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EXTRATHYROIDAL INFLUENCE OF HASHIMOTO'S THYROIDITIS – A LITERATURE REVIEW

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ABSTRACT

Hashimoto's thyroiditis (HT) is a chronic lymphocytic inflammation of thyroid gland. The incidence is estimated to be 5% in general population and is higher in women. Primary role in pathogenesis is given to two types of antibodies – anti-peroxidase (anti-TPO) antibodies and anti-thyroglobulin (anti-TG) antibodies that lead to chronic lymphocyte mediated inflammation and thyroid follicular cell destruction. Clinically it usually leads to hypothyroidism and its symptoms like weight gain, cold intolerance, bradycardia and fatigue. As chronic inflammation HT leads to elevated levels of inflammatory factors like Tumor Necrosis Factor α (TNF-α), Interferon-γ (IFN- γ) and high sensitivity C-reactive protein (hs-CRP). Levels of anti-TPO and anti-TG were positively correlated with levels of TNF-α and IFN-γ and severity of symptoms, while they were negatively correlated with general health and vitality score. The overall cancer risk in patients is increased, but HT is negatively associated with primary tumor size of 4 cm or greater, extranodal extension and distant metastasis in Papillary thyroid carcinoma. Hashimoto's thyroiditis may also have impact on the course of migraine by more migraine days monthly and higher risk of chronic migraine. Level of anti-TPO antibodies is a significant independent risk factor of depressive disorder, while negativity of anti-TG was correlated with lower anxiety levels. That finding suggests that autoantibodies are more important than thyroid hormone levels in pathogenesis of psychiatric disorders. Patients with HT also report lower health-related quality of life.

KEYWORDS

Hashimoto's Thyroiditis, Papillary Thyroid Cancer, Anxiety Disorder, Depressive Disorder, Migraine

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Introduction

Hashimoto's thyroiditis (HT) also called chronic lymphocytic thyroiditis, is an autoimmune condition of thyroid gland. Recently it has been included in a group of autoimmune thyroid disease (AITD) next to Graves' disease. Chronic lymphocytic thyroiditis is quite a common condition – the prevalence is estimated to be 5% in general population and is higher in women. Prevalence increases with age and with a diagnosis of another autoimmune disease like connective tissue diseases, celiac disease, pernicious anemia and myasthenia gravis. HT can also cooccur with other autoimmune endocrinopathies like Addison's disease and type 1 diabetes mellitus constituting autoimmune polyendocrine syndromes (APS).

Environmental factors like infections, cigarette smoking, chemicals exposure may trigger development of HT in genetically predisposed patients. Microbiome composition with decreased Bifidobacterium and Lactobacillus and increased Bacteroides fragilis are also associated with thyroiditis. [7] In its pathogenesis leading role is given to two types of antibodies – anti-peroxidase (anti-TPO) antibodies and anti-thyroglobulin (anti-TG) antibodies that lead to chronic lymphocyte mediated inflammation and thyroid follicular cell destruction. Thyroid gland as a main organ controlling metabolism affects many organs, so its dysfunction disrupts general homeostasis that leads to diverse manifestations. Clinically it usually leads to hypothyroidism and its symptoms like weight gain, cold intolerance, bradycardia, anemia, constipation, dry and yellowish skin, hair loss, myxedema, inability to concentrate, fatigue and depression, but also it can temporarily lead to hyperthyroidism (Hashitoxicosis) or does not affect thyroid function at all. Patients with hypothyroidism and HT need a replacement therapy with Levothyroxine (L-T4) to even out levels of thyroid hormones (FT3 and FT4) and thyrotropin (TSH). Hashimoto's thyroiditis as an autoimmune condition can enhance other disease susceptibility. As chronic inflammation HT leads to elevated levels of inflammatory factors like Tumor Necrosis Factor α (TNF-α), Interferon-γ (IFN- γ) and high sensitivity C-reactive protein (hs-CRP). [8]

Methodology

A literature search was conducted in the PubMed database. Searched articles were published between January 2020 and March 2026. The keywords used in search: Hashimoto's thyroiditis, cancer, migraine, depressive disorder, anxiety disorder. In the first stage 50 studies were identified, after screening 11 studies that met inclusion criteria were chosen. The inclusion criteria were original studies, cohort studies and meta-analyses. Case reports and studies lacking full text were excluded. Additional 8 studies were used to provide comprehensive background and context.

Hashimoto's thyroiditis and inflammation

J. Li et al. [8] studied a group of 108 patients with HT and 57 healthy patients. Inclusion criteria for HT group were age between 18 and 60 years, diagnosis made by at least one endocrinologist based on a clinical parameters and ultrasonography and positive anti-TPO or anti-TG with euthyroid status. Healthy patients were age and gender matched and did not have any thyroid disease. Both groups did not have any other autoimmune disease and did not use anti-inflammatory and immunosuppressant drugs. Blood was collected from participants to measure serum levels of anti-TPO, anti-TG, TSH, ft3, ft4, interleukins (IL-4, IL-6, IL-10, IL-17A, TNF-α, IFN-γ), biomarkers of liver and kidney function and lipid profiles. Participants filled SF-36 to measure health-related life quality. Severity of multiple extrathyroidal manifestations was determined with the Hashimoto's Thyroiditis Symptom Questionnaire, that has 8 domains related to respiratory, circulatory, digestive, endocrine, reproductive, mucocutaneous, movement and neuropsychiatric. Total of 49 symptoms scored from 0 (no symptom) to 10 (symptom seriously affecting life quality). Results showed that FT3, FT4 and TSH levels were similar in both groups. As expected, anti-TPO and anti-TG were remarkably higher in HT patients than in controls. Lipid metabolism biomarkers, pro-inflammatory factors (TNF-α, IFN-γ), hepatic function index and hsCRP were significantly higher in HT patients compared to controls, while all of them were still within normal range. Health-related life quality was significantly decreased in HT patients and despite being euthyroid HT patients they had multiple serious symptoms (constipation, diarrhea, chest tightness, chilliness, weight gain, forgetfulness, anxiety, depression, insomnia, fatigue, joint pain, dry skin, pruritus, hair loss). Levels of anti-TPO and anti-TG were positively correlated with levels of TNF-α and IFN-γ and severity of symptoms, while they were negatively correlated with general health and vitality scores. [8]

Hashimoto's thyroiditis and gut microbiota

Nowadays many articles focus on gut microbiota as a key factor in pathogenesis of many diseases and as a possible field for new treatments. There is a lot of evidence that intestinal dysbiosis, bacterial overgrowth and increased intestinal permeability (leaky gut) promote HT development. Commensal gut bacteria influence immunity by generated metabolites that can activate proinflammatory or anti-inflammatory processes. Gut microbiota regulates iodine uptake and levothyroxine bioavailability. It also can influence hypothalamus-pituitary axis and consequently TSH secretion. The short-chain fatty acids (SCFAs), that are metabolite from anaerobic microbiota fermentation are energy source for enterocytes and together with thyroid hormones induce differentiation of enterocytes and strengthen the epithelial barrier integrity. [3, 13, 19] Bifidobacterium and Lactobacillus are beneficial and produce SCFAs, while Bacteroides, Proteobacteria and Actinobacteria are harmful and disrupt balance of SCFAs, by decreasing their production and promoting inflammation. There is a positive correlation between SCFA and number of regulatory T cells, which mediate immune tolerance and lower concentrations of pro-inflammatory Th-17 cells. Deterioration of the intestinal barrier allows antigens to enter the circulation and activate immune system by stimulating the release of pro-inflammatory cytokines like TNF-α and IL-6, that can promote chronic inflammation. [13] Studies found that Lactobacillus, Bifidobacterium and Helicobacter pylori can induce thyroid autoimmune process, because bacterial proteins are structurally homologic with human thyroid globulin (TG) and thyroid peroxidase (TPO) and can selectively bind human anti-TPO and anti-TG antibodies. [19]

LCF. Cayres et al. [3] studied a group of 40 HT patients and 53 healthy controls. Blood, stool samples and food frequency questionnaire (FFQ) were collected. Patients with HT had increase in the relative expression units (REUs) of Bacteroides species and a significant decrease in the REUs of Bifidobacterium species. There were no significant differences in REUs of Clostridium coccoides, Clostridium coccoides-Eubacteria rectale, Clostridium leptum, Lactobacillus, Prevotella and Roseburia species between HT group and a control group. There was a positive correlation between the REUs of Clostridium coccoides and Clostridium coccoides-Eubacteria rectale and TSH levels. The REUs of Roseburia species inversely correlated with FT4 levels. There was also a positive correlation between Clostridium coccoides and duration of HT.

There was no correlation between gut microbes and levels of anti-TPO and anti-TG. A significant difference was found in the REUs of Lactobacillus between patients who supplemented levothyroxine and those who did not (0,8065 REU/200 mg stool vs. 47,73 REU/200 mg stool). To find out if patients with HT had leaky gut serum zonulin was evaluated. The zonulin serum concentrations were significantly increased in patients with HT (mean 30,92 ± 2,36 ng/ml) than in controls (mean 19,01 ± 2,98 ng/ml). Zonulin concentrations positively correlated with IFN-γ levels and inversely correlated with IL-2 concentrations in patients with HT. [3]

Changes in composition of a gut microbiota in HT promote growth of harmful Bacteroides with regression in number of commensal Bifidobacterium that results in disruption of intestinal barrier and chronic inflammation.

Hashimoto's thyroiditis and cancer

Papillary thyroid cancer (PTC) is the most common thyroid malignancy and has a favorable prognosis. Treatment of PTC depends on risk of mortality and recurrence. Some characteristics that worsen prognosis are older age, large primary tumor size, extrathyroidal extension (ETE), lymph node metastasis (LNM) and distant metastasis. [17]

It is reported that there is an association between Hashimoto's thyroiditis and papillary thyroid carcinoma [12, 16, 18] and between HT and thyroid lymphoma (TL). [12] Thyroid lymphoma includes extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (EMZL), diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) and may arise from a background of chronic inflammation due to an autoimmune disorder like HT. Longlasting inflammation enables evolution of often autoreactive B cells with their clonal expansion and eventual malignant transformation. [15] HT as chronic inflammation may contribute to cancer progression by providing inflammatory cells. Also, there are common genetic factors associated with both conditions. Elevated levels of anti-TPO correlate with multifocality of PTC. Anti-TPO acts as a protective factor of PTC progression, while anti-TG tends to promote progression of PTC. [18]

S. Xu et al. [17] conducted a cohort study using retrospective data from 2001 to 2014 about patients aged 18 to 75 who underwent thyroidectomy for PTC. Information about age, sex, preoperative antibody levels, tumor characteristics and treatment were received from medical records. Presence of Hashimoto's thyroiditis was determined by postoperative histopathology report that included diffuse lymphocytic and plasma cell infiltrate, oxyphilic cells, formation of lymphoid follicles and reactive germinal centers in a distant region from the PTC site. Levels of anti-TG and anti-TPO antibodies were measured within 30 days before surgery. Surgical procedures included lobectomy and total thyroidectomy. Postoperative pathologic examination included information about primary tumor size, ETE, gross ETE and LNM. Distant metastases were assessed in computed tomography (CT) or emission computed tomography. After surgery treatment consisted of thyrotropin suppression and radioactive iodine (RAI) ablation. 9210 patients with mean age of 43,6 years were included in the analysis. Prevalence of coexistent HT was 19% (1751 cases). Patients with coexisting HT were younger with mean age of 41,6 years compared to non-HT patients with age of 44,1 years. Also the group with HT had more women (92% vs 71%). Patients with HT had a smaller mean primary tumor size (1,2 cm vs 1,5 cm), fewer metastatic nodes (mean, 4 vs 5) and a low lymph node ratio (mean, 0,24 vs 0,30). Also, they were less likely to have ETE (38% vs 43%), lateral neck metastasis (23% vs 28%), extranodal extension (16% vs 29%), more than 3 cm of nodal metastasis (1% vs 4%) or distant metastasis (0,1% vs 1,1%). HT was negatively associated with primary tumor size of 4 cm or greater, extranodal extension, gross ETE and distant metastasis. No significant difference in follow-up time was observed between patients with or without HT (median, 84 months vs 85 months). PTC-related death involved 131 patients of which 2 had HT. Based on Kaplan-Meier curves patients with HT had significantly higher 10-year disease-specific survival rates than patients without HT (99,9% vs. 96,6%). Hashimoto's thyroiditis was associated with decreased PTC-related mortality in patients 45 years or older and in patients who underwent total thyroidectomy. In a group of patients younger than 45 years and those after a lobectomy with HT there was no PTC-related mortality. HT was also negatively associated with structural recurrence and had a greater 10-year recurrence-free survival. Pathologically confirmed HT (with or without antibodies) was correlated with lower PTC-related mortality rates. [17]

R. Li et al. [9] analyzed a cohort of 10329 patients with PTC who underwent thyroidectomy because of it. The Group with HT consisted of 992 patients. HT group was significantly younger, had higher rates of clinical N1a and N1b disease and had more frequent bilateral thyroidectomy than non-HT group. Patients with HT had lower rates of extrathyroidal extension, reduced multifocality, decreased bilateral carcinoma involvement, higher number of central lymph node dissection and greater proportion of pathological N0 stage tumors. [9]

Another large study performed by H. Huang et al. [6] on 9829 patients with PTC after surgical treatment. Among them 2389 patients had histopathologically diagnosed HT. Patients with HT were younger, had larger primary tumors and multifocal and bilateral tumors compared to non-HT patients. They also had higher rate of central lymph node metastasis, were less likely to have extrathyroidal and extranodal extension. Rates of distant metastasis and lymphovascular invasion were comparable in both groups. [6]

In another retrospective study A. Harmantepe et al. [4] investigated effect of Hashimoto's thyroiditis on PTC tumor progression. They chose 356 patients who underwent thyroidectomy and had histopathologically confirmed PTC diagnosis. Presence of chronic lymphocytic thyroiditis (CLT) in histopathologic report was an inclusion criterion to HT (+) group, lack of CLT included patients in HT (-) group. Group with HT (+) consisted of 111 patients (31,2%) and HT (-) group of 245 (68,8%) patients. There was no significant difference between both groups in tumor diameter, number of focuses, lymphovascular invasion and capsule invasion. Patients with HT had significantly higher rates of lymph node metastases and significantly lower rate of multifocality than patients without HT. [4]

X. Hu et al. [5] made meta-analysis of 23 case-controls and cohorts that collected data from 10 regions and included 12917 cases and 60509 control patients and investigated association between Hashimoto's thyroiditis and cancer. Analysis showed that patients with HT had increased risk of developing thyroid cancer, breast cancer, lung cancer, digestive system (including gastric, bowel, hepatobiliary) cancers, urogenital (including uterus, cervical, ovary, prostate, bladder, kidney) cancers and prolactinoma than patients without HT. The correlation between Hashimoto's thyroiditis and carcinogenesis is still unclear and needs further investigation with consideration of variables like TSH levels, lifestyle, region and ethnicity. [5]

Studies performed on larger patient groups [6, 9, 17] show that HT might have a protective factor against lymph node metastasis in PTC, while study performed on a much smaller group [4] shows that patients with HT had more lymph node metastasis than patients without HT.

Hashimoto's thyroiditis and migraine

Migraine is a second world cause of disability and first in young women. It affects 18% of women, 6% of men and chronic migraine affects 2% of global population. [1] It is linked to psychiatric, cardiovascular, hormonal and pain disorders. Studies showed that there is a bidirectional relationship between migraine and hypothyroidism and systemic autoimmune diseases. [11]

M. Nowaczewska et al. [11] retrospectively investigated the prevalence of HT among migraine patients. Patients were included if they had diagnosed migraine with or without aura. Patients with hypothyroidism were diagnosed by an endocrinologist and were treated with a stable dose of levothyroxine. Patients with HT were also diagnosed by an endocrinologist based on a thyroid ultrasound and high level of anti-TPO. 928 eligible patients were chosen, 592 with episodic migraine and 336 with chronic migraine. 106 patients were diagnosed with HT, 148 were diagnosed with hypothyroidism and 84 had both diagnoses, only 6 had hyperthyroidism. Thyroid diseases were the most frequent migraine comorbidities. Patients with HT were older (39,56 vs. 35,64 years) and had overall longer duration of migraine (19,68 vs. 15,52 years). They also developed more frequently chronic migraine and had more monthly migraine days. Patients with HT responded less frequently to topiramate and drank more caffeine and had a history of COVID-19 infection more frequently than patients without HT. Those results allow consideration that migraine and HT are comorbidities and that HT can cause migraine chronification. [11]

Hashimoto's thyroiditis and mental health

Clinical studies link the high levels of thyroid autoantibodies and psychiatric disorders regardless of the levels of TSH, FT3 and FT4. Also, it is stated that psychiatric disorders can arise from autoimmune diseases.

E. Aydin et al. in 2023 [2] studied a group of adolescent girls to investigate the link between autoimmune thyroid disease and psychiatric symptoms. The control group included 41 healthy girls aged 12 to 18 with normal thyroid function, negative autoantibodies and non-pathologic thyroid ultrasonography image. For the study group there were chosen 41 participants with normal levels of TSH and FT4 but had tested positive for anti-TPO and anti-TG and had ultrasonography image of thyroiditis and did not supplement Levothyroxine to level out thyroid hormone levels. Chronic diseases other than HT, medication use and physical disability were excluding criteria for this study. During the study both groups blood samples were collected to assess the levels of glycemia, insulin, FT4, TSH, anti-TPO, anti-TG, cortisol and value of homeostatic model assessment-insulin resistance (HOMA-IR). Then both groups underwent a psychiatrist evaluation – interview with a child and adolescent psychiatrist, Children's Depression Inventory (CDI) survey and Screen for Child Anxiety-

Related Emotional Disorders (SCARED). CDI test is a tool that measures severity of depression and the highest score on the scale is 54, while score 25 and higher out of 41 scores in total reached in SCARED test is a warning sign for anxiety disorder. During the psychiatrist evaluation, doctor conducted the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL), which consists of unstructured interviews and checked presence of estimated 200 symptoms. If there were positive symptoms, interviews were conducted to validate the diagnosis of affective, psychotic, anxiety, behavioral, drug abuse and other disorders. The results showed that the study group measured TSH level of average 2,1 mIU/mL and had statistically significantly higher levels of TSH than the control group which measured TSH level of average 1,7 mIU/mL, but both groups were in normal reference laboratory range. The psychiatric evaluation showed that median CDI was similar in both groups, but an average SCARED score was significantly higher in a study group than the control group. In both study and control groups 54,9% of patients reported that they suffered panic attacks. There was a major difference between groups' answers about social anxiety, 53,7% of the study group patients and 26,8% of the control group patients reported that they suffered that affliction. In the fields of panic attacks and separation anxiety the scores in the study group were higher but not significant. The Number of present depressive disorders (29,3%), generalized anxiety disorder (24,4%) and social phobia (31,7%) was meaningfully higher in a group with HT but due to an inconsiderable research group other diagnoses like separation anxiety, obsessive-compulsive disorder, panic disorder and attention deficit hyperactivity disorder were not statistically higher in the study group. As expected, comparison of the study and control groups with and without symptoms showed the difference was statistically significant between CDI and SCARED scores in all groups. No statistically significant correlations between levels of anti-TPO and anti-TG and the CDI and SCARED scores were found in the research group. Multifactor analysis pointed out that the level of anti-TPO antibodies was a significant independent risk factor of depressive disorder. That finding implies that autoantibodies are more important than thyroid hormone levels in pathogenesis of psychiatric disorders. [2]

Z. Tian et al. in 2025 [14] searched the NHANES database which is a national report evaluating health and nutritional status of U.S. population. Database is publicly accessible. The data analyzed was from three cycles 2007-2008, 2009-2010 and 2011-2012 and consisted of information on depression and possible thyroid indicators like autoantibodies levels. Data about the depression were retrieved from Patient Health Questionnaire-9 (PHQ-9) that used a two-week period of time to describe nine basal symptoms on a 4-point scale (0 as "not at all" and 3 as "nearly every day"). The symptoms were anhedonia, depressed mood, sleep disturbances, fatigue, appetite changes, feeling of low self-esteem or failure, concentration difficulties, psychomotor disturbances and suicidal ideation. The Range of points is from 0 to 27 with a cut-off score of 10 and above. Categories based on a score of PHQ-9 are: no depression (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19) and severe depression (20-27). Collected thyroid-related indicators were anti-TPO, anti-TG, FT3, FT4, TSH and Thyroglobulin (TG). Based on a reference cutoffs, euthyroid patients were divided into four groups: a control group with both negative antibodies, the first study group with only positive anti-TPO, the second study group with only positive anti-TG and the third study group with both positive antibodies. Additionally, other variables like age, sex, ethnicity, education level, marital status, smoking, alcohol use, history of diabetes mellitus and hypertension were analyzed in this study. Laboratory results were divided into two groups. The first one, the clinical and metabolic markers consisted of body mass index (BMI), triglycerides, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total cholesterol, glycohemoglobin, fasting glucose, insulin, creatinine and uric acid, while the second one, nutritional and micronutrient status consisted of iodine as an important element for thyroid function. The patient groups consisted of: the control group - 2530 patients, the anti-TPO group – 171 patients, the anti-TG group – 88 patients and the group with anti-TPO and anti-TG – 108 patients. Even though all patients were euthyroid, the three groups with positive thyroid antibodies had significantly higher TSH levels and significantly lower thyroid hormones levels than the control group. The results showed that there was no significant difference between the four considered groups in depression levels, based on a PHQ-9 depression score. A further comparison of thyroid-related indicators showed that anti-TG were negatively associated with depressive symptoms and there was also a significant correlation between lower FT3 levels within the normal range and more severe depressive symptoms. Other markers like TSH, FT4 and TG levels did not show any significant correlation with PHQ-9 scores. The analyses demonstrated that males had lower PHQ-9 scores than women, that living with a partner was associated with reduced depressive symptoms, age was negatively associated with PHQ-9 scores, and that smoking, diabetes mellitus, BMI and insulin levels were linked to higher PHQ-9 scores. [14]

G. Martino et al. in 2021 [10] studied alexithymia, emotional distress and perceived Quality of Life in a small group of euthyroid patients. As a control group they chose patients with nodular goiter taking Levothyroxine or antithyroid medication and patients on a Levothyroxine- replacement therapy after thyroidectomy. They stayed euthyroid and had been tested negative for the presence of anti-TPO and anti-TG autoantibodies. Those with goiter also had normal thyroid echogenicity in an ultrasound image and those after thyroidectomy had benign nodules and absence of lymphocytic thyroiditis in a histopathology report. The study group had been diagnosed with Hashimoto's thyroiditis based on a positive result of thyroid antibodies and/or hypoechoic and inhomogeneous echotexture of thyroid in ultrasound pointing to an autoimmune thyroiditis. All of them were on Levothyroxine replacement therapy. The exclusion criteria were age under 18, neuropsychiatric disturbances according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* and TSH level ≤0.4 or ≥4.0 mU/L. The control group numbered 16 and study group 21 patients. Both groups underwent blood tests for TSH, FT4 and thyroid autoantibodies levels. Also, data about gender, age, education level and BMI were collected. All the patients had a psychological assessment consisting of psychological interview and psychodiagnostics examination based on DSM-5. To measure alexithymia traits the Italian version of the Toronto Alexithymia Scale (TAS-20) was used. The questionnaire had 20 items evaluated on a five-point scale and indicated frank alexithymia, possible alexithymia and normality. Depressive symptoms were measured with The Beck Depression Inventory, second edition (BDI-II), which consists of 21 items scored on a four-point scale with the total of 63 to detect somatic-affective (e.g. loss of interest, loss of energy) and cognitive depressive symptoms (e.g. self-dislike, pessimism). Total scores indicate minimal, mild, moderate and severe depression. Anxiety symptoms were measured by The Hamilton Anxiety Rating Scale (HAM-A) detecting psychological (e.g. fears, tension) and somatic symptoms (e.g. gastrointestinal, cardiac). It consists of 14 items assessed on a five-point scale with a total of 30. Total scores point out minimal, mild, moderate and severe anxiety. Patients perceived Health-Related Quality of Life (HRQoL) was measured with the Italian version of the Health Survey Short-Form 36 (SF-36). It uses eight life domains to assess two components – physical component summary (PCS) and mental component summary (MCS). Both groups consisted of more women. Age and BMI were similar in study and control groups. There was no difference in education level in both groups. TSH and FT4 levels did not differ in both groups. Among 21 patients with HT 14 had positive both thyroid antibodies, 6 patients had negative both antibodies and one patient had positive only TG antibody. 19 of 21 patients had typical features of HT. All the control and study group patients had mild depression. 17 patients were alexithymic, 16 were possibly alexithymic and 4 were not alexithymic. Both groups were similar regarding alexithymia. Both groups had also generally lower Health-Related Quality of Life. The HT group had a mean HAM-A score >17, while the control groups' mean score was >24, overall anxiety levels were from moderate to severe. There was no significant difference between the study and the control group in all assessed psychological factors. Among the study group negativity of anti-TG was correlated with lower anxiety levels, while anti-TPO positivity was correlated with higher anxiety levels. The patients with positive anti-TG or positive anti-TPO had higher scores in a somatic component of HAM-A scores than anti-TG negative or anti- TPO negative patients. There was no association between ultrasound image of thyroid and the psychometric tests. [10]

The aforementioned studies suggest that depressive disorder and anxiety might be correlated more with thyroid antibodies rather than with thyroid hormones. Presence of anti-TPO and anti-TG are positively correlated with anxiety, somatic component of anxiety and depression.

Discussion

The presented studies show that Hashimoto's thyroiditis has an impact on many aspects of organism functioning. Firstly, as an autoimmune condition it promotes a chronic inflammation mediated mostly by TNF-α and IFN-γ, which are positively correlated with levels of TPO and TG antibodies. [8] Gut microbiota changes in favor of harmful Bacteroides, Proteobacteria and Actinobacteria, that decrease production of short chain fatty acids (SCFAs), that are crucial for the properly functioning intestinal barrier. As a result, increased intestinal permeability allows antigens to enter the circulation and induce chronic inflammation mediated by TNF-α and IL-6. The advantage of harmful bacteria on commensal Bifidobacterium and Lactobacillus results in dysregulated iodine uptake, levothyroxine availability and immune tolerance. [3, 13, 19] Gut microbiota seems to be one of the factors contributing to thyroid dysfunction in Hashimoto's thyroiditis, which needs to be further investigated especially considering the region, diet and other factors influencing microbiome. Overall cancer risk in HT patients seems to be greater than in patients without thyroid disease. [5] On the one hand, studies performed on groups bigger than 9 000 participants show that HT lowers the risk of lymph node

metastasis, distant metastasis and is correlated with smaller primary tumor size and with lower risk of recurrence in PTC [6, 9, 17, 18], but on the other hand, smaller studies show that patients with HT had more lymph node metastasis and did not differ from patients without HT in tumor size [4]. This raises the question whether patients with HT should be mandatorily screened for cancer. Hashimoto's thyroiditis as the chronic condition has a huge impact on mental health, it increases the risk of depressive and anxiety disorders and due to many symptoms and comorbidities patients have lower health-related quality of life. [2, 10, 14] Although conclusions of the works about mental health are similar, there was a disadvantage as to a small number of participants in two of those studies [2, 10]. The presented evidence should be considered in clinical practice as guidance to holistic care for patients with Hashimoto's thyroiditis.

Conclusions

Hashimoto's thyroiditis promotes chronic inflammation, increases risk of depressive and anxiety disorders and by multiple symptoms lowers quality of life. Patients with HT have an increased risk of migraine chronification. They also have an increased risk of developing a papillary thyroid cancer. HT may improve prognosis in papillary thyroid cancer. It also leads to deterioration of intestinal barrier, which also promotes inflammation.

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