



The importance of gluten exclusion in the management of Hashimoto's thyroiditis

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

Ihnatowicz P, Wątor P, Drywień ME. The importance of gluten exclusion in the management of Hashimoto's thyroiditis. *Ann Agric Environ Med*. doi: 10.26444/aaem/136523

Abstract

Introduction and objective. There is a growing interest in a gluten-free diet (GFD) in the management of various autoimmune diseases, including Hashimoto's thyroiditis (HT). Even medical professionals claim that gluten elimination may improve a patient's treatment. Some studies suggest a relationship between gluten intake and HT development or progression. The aim of the study was to analyze and describe available knowledge regarding the effect of gluten or a gluten-free diet on thyroid autoimmunity in HT with or without celiac disease.

Brief description of the state of knowledge. Potentially applicable records were obtained through review and analysis of the PUBMED (MEDLINE) and Google Scholar database by using the following phrases: 'hypothyroidism gluten', 'Hashimoto gluten' and 'thyroiditis gluten'. If a record focused on the subject by title and abstract, the full paper was screened. Authors' scientific achievements and references of eligible records were screened for possibly omitted studies. The review was focused only on human studies.

Discussion. Gluten exclusion might increase the risk of HT development because of the potential nutritional deficiencies related to the low quality of gluten-free products. Gluten intake from crops grown on selenium-depleted soil increases the risk of HT development. Only a few studies suggest that GFD would be beneficial for HT patients, even without the coexistence of CD. The strongest connection between gluten intake and thyroid destruction seems to be based on a mechanism of molecular mimicry between gut and thyroid tissue transglutaminase.

Conclusions. Studies conducted so far do not support the claim that HT patients should eliminate gluten from their diet. In view of the limited number of studies, with major limitations and ambiguous results, a gluten-free diet is not recommended.

Key words

hypothyroidism, Hashimoto's thyroiditis, gluten, thyroid peroxidase antibodies, thyroid functions

INTRODUCTION

Gluten is a common name for the group of proteins that are found in wheat, barley, rye, and contaminated oat-products. Because it is an autogenous antigen in celiac disease (CD), those patients must eliminate gluten from their diet to avoid autoimmune reactions [1]; however, 'pure oat' is tolerated by most of CD patients [2]. The common characteristic of the disease is the presence of antibodies directed against immunogenic gliadin peptides, as well as tissue transglutaminase itself [1]. However, a gluten-free diet (GFD) is quite difficult to follow and it contributes to the potential risk of nutritional deficiencies and insufficient intake of fibre [3, 4, 5]. It has been reported that people on GFD consume an inadequate amount of vitamins B and C, folates, iron, zinc, and magnesium (Mg). Especially for the latter, a GFD may deteriorate Mg deficiency and constrict HT therapy. This might be specifically in the case of a mitochondrial background of the disease in which Mg supplementation was found to be therapeutic [6, 7, 8]. Moreover, gluten-free products may have a higher glycaemic load and index than those containing gluten. In 2018, the Polish experts from the POLSPEN group stated their position

about the recommendation of GFD in HT. Given the fact that the aspect of the importance of gluten elimination in HT merits a more explicit discussion than in their statement, this review focuses particularly on this matter.

HT is also an autoimmune disease, the common characteristics of which result from the infiltration into the thyroid gland by lymphocytes and the production of antibodies directed against thyroid peroxidase (anti-TPO), thyroglobulin (anti-TG) and thyrotropin receptor (TRAb, in only ~10% of patients) [1]. Unlike CD, no food compound consumption triggers an immune response in HT. Among the nutritional risk factors for the development of HT are iodine deficiency and excess, selenium and vitamin D deficiency, but not gluten intake [9]. Selenium (Se) seems to be one of the most important nutritional factors affecting thyroid metabolism and the risk of autoimmunity development. Despite that, the thyroid gland is well supplied with Se, even at a deficiency state [10] a low intake of it significantly increases the risk of HT incidence [11]. The reason is that Se is a part of multiple selenoproteins associated with immune function and the thyroid gland. They are iodothyronine deiodinases responsible for thyroid hormones synthesis and glutathione peroxidases implicated in antioxidant defence of thyrocyte from hydrogen peroxide. The latter is naturally produced as a byproduct during thyroid hormones production and may cause oxidative damage and cell death. Thus, Se supplementation trials have been successful in HT,

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Received: 16.03.2021; accepted: 10.05.2021; first published: 28.05.2021

and Se deficiency is a relevant risk factor of HT, although studies are inconclusive [10]. Se content in foodstuffs reflects the Se content in the soil; therefore, crops, cereal, and gluten-containing products may be either an important source of Se, or the cause of its deficiency. Thus, gluten intake may be associated with HT incidence dependent of the Se content of food products included in the diet [11].

Moderate alcohol consumption is also a protective factor for hypothyroidism with no difference between wine and beer. Although the mechanism responsible is still not known and studies indicate only an association, such a finding is supported by several studies. Alcohol alters the function of either natural cell killers or both Th1- and Th2-mediated immunity [12, 13]. But there is also a possibility that it is caused by an increased Se intake with alcohol products. Moreover, brewing yeast increases Se bioavailability as it biotransforms inorganic sodium selenite to its bioactive organic form [14]. In genetically predisposed individuals, exposure to nutritional and environmental factors, such as nutrients excess or deficiency, stress, smoking, infections and medication, develop autoimmune HT. Both CD and HT share common risk factors, among them, a genetic background has been proved to be significant [9].

An interesting mechanism of action linking gluten intake in celiac patients with a higher risk of thyroid autoimmunity development is molecular mimicry between gut and thyroid tissue transglutaminase. In celiac disease, this protein is a CD-related autoantibody [15], except that other possible causes connecting CD with HT are deficiencies in nutrients caused by disrupted gastrointestinal health or deficient GFD. Some of the nutrients are necessary for thyroid function, and thus might be a cause of higher HT incidence in CD patients.

Most studies have focused on the incidence of both diseases and the impact of GFD. Prior to the preparation of the current review, only two control studies had been performed on a gluten exclusion diet in HT patients who had not been diagnosed as CD patients. The obtained results support the claim that GFD might be helpful in HT disease, at least in the studied population. Additionally, in the last years only three case-study surveys have been published. The strongest limitation of these studies is that gluten exclusion is a part of an integrative approach, and it cannot be concluded that GFD had any effect on the patient's outcomes. Nevertheless, because of the literature gap in this area, it was decided to include those papers in the present review.

The described scientific knowledge indicates whether a GFD may be beneficial for thyroid function and thyroid autoimmunity in HT with or without CD. The coexistence of both diseases and potential causes were studied. For the current literature review, the following phrases were used: 'hypothyroidism gluten', 'Hashimoto gluten' and 'thyroiditis gluten' in the Google Scholar scientific browser and National Library of Medicine PubMed until November 2020. To increase the scope of the revised document and to avoid the possibility of omitting papers, both the scientific achievements of all authors and references in their publications were included. The authors focused only on human studies. Because of the lack of sufficient studies done on the subject, the current review is not a systematic review and does not include all studies on the subject. A total of found 64 papers were found in which HT patients were studied for prevalence of CD titers, or CD patients for antithyroid titers. In some of those papers, the effect of gluten exclusion was studied.

Most of the studies were observational, of which only a few were case reports on HT patients in which GFD was a part of a broader medical intervention. Two are described in detail in the presented review to indicate a possible dietary/interventional approach to HT patients. There were also only two controlled studies on the subject, which are described later in the review, while other articles studied the effect of GFD on thyroid autoimmunity. It was not considered necessary to include all the studies collected for this review, and to prevent any bias, the studies with extreme results have been described, taking into consideration studies focused only on few patients as not valuable for description in the paper. A review of the latest studies is included at the end of the presented review (Tab. 3, 4).

Celiac disease and Hashimoto's thyroiditis. HT is the most common autoimmune disease concurring with CD. Both diseases have a significant proportion of the same risk factors but the most significant is the genetic background [9]. One of the autoantibodies produced in CD is the intestine tissue transglutaminase (tTG2) which deaminates gliadin, hence the measurement of its level is used for the diagnosis [1]. Due to the presence of the tTG2 in tissues other than intestinal, autoimmune cross-reactions with other tissues are possible. This enzyme is also found in the thyroid gland and it was suggested that it is one of the reasons for CD patients becoming more prone to HT, a hypothesis that was confirmed by the immunofluorescence study by Naiyer et al. [15] in which indirect staining of follicular cells and the extracellular matrix of the thyroid have bound anti-tTG2 antibodies. Which suggests that CD patients with positive anti-tTG titers may have an increased risk of developing hypothyroidism due to an autoimmune cross-reactivity [15]. On the other hand, the results of intestinal biopsies from HT patients indicate a higher frequency of CD in comparison with healthy participants, particularly in the case of children. In a meta-analysis, in which both autoimmune thyroid diseases, HT and Graves-Basedow disease were included, the CD was diagnosed in one out of 62 patients [16]. The authors indicated that thyroid autoimmune patients should be examined for CD comorbidity [16], which is consistent with the recommendations of the European Society for Gastroenterology, Hepatology and Nutrition (ESPGHAN) [17].

Based on current studies (Tab. 1), 7.9% [18] and 6.4% [19] of HT child patients had increased CD-related antibodies in comparison to the control groups in which either none [16] or 3.3% were found to be serologically positive [19]. Such differences are also similar for HT adult patients as CD-related antibodies were diagnosed in 5.9% – 22.5% [19, 20, 21]. Moreover, Riseh et al. [21], based on 40 HT patients and a healthy age-matched control group, found in the ordinal regression model that IgG-anti-tTG and IgA-anti-gliadin were significant predictors for thyroid antibodies [21]. In another study, Marwaha et al. [19] found that increases of anti-tTG and anti-GAD (diabetes-associated antibody) were associated with the anti-TPO level.

Although further studies have been conducted from the aspect of the occurrence of antibodies related to HT in CD patients and *vice versa*, there was no need to cite them all in the current review and only those significant for the subject are described.

Celiac patients should also be monitored for antithyroid antibodies positivity (Tab. 2) because up to 41% of CD

Table 1. CD-related antibodies in HT patients [%]

Antibody tested	HT children patients [%]	Control group [%]	Comment	Ref.
IgA-anti-tTG	7.9	0	-	18
Anti-tTG	6.4	3.3	Anti-tTG antibodies level increased with anti-TPO.	19
Anti-tTG	7.4	3.5	Anti-tTG antibodies level increased with anti-TPO.	19
IgA-anti-tTG	5.9	0.8		20
IgG-anti-tTG	15	7	IgG-anti-tTG and IgA-anti-gliadin were significant predictors for thyroid antibodies	21
IgA-anti-tTG	22.5	17		21
IgG-anti-gliadin	9.5	5		21
IgA-anti-gliadin	15	12		21

children, compared to 3.6% of the control, were positive [22]. Meloni et al. found that the prevalence of HT in the CD child patients in Sardinia was about four times greater than in the age-matched control group [23]. From 324 CD patients, 34 were positively tested for antithyroid antibody titers and 23, of whom 34 followed the GFD. This indicates that the autoimmune thyroid is independent of gluten exposure [23]. Considering CD adult patients, 10.1% compared to 1.6% from the control group were diagnosed for autoimmune hypothyroidism, although the differences in circulating thyroid antibodies were not statistically significant between groups [24]. In other studies 29.7% vs 9.6% [25] and 30.5% vs 9.7% of CD patients vs control were anti-TPO positive [26], or 10.1% had thyroid dysfunction compared to 3.3% from the control group [24]. Compared to healthy, age- and gender-matched people, adult patients were at higher risk of developing HT [27]. This was also proved in child CD patients compared to an age-matched control group [23]. A contradictory result is provided by Guariso et al. [28], who followed-up 170 CD children for 47 +/- 31 months in complete remission on GFD. In comparison to the control group, the obtained results suggested that GFD may delay or prevent the onset of another autoimmune disease, including HT.

Thyroid autoantibodies may fluctuate over time in the natural course of the disease, even more so, a hyperthyroid patient can become hypothyroid and *vice versa* [29]. To exclude the possible improvement of thyroid autoimmunity during GFD, other parameters, such as serum TSH and the ultrasonographic pattern of the thyroid, should be taken into account.

Possible causes of coexistence of CD and HT. There are direct and indirect possible causes for the coexistence of both diseases (Fig. 1), the most significant of which is the genetic background. Although the exact mechanism responsible is not known, two mechanisms involving the human leukocyte antigen (HLA) system are discussed. One of the functions of HLA molecules is to bind antigens and display them on the cell surface for recognition by T-cells. It is suggested that different HLA alleles differ in affinities for peptides from autoantigen, and thus when presented can be recognized by T-cells that have escaped tolerance. There are two possible mechanisms responsible for susceptibility to both HT and CD in HLA class II. The first refers to the HLA binding groove structure of class II DR3 and DQB1 molecules with linkage disequilibrium. They have different binding grooves but together are present in antigen-presenting cells. The second

Table 2. HT-related antibodies in CD patients.

Antibody tested	CD children patients [%]	Control group [%]	Comment	Ref.
Antimicrosomal (Anti-TMA)	14	0	Collectively, the presence of elevated titers (anti-TMA and/or anti-TPO and/or anti-TG) was demonstrated in 41.1% CD patients vs 3.6% in control group. Anti-TMA is rarely studied in HT.	22
Anti-TG	32.3	3.5		
Anti-TPO	11.7	3.5		
Anti-TPO and anti-TG	10.5	2.9	Most of the diagnosed patients were on GFD, indicating that gluten exclusion does not protect from thyroid autoimmunity.	23
Anti-TPO	11.4	5.1	10.1% CD patients vs 1.6% from control group were diagnosed for HT and 10.1% vs 3.3% for SHT. The differences in thyroid antibodies were not statistically significant. Anti-TPO and anti-TMA in CD were associated with an echo pattern of thyroid.	24
Anti-TMA	17.7	15.7		
Anti-TG	8.8	5.1		
Anti-TPO	29.7	9.6	-	25
Anti-TPO	30.5	9.7	-	26

suggestion is that different antigen-binding structures can be expressed together and accommodated. Some studies have demonstrated a concurrent susceptibility for both HT and CD in Caucasians and Asians. Besides HLA genes, the coexistence of different autoimmune diseases could also be explained by aberrant immune regulation by susceptible genes, e.g. that are involved in the activation of Treg cells [30]. Among others listed in the literature are the following:

- **Selenium:** malabsorption of nutrient sources, including Se, is observed in CD [31], and in the Polish population [32]. Selenium, as one of them, is associated with an increased risk of the development and progression of HT [33]. Selenium malnutrition was often observed in HT patients [10].
- **Vitamin D:** similar to Se in CD, the absorption of vitamin D from food may be reduced [34]. It plays an important role in the functioning of the immune system and in autoimmune processes, e.g. through increasing the body's tolerance to its tissues and by anti-inflammatory properties [33]. Among Polish HT patients of both genders, both a too low food intake [35, 36] and too low vitamin D level in the blood were observed [35, 37, 37].
- **Iron:** a component for which the absorption may be reduced due to CD [34], resulting in an increased risk of anaemia in this group by as much as 70% [38]. Iron participates in the synthesis of thyroid hormones [39], and its deficiency may reduce thyroid function [40, 41]. In HT, insufficient iron levels are observed in both children [42] and adults [43].
- **Gut microbiota:** is a part of the immune system and its disorders may stimulate autoimmune processes [44], thyroid dysfunction [45] and HT underdevelopment [46, 47].
- **Gut permeability:** increased intestinal permeability was associated with the development of autoimmune diseases [48] including HT [49]. This means that an excessive space in the intercellular space between enterocytes promotes the transport of inflammatory molecules, e.g. bacterial toxins, from the intestine to blood [50, 51].

– *Molecular mimicry*: due to the presence of the tTG in the thyroid gland, this gland may be destroyed as a result of a cross-reaction in CD [15]. Patients with thyroid autoimmunity should be tested for anti-tTG antibodies [52]. When the anti-tTG test is positive, gluten elimination may be beneficial for thyroid autoimmunity [36].

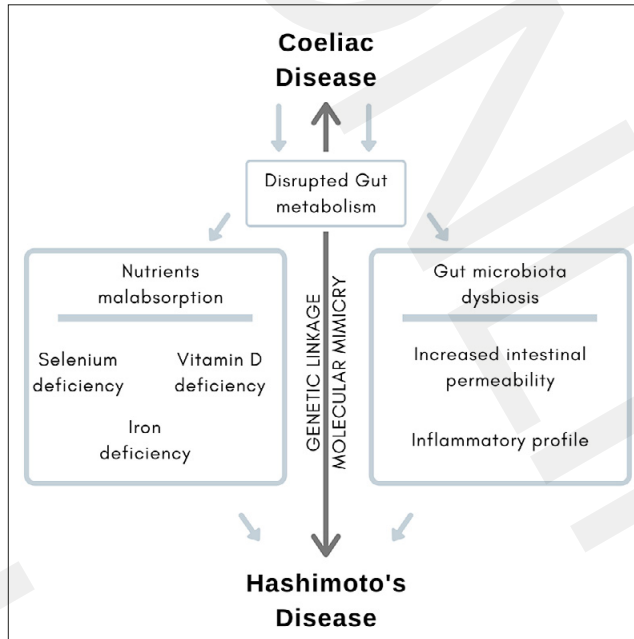


Figure 1. Possible causes of the coexistence of both diseases. Light grey arrows: the indirect connection between diseases. Dark grey arrows: direct connections

The most significant linkage for CD and HT is the genetic background, thus genetically susceptible patients are at increased risk of developing other autoimmune diseases. However, the main reason for overlapping autoimmune diseases is the misregulation of regulatory T cell development that suppresses the autoimmune reactions of effector cells. Among other possible causes are deficiencies in nutrients caused by disrupted gut metabolism and nutrients malabsorption observed in CD. Those nutrients, e.g. Se or iron, are necessary for thyroid metabolism, and their deficiencies might increase the risk of developing autoimmune hypothyroidism. Gut microbiota dysbiosis observed in CD is also associated with increased gut permeability and inflammatory processes. Both are known to be linked with autoimmune diseases. Besides that, anti-tTG recognizes tTG2 in the thyroid gland.

The presence of autoantibodies is not indicative of the disease as they are present in all normal tissues. Naturally occurring autoantibodies are part of metabolism responsible, e.g. for cell debris clearance or removing damaged cells. Thus, an autoimmune disease is a matter of the escalation of already existing autoimmune responses and loss of self-tolerance [53]. One of the main reason for this, and as a result of the overlapping of autoimmune diseases, is the misregulation of the development of either natural regulatory T cells (nTreg) in the thymus (central tolerance) and/or adaptive/induced Treg (iTreg) cells in the second organs (peripheral tolerance), and/or a deficiency in their count or function [54, 55]. Regulatory T cells (Treg) are immunoregulatory lymphocytes that mediate peripheral tolerance, and their role is to suppress the immune response of conventional T cells

to environmental antigens. As they limit immune response, they act anti-inflammatory what is beneficial for patients with inflammatory or autoimmune diseases. Other T cells, B lymphocytes and innate immune cells, are also implicated in immune tolerance [56]. In a comment to Sudhir Paul's opinion that 'there is so much, that can go wrong (...)' [57] we need to know more about where it can go wrong, how it happens, and how we can deal with it [55]. The question arises, for example, whether a gut disruption in celiac disease yields to autoimmune thyroid disease through foreign and self-nucleic acids or damage and pathogen-associated molecular patterns? It is known that those molecules are involved in thyroid autoimmunity exacerbation through toll-like receptors [58].

Another issue is the existence of environmental agents. Based on twins studies, it is known that about half [59] or even three-quarters [60] of the risk of developing autoimmunity accounts for genetic traits, and thus the other part concerns non-genetic factors. Those are, e.g. endocrine disruptors like bisphenol A, F, S, drugs, heavy metals, viruses, among others [61, 62]. In susceptible subjects, they may trigger the appearance of autoimmune thyroid disease [63]. Celiac patients, like other autoimmune disease patients, are those genetically susceptible to environmental agents, which might be another explanation for the observed higher risk of thyroid autoimmunity development in CD patients [64].

Thyroid gland in patients with CD eliminating gluten. A study by Ventura et al. revealed that 13 out of 90 (14.4%) individuals with CD had increased anti-TPO levels (>75 IU). The number of positive anti-TPO patients decreased from 13 to 10, 6 and 2, respectively in 6, 12 and 24 months after the introduction of GFD. After two years of a GFD, only two people were still anti-TPO positive, although its value decreased quite significantly in comparison with the baseline level [65]. Oderda et al. [66] also observed decreased levels of antibodies in children with CD, while a GFD was applied for 1–5 years but anti-TPO titers decreased in only two of six children, and increased in the rest. The authors suggested that early elimination may be useful to stop the development of thyroid autoimmunity at the initial stage, but it might be not helpful when thyroid autoimmunity has developed. The biggest limitation of the study was the small number of participants [66]. Toscano et al. [67] studied the presence of antithyroid and antipancreas antibodies in CD patients. The antibodies against one of the examined organs were found in 15 out of 44 subjects (34%), whereas antithyroid antibodies, namely anti-TPO or anti-TG, were increased in seven (15.9%) and six (13.6%) subjects, respectively. In the subgroup of patients on GFD (25 out of 44, 56.8%), the frequency of positive results for antibodies directed against the pancreas or thyroid was 20% in comparison to 52.6% for patients who did not exclude gluten. The authors indicated that the molecular mimicry and the occurrence of cross-reactions were the possible mechanisms responsible for their observations [67]. Toscano also referred to the Magazzu et al. study [68], in which GFD led to 'complete resolution of the [thyroid] dysfunction after two months' [67]; however, the authors of the current study were unable to find this article. Another study suggesting the link between gluten intake and autoimmune diseases is an observational study carried out in a group of 924 patients (including 178 individuals with a different immune disease than CD). Those who ate

gluten doubled the risk of developing another autoimmune disease in comparison with gluten non-eaters. The group at the highest risk consisted of subjects who had been diagnosed previously, and those with a family history of autoimmune disease [69].

To-date, the presented review is the only research indicating a possible relationship between gluten intake by CD patients and their development of thyroid autoimmunity. Other studies, however, do not confirm the possibility of such an association. Gluten elimination may not reduce the risk of developing comorbid autoimmune diseases [70–73, for example, Cassio et al. indicated that the GFD applied for a long time (~ 9 years) did not reduce the occurrence of positive results of thyroid antibodies in CD. Among 135 examined children, the number increased from 12 to 23%, indicating that gluten is not so important, if at all [74].

Thyroid gland in CD and HT patients eliminating gluten.

When CD and HT coexist, gluten elimination may inhibit thyroid damage or decrease anti-TPO [66, 75], but studies are equivocal [72]. In the study by Sategna-Guidetti et al. [75], HT occurred three times more often in 241 patients with CD (12.9%) in comparison with the control group (4.2%). This was related mainly to subclinical hypothyroidism (SHT) with organ dysfunction without the autoimmune component. Normalization of SHT was observed after a year only in a group following a GFD. Moreover, 5.5% of CD patients with normal thyroid function who did not exclude gluten, developed a thyroid dysfunction [75]. Contrarily, in study by Metso et al. [72], after a year on a GFD, it neither decreased the anti-TPO level nor stopped the destruction of the thyroid gland, and its volume at the end of the study was 5.6 cm³ in comparison with the initial 6.4 cm³ [72]. In Rasheed et al. study, gluten exclusion for one year had some beneficial effects on autoimmune thyroiditis in a few subjects, and maintained euthyroidism in CD child patients. They pointed out that GFD compliance did not affect the presence of antibodies as new anti-thyroid antibody-positive cases appeared [76].

Thyroid gland in HT patients eliminating gluten.

Unfortunately, there is a lack of publications regarding the effect of gluten and its elimination on HT. The study by Krysiak et al. tested the effect of gluten elimination on the level of antithyroid antibodies in women with thyroid autoimmunity in the euthyroid state [35]. All the patients were anti-tTG positive without clinical symptoms of CD. They were divided into an intervention group (n=16) on a GFD for six months and a control group (n=18) free from intervention. Positive anti-tTG titers decreased only in patients who eliminated gluten by 62% (10/16), and both anti-TPO and anti-TG concentrations decreased by 24%. Vitamin D increased by 25% (from 20 to 25 ng/mL) and the secretory capacity of the thyroid gland measured with the SPINA-GT index was elevated by 15%. These differences were statistically significant compared with the control group. Gluten elimination did not lead to changes in other measured indicators [35]. At the beginning of the study, anti-TPO concentration was correlated with anti-tTG, which was inversely correlated with plasma vitamin D and SPINA-GT. However, at the end of the study, the values of these parameters improved and autoimmunity was reduced. In most of the patients, the decrease in thyroid antibody levels was associated with a decrease in anti-tTG antibody levels.

The most likely explanation for the results is an increase of vitamin D concentration in serum, which may have influenced the functions of the immune system and thyroid autoimmunity [33, 77]. However, the authors also indicated that the vitamin D level increase was too low to be fully responsible for the results [35]. Another possible cause of the changes observed is an improvement in Se nutrition [78]. Se intake was found to potentiate the effect of vitamin D on thyroid autoimmunity when taken together [79]. The subjects, as well as those described above, came from an area with a low intake of Se, and thus were Se-deficient [32, 80]. This may be confirmed by the low peripheral deiodinase activity at the beginning of the study; however, the lack of significant differences at the end of the study rather indicates that other mechanisms should be taken into account [35]. The authors also mentioned the results obtained in a mice study [81] and on CD patients [82] to explain the possible mechanism responsible for improving the parameters. In the studies, gluten elimination led to an improvement in the secreted cytokine profile in the anti-inflammatory direction. Although there are a few possible explanations for the obtained results, they lack sufficient evidence to support them. Krysiak et al. concluded that GFD may inhibit thyroid autoimmunity and improve its secretory capacity [35].

Due to the association of antithyroid antibodies with the development of SHT and HT [83, 84], it can be suggested that gluten elimination may delay the development of hypothyroidism in the group of euthyroid, autoimmune thyroid patients with positive anti-tTG antibody titers. It is worth mentioning that the most significant effect was observed in those whose level of antithyroid antibodies was the highest and those patients might benefit most from GFD.

Lack of changes in the Jostel index and SPINA-GD indicate no effect of gluten on thyrotropic cells producing TSH and the activity of Se deiodinases thyroid metabolizing hormones. There are a few disadvantages of the study: the low number of participants and short duration of intervention. Some questions arise: whether negative anti-tTG titer patients would benefit from a GFD? Would they benefit if they had normal vitamin D status and/or normal Se status? What results could be achieved if they had thyroid dysfunction? [35]. In another study conducted among 98 drug-naive women with HT and TSH levels between four and eight μ IU/ml and normal fT4 and free fT3 levels, gluten exclusion with selenomethionine (200 μ g Se) intake improved thyroid function and autoimmunity after six months [85]. The participants of the study were divided into two groups, one taking Se with GFD, and the second, only on Se supplementation without additional dietary intervention. At the end of the study, 37/50 (74%) participants on GFD achieved euthyroidism, compared to 28/48 (58.3%) participants from the second group. Serum anti-TPO decreased more in the GFD group (by 49%) than in the control group (34%). In both groups, TSH and anti-TG levels decreased; however, gluten exclusion had an additive effect on anti-TPO. The authors also measured free thyroid hormones, but their levels probably did not change during the intervention as they were not mentioned in the study abstract (no full text available), but their concentrations were normal initially [85].

CASE STUDIES

The study conducted by Krysiak et al. [35] and Asimi et al. [85] were the only controlled studies that presented the effect of gluten elimination in HT patients without CD. Other publications are case study reports in which GFD was only a part of broader interventions. Avard et al. described a 23-year-old girl who declared decreased mood, energy loss, constant fatigue, hair loss, insomnia, and gastrointestinal problems, which intensified especially in stressful situations [86]. The feeling of fatigue along with decreased mood had appeared after a stressful vacation, which probably appeared due to a decrease in blood magnesium level as a result of stress [6]. As mentioned earlier, this mineral is essential for the proper functioning of the thyroid gland [7, 8]. For two weeks before starting therapy, the patient excluded cereals and dairy products as a part of a paleolithic diet. It was also found that the patient consumed insufficient amounts of animal protein. A therapy intervention included the continuation of the paleolithic diet, stress management, and physical activity in the form of a 30-minute walk twice a week. Thyroid nodules that were found on the gland and Muehrcke's nails indicated zinc deficiency [87]. Serological tests revealed the level of anti-TPO antibodies above 1,000 IU/mL, normal vitamin D status of 36 ng/mL, and indirectly low activity of processes related to methylation [86]. Methylation processes depend on the availability of nutrients, such as folates and B vitamins [89], initially and participate in epigenetic processes, including those responsible for regulating autoimmune processes [89] and thyroid autoimmunity [90, 91]. A deficiency of substrates for methylation processes leads to autoreactivity what may stimulate autoimmunity [92]. Nutritional intervention, including diet, as well as supplementation, are aimed particularly at improving the function of the immune system, namely the functions of selenoprotein and methylation along with a reduction of oxidative stress [86]. Taking into account the link between intestines health and autoimmune diseases [93, 94], the bowel function and tissue barrier were addressed by modulation of the intestinal microbiota through the use of probiotics to reduce inflammation [86].

The gluten exclusion was motivated by a decrease in the secretion of zonulin – an exogenous protein associated with intestinal permeability [48]. The methylation processes were supported by providing methylcobalamin, vitamins B, zinc, and Se. After 21–22 months, the symptoms were reduced and a decrease in TSH levels from 2.79 to 1.11 mU/L, an increase in free T4 from 10.8 – 12 pmol/L, increase in anti-TG from 56 – 322 IU/mL, and a decrease in anti-TPO titers from >1,000 – 295 IU/mL were observed [86]. The authors suggested that the increase of anti-TG observed after 15 months of intervention might have been a result of a natural worsening of the disease, or a diet ineffectiveness, although most important anti-TPO titers decreased. The patient's subjective energy level increased from two to 6–8 on a 10-point visual scale. The subjective sleep quality and gastrointestinal functioning also improved [86]. It is possible that the supplementation of vitamin D and its blood concentration increase from 36 to 50–60 ng/mL would contribute to better results [95]. In this case, however, gluten elimination did not have any positive effects. Besides, the patient compliance to the elimination was not fully complete throughout the study. The observed changes may have resulted from improved nutrition and

supplementation, and above all, environmental stress management.

A similar dietary intervention was conducted by Abbott et al., who describe 12 patients in their study who were treated with the so-called 'autoimmune protocol' [96]. This is a non-defined dietary model aimed at improving the immune system's tolerance to its tissue, and reducing the intensity of autoimmune processes. In the referred study, a modified paleolithic diet was applied, while cereals, dairy products, and food additives were eliminated. The intake of vegetables, fruits, and nuts was increased. The report focused on the improvement of the state of intestinal microbiota and permeability. Fermenting ingredients of diet, like fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP), were also eliminated in some cases [96]. The application of the autoimmune protocol was motivated by the positive results obtained by the authors in patients with inflammatory bowel disease [97]. After 10 weeks of therapy, symptoms of the disease, measured by the Medical Symptoms Questionnaire, reduced from 92 to 29 points, and the quality of life measured by 36-Item Short-Form Health Survey improved significantly [96]. It is known that the quality of life of HT patients is reduced what might remain even after levothyroxine therapy [98]. There was no improvement in the thyroid function and antithyroid antibodies serum concentration, although the number of immune cells and high sensitivity C reactive protein, an inflammatory processes marker, decreased from 1.63 to 1.15 mg/L (-29%). As mentioned above, it is difficult to indicate what was responsible for the observed results, but it is important that dietary intervention and gluten exclusion did not affect thyroid function or serological results [96].

Another case study concerned 23-year-old woman with anorexia, ovarian failure, and multiple autoimmune diseases: HT, Addison's disease, and CD. AGFD was advised, combined with thyroid hormone therapy and corticosteroids. After three months, the need for thyroid replacement therapy decreased progressively. Thyroid functions, TSH and antithyroid titers improved, while comparing indicated parameters for 6, 12 and 18 months of therapy, although anti-TPO at the end of the study was still increased [99]. Thyroid hormone replacement therapy and corticosteroids applied in the intervention was unable to assess whether gluten had any effect on the obtained results.

CONCLUSIONS

Studies conducted to-date do not support the claim that HT patients should eliminate gluten from their diet. Because of the limited number of study which have major limitations and ambiguous results, the elimination of gluten from the diet cannot be recommended. It is not known whether the gluten elimination in patients without CD and a positive anti-TPO titer may be beneficial, but it is known to be potentially harmful. On the other hand, patients with CD and suffering from thyroid autoimmunity, may support their treatment by an elimination diet, although studies regarding the potential improvement of their thyroid condition or reduction of its damage are equivocal. It was observed in a Polish study that a GFD improved the level of anti-TPO in a group of euthyroid HT patients without CD, but with positive anti-tTG titers. There are some possible causes for a GFD or

gluten foodstuffs consumption on the development or exacerbation of HT (Fig. 2). More studies are needed on the molecular mechanisms involved in the generation of autoantibodies. The conclusion of the presented review is consistent with the opinion of the POLSPEN, indicating that a GFD should not be recommended to HT patients without concurrent gluten-related diseases.

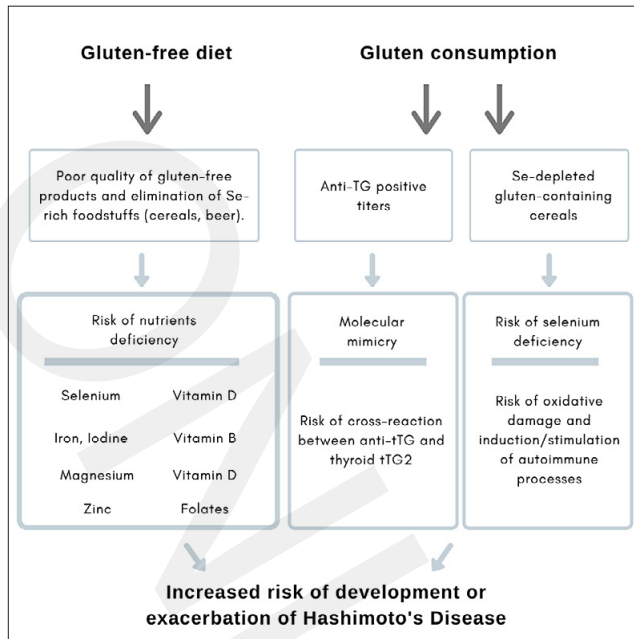


Figure 2. Possible relationship between gluten intake and HT

There are a few possible relationships between gluten intake and risk of HT development or exacerbation. A gluten-free diet

when inadequate applied may cause nutritional deficiencies, which is often reported in HT patients. Moreover, if GFD relates to the elimination of selenium-rich cereals, that might be the most significant negative impact of GFD on thyroid health. On the other hand, if crops are grown on selenium-depleted soil, gluten consumption may be associated with low Se intake and a high incidence of HT. Crops grown on soil rich in Se are a source of this compound in the diet. In this case, gluten consumption can be related to lower HT incidence. This claim is supported by a study in China [11]. A cross-reaction existing between tissue transglutaminase antibody (anti-tTG) and thyroid tissue transglutaminase 2 might be responsible for thyroid destruction in people with positive anti-tTG test results [15].

Diet therapy guidelines for dietitians. If a GFD is essential, a physician or dietitian should bear in mind that it is difficult to handle, and that it is associated with potential deficiencies, including magnesium and B vitamins [3–5]. In the case of magnesium, its deficiency may be responsible for some HT symptoms [6–8] and may be a part of the mitochondrial background for the disease [6, 100]. In such cases, introducing an elimination diet may lead to an increased severity of the disease if the patient does not have adequate dietary support. Each patient should be guided properly regarding the importance of nutrition and the sources from which credible knowledge may be achieved, preferably by the dietitian.

Table 3. Summaries of recently published studies on HT patients regarding CD prevalence or CD-associated antibodies positivity

Population screened	Country	Prevalence of positive antibodies in tested vs control group [%]	Comment / other results	Ref.
577 anti-TPO positive cases vs age and gender-matched control	India	Anti-tTG positivity was detected at 6.4% vs 3.3% children patients and 7.4% vs 3.5% in adult patients. Anti-GAD positivity was detected in 10.6% and 13.8% of child and adult patients vs 3.3% and 5% in control group.	40.2% anti-TPO positive cases had hypothyroidism vs 4.9% in the control group. In those 40.2%, 13.1% vs 0% had HT. The rest was SHT. Anti-tTG and anti-GAD antibodies level increased with anti-TPO.	[19]
914 autoimmune hypothyroid patients	Jordan	12.8% (117/914) had IgA and IgG anti-EMA positive titers	87/117 underwent duodenal biopsy and 39/87 (44.8%) had positive histological findings of CD which is 4.3% of CD prevalence in the studied group. If those who did not subject to duodenal biopsy underwent and had the same rate of CD, the rate would be 5.7%.	[102]
111 HT vs 100 control	Brazil	IgA-EMA was positive in 4/111 (3.6%) HT patients vs 0% control	3/4 of them (2.7%) had biopsy-proved CD	[103]
53 AITD patients (not specified, diagnosed based on increased anti-TPO and anti-TG and altered TSH level).	Brazil	5/53 (9.3%) had positive IgA-tTG or IgA-EMA titers, none of them had both antibodies positive	Only 2/5 serologically- positive CD patients underwent upper digestive endoscopy, one of whom had duodenal mucosa histological changes characteristic for CD	[66]
499 hypothyroid patients	USA	Anti-tTG positivity detected in 10/499 (2%)	CD based on biopsy detected in 9/500 patients (1.8%). The higher need for LT4 dose was detected in those with higher prevalence of CD.	[104]
80 HT patients	Turkey	IgA-anti-tTG found positive in 1/80 (1.25%)	Biopsy proved CD	[105]
40 HT, 42 age-matched control woman	Iran	IgG, IgA anti-tTG and IgG, IgA anti-gliadin, compared to controls were increased in 15% vs. 7%, 22.5% vs. 17%, 9.5% vs. 5%, and 15% vs. 12% participants	Ordinal regression model showed that IgG anti-tTG and IgA anti-gliadin were significant predictors for antithyroid antibodies in HT	[21]
757 patients with AITDs (86.7% had HT)	Argentina	5/757 (0.6%) were previously affected with CD. 30/757 (3.9%) patients were newly- diagnosed with CD.	-	[106]

Table 4. Summaries of recently published studies on CD patients regarding HT prevalence or HT-associated antibodies positivity

Population screened	Country	Prevalence of positive antibodies in tested vs control group [%]	Comment / other results	Ref.
335 CD and 1695 control	Sweden	7.2% (24/335) had elevated titers of TPOAb, compared to 2.8% (48/1695) from control group	-	[107]
67 cases, children	Turkey	16.4% cases became positive for antithyroid antibodies 2–3 years after the diagnosis of CD	GFD did not affect thyroid antibodies positivity	[108]
288 untreated CD patients, 250 controls	Iran	In CD group, 30/288 (10.4%) had hypothyroidism, 5/288 (1.7%) had positive anti-TPO titers compared to 7/250 (2.8%) and 1/250 (0.4%) in control group, respectively.	Thyroid disease (hyper-, hypothyroidism) prevalence was 39/288 (13.6%) in CD patients and (8/250) 3.2% in control group. Thyroid disease prevalence was 4-fold higher in CD patients than in control group	[109]
100 patients (1–12-years-old) with CD	Pakistan	14/100 (1.4%) had autoimmune thyroiditis at enrollment, and a further 6/86 (7%) were later diagnosed at follow-up period of 1 year.	Autoimmune thyroiditis frequency was 20% over a one year period follow-up. Patients were on GFD with poor compliance (52%). 4/20 (28.6%) of autoimmune thyroiditis patients improved on GFD. 3/6 (50%) autoimmune thyroiditis patients at diagnosis became hypothyroid and all were non-compliant.	[110]
62 CD patients, children,	Greece	12.9% had positive antithyroid antibodies	4-fold higher antithyroid antibodies positivity in CD patients compared to Greek paediatric population (4.3%)	[111]
74 untreated CD patients	Indian	20/74 (27%) were positive for anti-TPO antibody.	14/74 (18.9%) had autoimmune, clinical or subclinical hypothyroidism	[112]
92 CD patients, 237 healthy control group	Italy	11/92 (12%) were positive anti-TPO titers	One-third of adult CD patients at diagnosis were positive for at least organ-specific autoantibody (thyroid, pancreas, gastric and adrenal).	[113]
64 CD children, 143 control group on GFD diet from 3 months to 15 years (median 4 years)	Turkey	8/64 (12.5%) compared to 6/143 (4.2%) had autoimmune thyroid disease.	9.3% vs 2.8, 3.58 vs 3.95 ml, 12.5% vs 2.1%, 25% vs 4.2% of patients, compared to control had abnormalities in thyroid functions, mean thyroid volume, parenchymal heterogeneity, incidence of thyroid nodules, respectively.	[114]
107 CD children	Iraq	3/107 (2.8%) had concomitant AIT	No significant association between CD groups with AIT were found	[115]

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