT

Many studies have shown a negative impact of HT on the patient's health-related quality of life (HRQOL), observed also in patients in the euthyroid stage. HT can negatively affect both physical and mental health. Elevated levels of TPOAb are associated with a higher number of symptoms experienced by patients, which are reported during medical visits. The mechanisms responsible for this are not clearly defined, which is why it is the subject of extensive research [12, 13].

The progres in endocrinology and psychology has led to an investigation of the impact of endocrine disorders on the mental state of patients. Psychoneuroendocrinology, is a branch of psychology which deals with the study at the clinical, pathophysiological and genetic levels of the interdependence of psychiatry and endocrinology [3].

In response to the development of psychoneuroendocrinology and because thyroid diseases affect the quality of life, a special thyroid disease-specific quality of life questionnaire (ThyPRO) form was created. It appears in 13 languages, and the Polish version is thyroid disease-specific quality of life questionnaire (ThyPRO.pl), which is recommended for the assessment of HRQOL in patients with benign thyroid diseases [14, 15].

Somatic symptoms, laboratory abnormalities and comorbidities in HT

Autoimmune diseases, including HT, are multifactorial disorders and promote the development of multiple comorbidities, which explains many of the symptoms described below. Local and systemic symptoms are observed in patients with HT. Local symptoms may occur due to compression of anatomical structures of the neck by the thyroid gland. These can include dysphonia following involvement of the retrobulbar laryngeal nerve, dyspnea due to tracheal compression, or dysphagia as a consequence of esophageal compression. In addition, some patients experience neck pain, throat discomfort or obstructive sleep apnea. Goiter in HT may be present in up to 40-50% of patients, resulting from chronic inflammation of the thyroid gland. Therefore, regular US monitoring is crucial for early detection and assessment of potential structural changes [16].

HT negatively affects the skin , hair and nails. HT increases the brittleness of nails. Despite a euthyroid hormonal status, patients with HT may present with cutaneous manifestations such as xerosis, epidermal roughness, and vitiligo. These findings suggest that chronic inflammation and autoimmune mechanisms contribute to skin changes independently of thyroid hormone levels. The presence of elevated anti-thyroid antibodies negatively affects the hair cycle by excessively inducing the telogen phase. All of these changes, by negatively affecting appearance, reduce the quality of life in HT patients [17].

About 6% of HT patients have ocular symptoms associated with TSHR Ab stimulators [18].

Some HT patients also have musculoskeletal pain, including arthralgia (joint pain) and myalgia (muscle pain) [19]. HT often coexist with autoimmune diseases in the field of rheumatology, including rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, Sjogren's syndrome or other connective tissue diseases [20].

HT may be associated with various hematological manifestations, in particular vitamin B12 or iron deficiency anemia, coagulation disorders or platelet dysfunction. A variety of factors may contribute to these hemostatic disturbances, including an increased incidence of comorbid autoimmune conditions such as pernicious anemia (Addison-Biermer disease), celiac disease, antiphospholipid syndrome, and autoimmune thrombocytopenia. Additionally, dietary interventions and pharmacological treatments commonly used in this patient population—such as metformin—may further exacerbate these abnormalities [21, 22].

Another important factor that negatively impacts HRQOL in females with HT are pregnancy complications. HT even with normal thyroid hormone levels, is associated with a higher risk of complications like miscarriage, preterm birth, and other pregnancy-related issues. Compared to patients without HT, female infertility is approximately 8% more prevalent in the HT group, miscarriage rates are 3 to 4 times higher, and the incidence of preterm births is doubled. Additionally, approximately 50% of patients positive for antithyroid antibodies develop postpartum thyroiditis [23]. It has been noticed that patients with HT also have an increased risk of polycystic ovary syndrome (PCOS). PCOS coexists with HT in approximately 25% of affected individuals. Moreover, the concomitant presence of PCOS and HT is associated with a more severe clinical course of both conditions. This is associated with other symptoms, such as metabolic disorders, cardiovascular disease, irregular menstrual cycles and infertility, which further reduce HRQOL [24].

Patients with HT despite normal thyroid hormone function may also experience gastrointestinal symptoms, such as abdominal bloating, constipation, diarrhea, food intolerances, among others. .Autoimmune gastritis is also more commonly observed in patients with HT [25].

Patients with HT, even those in a euthyroid state, exhibit a higher prevalence of metabolic disorders, as well as an

increased incidence of atherosclerosis and elevated cardiovascular risk. HT is frequently associated with elevated systolic and diastolic blood pressure, and dyslipidemia characterized by increased levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and decreased high-density lipoprotein cholesterol [26]. Moreover, abnormalities in carbohydrate metabolism, including impaired fasting glucose, impaired glucose tolerance, insulin resistance, and type 1 diabetes mellitus, occur more commonly in patients with HT. These metabolic disturbances coexist in up to 50% of affected individuals [27]. Excessive weight gain is also reported by a subset of HT patients. Recent studies have demonstrated a correlation between obesity and HT, with antithyroid antibodies being more prevalent in obese individuals compared to those with normal body mass. Patients with HT typically present with a higher body mass index, increased waist-to-hip ratio, and greater fat mass [28]. Elevated levels of antithyroid antibodies, particularly anti-TPO Ab, correlate positively with the extent of endothelial damage. Chronic inflammation and immune system dysregulation contribute to reduced elasticity of the vascular walls, leading to arterial lumen narrowing and impaired blood flow. These vascular changes promote the development of atherosclerosis, increase the risk of cardiovascular diseases, and contribute to the occurrence of cerebrovascular events such as stroke [29].

Among others. HT can also be as a component of autoimmune polyglandular hypothyroidism syndromes like type 1, type 2 or immune dysregulation polyendocrinopaty enteropathy X-linked syndrome [30].

Several studies have shown that HT increases the risk of papillary thyroid cancer. In patients with papillary thyroid cancer, HT coexists in about 30%. It also affects, although to a lesser extent, the risk of follicular carcinoma. In contrast, medullary carcinoma is not more common in HT [2, 31]. Thyroid lymphomas are rare and can have many histopathological subtypes. Often, the first sign of thyroid lymphoma is a rapidly enlarging goiter, with enlarged or not lymph nodes. Lymphoid tissue not present in a healthy thyroid gland may follow chronic autoimmune inflammation. Most often, thyroid lymphoma is preceded by long-term other thyroid disease. HT leads to this lymphoma in about 0.5%. They mainly increase the risk of B-cell lymphoma, but can also affect T-cell lineage carcinogenesis [32].

Some studies indicate an increased risk of breast cancer in HT patients [33]. This results in the need for greater oncological vigilance in HT patients. Fear of increased cancer risk further lowers HRQOL. However, there are doubts as to whether HT actually predispose to the development of these cancers, or whether it is a coincidental occurrence of two fairly common diseases [34].

Mental disorders co-occurring with HT

Patients with HT are more likely to have neuropsychiatric symptoms, including fatigue, cognitive impairment ("brain fog"), memory impairment or impaired concentration. All of these symptoms can further decrease HRQOL [35].

HT also affects mood disorders, mainly depression and anxiety. In patients with depression, elevated levels of antithyroid antibodies are found in about 20%, while in the general population they are already found in only 5-10% [36].Depression is the most common psychiatric disorder comorbid with HT. It occurs about 6 times more often in patients with HT. In patients with depression, a positive correlation has been demonstrated with the presence of TPO Ab and decreased serotonin levels. The prevalence of depressive disorders in patients with HT is approximately 30–50% [37].

Depression in patients with HT is frequently characterized by atypical features or resistance to standard antidepressant therapy. Moreover, depressive disorders in this population are particularly prevalent among women during early pregnancy and the perinatal period [38]. The second most common psychiatric disorder coexisting with HT are anxiety disorders. Clinical research suggests that approximately 20% to 40% of individuals with HT experience symptoms consistent with anxiety disorders. The most common anxiety disorder in HT is obsessive-compulsive disorder, which may indicate their autoimmune pathogenesis.These symptoms show a positive correlation with the presence of TPO Ab. [39].

It is also more common to see patients with elevated TPO Ab levels in bipolar affective disorder (BD). Epidemiological data suggest that approximately 5–15% of patients with HT may have comorbid BD (bipolar disorder). The association between HT and BP is thought to be mediated by shared immunological and neuroendocrine pathways[40].

Another neurological disorder that can co-occur with HT is Hashimoto's encephalopathy (HE).

HE in the general population is estimated to be approximately 2 cases per 100,000 individuals. Among patients with autoimmune thyroiditis HE remains rare, affecting fewer than 1% of cases. The condition occurs significantly more often in women, who comprise approximately 80% of reported cases. The typical age of onset is between the fourth and sixth decades of life. It is characterized by altered mental status, hallucinations, delusions and sometimes seizures, and coexists with high levels of antithyroid antibodies. The background of the disease is not fully understood, while studies to date indicate an autoimmune etiology related to vasculitis or other inflammatory process. The diagnosis is based on the previous exclusion of other causes of encephalopathy, including autoimmune encephalitis. Imaging studies of the brain and cerebrospinal fluid are normal or non-specific. The disease usually responds well to treatment with high-dose corticosteroids [41]. Recent literature increasingly reports clinical cases that are resistant to steroid therapy or where the use of corticosteroids is contraindicated. In such situations, alternative treatment options include azathioprine, cyclophosphamide, and intravenous immunoglobulin therapy [42].

Uzun et al. examined the mental state of patients with HT. The study used questionnaires: the Strengths and Difficulties Questionnaire (SDQ) and the Mindfulness Awareness Scale (MAAS). Higher TPO Ab titers correlated positively with the behavioral problems subscale of the Strengths and Difficulties Scale (SDQ), and the level of mindfulness was inversely correlated with higher levels of Tg Ab [43]. Coexisting somatic symptoms and other illnesses further exacerbate psychiatric symptoms and predispose to mood disorders in HT patients.

Causes of neurological disorders in patients with HT

Neurological and psychiatric symptoms in HT patients have led to a search for their causes in imaging studies and cerebrospinal fluid (CSF) examination.

Cognitive impairment can be caused by neuroinflammation and neurotransmitter imbalance e.g. L-glutamic acid.

Patients with these symptoms are often accompanied on neuroimaging studies by structural and functional changes in the brain, mainly around neurocognitive and emotional areas e.g. hippocampus [44].

Hardoy et al. showed that patients with HT and depressive disorders have reduced cerebral blood flow in certain areas of the brain on Single Photon Emission Computed Tomography (SPECT). Hypoperfusion was present in the frontal lobe, right temporal lobe and parietal lobe, but was absent in the left temporal lobe [45]. Dersch et al. investigated the intrathecal synthesis of antithyroid antibodies (ASI) in patients with HT and unipolar depression. Seropositive patients showed intrathecal synthesis of TPO Ab and, less frequently, Tg Ab in the CSF. Elevated ASIs are interesting biomarkers in neurological diseases, which may be a sign of central autoimmunity in these patients [46]. Increased ASI has also been described in Hashimoto's encephalopathy and schizophrenia. ASI is more frequent and in higher concentrations in Hashimoto's encephalopathy [47].

Treatments that may improve HRQOL

In symptomatic euthyroid patients with HT it is important to explore strategies to improve HRQOL. Regular physical activity is a positive factor influencing the course of the disease. [48].

In patients with HT, adherence to a nutritionally balanced diet, consistent with evidence-based dietary guidelines, may have a beneficial impact on HRQOL. The recommended dietary pattern should include high-quality proteins, complex carbohydrates, and polyunsaturated fatty acids. Sufficient intake of key micronutrients—particularly iodine, selenium, iron, and zinc—as well as vitamins B12, D, C, and E, is essential to support both thyroid function and overall metabolic health [49]. Lactose intolerance may coexist in some individuals; in such cases, a lactose-free diet may contribute to symptom relief and improved gastrointestinal tolerance. Given the increased prevalence of celiac disease and other gluten-related conditions in this population, screening should be considered, and in confirmed cases, strict adherence to a gluten-free diet is indicated. Several studies have suggested that a gluten-free diet may reduce the severity of symptoms, enhance intestinal absorption, and lower the required dosage of levothyroxine in patients with HT without concomitant celiac disease. However, despite these findings, there is currently insufficient high-quality evidence to support a generalized recommendation of a gluten-free diet in patients with HT alone.[50,51].

A number of papers have described the influence of the thyroid-gut axis on HT. Cesar et al. examined stool samples from female patients and showed increased Bacteroides and decreased Bifidobacterium in patients with HT. Zonulin was higher with HT, suggesting most leaky gut. Zonulin is a protein that regulates the permeability of substances from the intestines to the bloodstream.[52]. After correlating the results with dietary habits, it was shown that diet affects the microbiota and inflammation in the body. An anti-inflammatory diet, with restriction of simple carbohydrates, saturated fat or highly processed foods, is considered [53].

In some HT patients with persistent symptoms despite biochemical euthyroidism, thyroidectomy may be considered. In Thatipamal's et al. study, 19 patients underwent thyroid removal. In the aforementioned study, 87.5% of the participants reported that they were satisfied with the surgery [54]. Similary, in a study by Memeh et al., it was showed that total thyroidectomy was the optimal procedure with thyroiditis and ongoing symptoms despite euthyroidism. In the above paper, the authors also counted the cost of therapy; a more cost-effective therapy in euthyroid patients with persistent symptoms is thyroidectomy than conservative therapy alone [55]. In the study by Hoff et al., 154 euthyroid patients underwent total thyroidectomy and were followed up 18 months after the procedure. There was an improvement in overall health, a reduction in TPOAb levels, but at the expense of severe complications such as retrobulbar nerve palsy and hypoparathyroidism [56]. That is why thyroidectomy as a treatment option in HT, should be performed in specialized centers, and further research into this form of therapy is needed.

Conclusions

HT is a multifaceted autoimmune disease that impacts patients' quality of life beyond thyroid hormone levels. Although it remains the most common cause of hypothyroidism in developed countries, studies show that even euthyroid individuals with HT often experience reduced physical and psychological well-being. This is likely due to its broad range of symptoms, frequent comorbidities including metabolic, psychiatric, and other autoimmune disorders—and the often weak correlation between lab results and patient-reported symptoms.

Effective management requires a comprehensive, multidisciplinary approach that addresses hormonal balance, inflammation, mental health, and lifestyle factors. Emerging research into immune mechanisms, gut microbiota, and novel biomarkers (e.g., intrathecal thyroid antibody synthesis) offers promising insights into disease pathogenesis. In some patients with persistent symptoms despite optimal therapy, thyroidectomy may be beneficial, though it necessitates careful consideration.

Future progress will depend on rigorous clinical trials and deeper molecular understanding, which could lead to targeted, disease-modifying therapies and improved long-term outcomes.

Conflict of interest

The authors declare no conflict of interest.

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