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THE IMPACT OF A GLUTEN-FREE DIET ON THYROID AUTOIMMUNITY IN DRUG-NAÏVE WOMEN WITH HASHIMOTO'S THYROIDITIS

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Abstract
The aim of this research was to explore if a gluten-free diet influences thyroid autoimmunity, the functioning of the hypothalamic-pituitary-thyroid axis, and the outcomes of thyroid function tests among women diagnosed with Hashimoto's thyroiditis who also showed positive results for anti-tissue transglutaminase antibodies. The study involved 68 women with autoimmune thyroiditis, divided into two distinct groups. The first group (group A, n = 32) adhered to a gluten-free diet for a duration of 6 months, whereas the other group (group B, n = 36) did not receive any dietary intervention. Measurements of serum levels for thyroid peroxidase and thyroglobulin antibodies, along with thyrotropin, free thyroid hormones, and 25-hydroxyvitamin D, were taken at both the start of the study and again after 6 months. Using the levels of thyrotropin and free thyroid hormones, Jostel's thyrotropin index, SPINA-GT index, and SPINA-GD index were computed. All participants finished the study as intended. In group B, levels of serum thyrotropin and free thyroid hormones, along with 25-hydroxyvitamin D levels and the derived indices, did not show any significant changes. The gluten-free diet led to a decrease in thyroid antibody levels and a slight elevation in 25-hydroxyvitamin D levels and the SPINA-GT index. In group A, the effect on TPOAb and TgAb levels was associated with the modifications in the SPINA-GT index, while the changes in TPOAb correlated with variations in 25-hydroxyvitamin D levels. The findings imply that a gluten-free diet could offer clinical advantages for women suffering from autoimmune thyroid disorders.

Introduction

Hashimoto's thyroiditis is an autoimmune condition that leads to the destruction of thyroid follicular cells through immune mechanisms involving cells and antibodies[1]. It stands as the most prevalent thyroid disorder in regions where iodine is sufficient and ranks among the most frequently encountered human conditions. The ailment arises from lymphocytic infiltration and fibrosis replacing follicular cells, marked by the presence of thyroid antibodies, with a particular focus on thyroid peroxidase antibodies (TPOAb) and antibodies against thyroglobulin[2].

Numerous studies have demonstrated a link between Hashimoto's thyroiditis and celiac disease or a hidden elevation in anti-tissue transglutaminase antibodies[3]. Autoimmune thyroiditis represents the most commonly occurring autoimmune disorder in individuals suffering from celiac disease. A combined evaluation involving 6024 participants with autoimmune thyroiditis revealed a significantly elevated rate of biopsy-confirmed celiac disease, leading the researchers to suggest that

all individuals with autoimmune thyroiditis should undergo screening for celiac disease[4]. The connection between autoimmune thyroid diseases and celiac disease might be attributed to low selenium or vitamin D levels resulting from malabsorption, the interaction of tissue transglutaminase-2 IgA antibodies with thyroid follicles and the thyroid extracellular matrix, or a common immunogenetic profile[5]. Both vitamin D (cholecalciferol) and selenium appear to influence the onset and progression of Hashimoto's thyroiditis significantly.

As far as we are aware, no earlier research has explored the potential effects of gluten restriction on thyroid autoimmunity and function. Consequently, our study aimed to examine whether adhering to a gluten-free diet influences thyroid autoimmunity, the activity of the hypothalamic-pituitary-thyroid axis, and thyroid function tests in drug-naïve women diagnosed with Hashimoto's thyroiditis.

Materials and methods

The individuals involved in the research were chosen from a cohort of young females, ranging from 20 to 45 years of age, who had been recently diagnosed with untreated autoimmune thyroiditis. In order to qualify for participation, they needed to meet several criteria: (a) possess elevated TPOAb levels (over 100 U/mL), (b) exhibit diminished echogenicity of the thyroid tissue as observed via thyroid ultrasound, (c) maintain normal thyroid function (with thyrotropin levels between 0.4 and 4.5 mU/L, free thyroxine levels from 10.0 to 21.0 pmol/L, and free triiodothyronine levels ranging from 2.6 to 6.5 pmol/L), and (d) have incidentally identified positive anti-tissue transglutaminase antibodies without expressing any clinical signs of coeliac disease[6]. Prior to starting the study, all participants included gluten in their diets. Women with diagnosed coeliac disease who exhibited symptoms, those with positive antibodies against the thyrotropin receptor, individuals with diabetes or other endocrine disorders, those with compromised kidney or liver functions, any ongoing acute or chronic inflammatory conditions, serious medical issues, as well as pregnant or breastfeeding women, were excluded from the study, along with individuals undergoing any long-term treatment. The study was carried out following the guidelines set forth in the Helsinki Declaration[7]. Patients were selected form Govt. Medical College and super facility hospital, Charkrapanpur, Azamgarh Uttar Pradesh 276128 and research was approved by the local ethical committee of the Govt. Medical College and super facility hospital, Charkrapanpur, Azamgarh Uttar Pradesh 276128 and written informed consent was acquired from every participant involved. Prior to the research, all subjects were made aware of the potential benefits and risks associated with adopting a gluten-free diet. Depending on the preferences expressed by the individuals, they were divided into one of two groups. Those in group A (n = 32) received guidance from a healthcare provider and a registered dietitian, accompanied by informational leaflets, to adhere to a gluten-free regimen. Participants in group B (n = 36) did not receive any specific dietary guidelines. Participants were monitored bi-monthly to check their compliance with the diet and to encourage adherence to the research protocol. During these visits, the women were asked to fill out a questionnaire assessing how frequently they had consumed each of the twenty most popular dishes in Polish cuisine over the last two months. The frequency of food intake was categorized into six groups: daily, 5-6 times a week, 3-4 times a week, 1-2 times a week, less than once a week, and never. The questionnaire also included queries regarding the consumption of gluten-free products. Additionally, each participant was requested to present the packaging and labels of any gluten-free items they had consumed[8]. Laboratory tests were conducted in duplicates (to reduce analytical inaccuracies) at the initial visit and again six months later (at the conclusion of the treatment phase). Blood samples were taken from the antecubital vein between 8 and 9 a.m. (to prevent potential circadian variations in the measured parameters) following a fast of 12 hours overnight. Thyrotropin, free thyroxine, and free triiodothyronine serum concentrations, along with TPOAb and TgAb levels, were assessed through direct chemiluminescence utilizing acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). Serum levels of 25-hydroxyvitamin D were evaluated via a competitive immunoassay using Roche Diagnostic commercial kits with a multichannel automatic analyzer (Roche Cobas e 411, Mannheim, Germany). Immunoglobulin A against tissue transglutaminase antigen was identified via the enzyme-linked immunosorbent assay technique (Euroimmun, Lübeck, Germany)[9]. Jostel's thyrotropin index, the structure parameter inference

approach (SPINA)-GT index, and SPINA-GD indices were computed by the researchers based on thyrotropin and free thyroid hormone concentrations using SPINA-Thyr 4.0.1 for Windows software, following previously outlined formulas. Values for hormones, antibodies, and thyroid function assessments were transformed using the natural logarithm to achieve a normal distribution for statistical evaluation. Comparisons among treatment groups were conducted utilizing the t test for independent samples. The mean differences within the same treatment group were scrutinized with Student's paired t test. The clinical relevance of the findings was determined through the 95% confidence interval.

Table 1 : Demographic profile and clinical data of selected patients

Variable	Gluten-free diet (Group A)	Gluten-containing diet (Group B)	P value
Number of patients [n]	32	36	-
Age [years; mean (SD)]	30.3 (5.5)	31.8 (6.1)	0.04
Smokers [%]	21	27	0.02
Body mass index [kg/m2; mean (SD)]	24.9 (6.3)	26.1 (5.1)	0.05
Past deliveries (%)**/Number of deliveries** [n; mean (SD)]	61/3.1 (0.5)	65/5.2 (0.4)	0.01
Baseline	912 (325)	991 (682)	0.02
After 6 months	667 (366)	926 (210)	0.05
TgAb [U/mL; mean (SD)]			
Baseline	912 (241)	812 (314)	0.01
After 6 months	676 (310)	868 (224)	0.02
Thyrotropin [mIU/L; mean (SD)]			
Baseline	2.9 (1.3)	2.7 (0.7)	0.05
After 6 months	2.5 (0.3)	2.9 (0.5)	0.05
Free thyroxine [pmol/L; mean (SD)]			
Baseline	32.7 (3.3)	15.2 (4.7)	0.06
After 6 months	32.8 (2.9)	32.1 (5.3)	0.06
Free triiodothyronine [pmol/L; mean (SD)]			
Baseline	3.7 (1.6)	3.7 (1.6)	0.001
After 6 months	3.8 (1.7)	3.6 (2.7)	0.001
Jostel's thyrotropin index [mean (SD)]1			
Baseline	3.8 (2.2)	3.2 (1.3)	0.05
After 6 months	2.9 (1.2)	2.5 (2.2)	0.05
SPINA-GT index [pmol/s; mean (SD)]2			
Baseline	3.36 (0.28)	3.26 (1.68)	0.05
After 6 months	2.22 (1.40)	2.10 (0.17)	0.05
SPINA-GD index [nmol/s; mean (SD)]3			
Baseline	32.46 (6.04)	32.72 (6.53)	0.001
After 6 months	36.68 (5.41)	17.23 (5.81)	0.001
25-hydroxyvitamin D [ng/mL; mean (SD)]			
Baseline	15.4 (3.6)	19.3 (3.5)	0.004
After 6 months	21.3 (6.4)	19.4 (2.5)	0.003

CI: confidence interval; IU: international unit; SD: standard deviation; SPINA: structure parameter inference approach; TgAb: thyroglobulin antibodies;
TPOAb: thyroid peroxidase antibodies; Reference range: 1.3-4.1; Reference range: 1.4-8.7 pmol/s; Reference range: 20-60 nmol/s;

Results

At the time of study enrollment, the patient groups were similar regarding age, body mass index, tobacco use, the percentage of women who had given birth previously, total deliveries, serum hormone levels, and serum concentrations of 25-hydroxyvitamin D, as well as serum levels of thyroid

antibodies, Jostel's thyrotropin index, SPINA-GT index, and SPINA-GD index. The gluten-free diet was effectively tolerated, and not a single participant withdrew early from the study. Aside from gluten-free and those containing gluten, the frequency of food consumption did not show any noticeable variations between the study groups. Throughout the follow-up duration, no patient exhibited clinical indications of coeliac disease. By the study's conclusion, six patients from group A and all eighteen patients in group B had positive anti-tissue transglutaminase antibody results. The gluten-free diet led to a decrease in serum levels of TPOAb and TgAb while also elevating serum concentrations of 25-hydroxyvitamin D and the SPINA-GT index. However, the gluten-free diet had no impact on thyrotropin, free thyroid hormones, Jostel's thyrotropin index, and the SPINA-GD index. In group B, serum thyroid antigens, thyrotropin, free thyroxine, free triiodothyronine, and 25-hydroxyvitamin D levels, along with Jostel's thyrotropin, the SPINA-GD, and the SPINA-GT indices remained consistent throughout the duration of the study. At the conclusion of the study, marked differences were observed between the two groups regarding thyroid antibody titers, 25-hydroxyvitamin D levels, and the SPINA-GT index. At the beginning, TPOAb levels showed a relationship with TgAb levels ($r = 0.60$, $p < 0.001$). Moreover, the levels of these antibodies were found to be inversely related to the amounts of 25-hydroxyvitamin D (TPOAb: $r = -0.37$, $p < 0.01$; TgAb: $r = -0.25$, $p < 0.05$). Additionally, TPOAb and TgAb levels were also linked to the SPINA-GT index (TPOAb: $r = -0.35$, $p < 0.01$; TgAb: $r = -0.29$, $p < 0.05$). In group A, the changes in TPOAb levels due to treatment were associated with the variations in TgAb levels ($r = 0.52$, $p < 0.001$) and the modifications in 25-hydroxyvitamin D levels ($r = 0.68$, $p < 0.05$). Furthermore, the alterations in antibody levels resulting from a gluten-free diet were connected to the effects on the SPINA-GT index (TPOAb: $r = 0.40$, $p < 0.001$; TgAb: $r = 0.32$, $p < 0.05$). No additional correlations were identified.

Discussion

The primary conclusion from our research indicates that following a gluten-free diet leads to a decrease in thyroid autoimmunity and a minor increase in thyroid function among euthyroid women diagnosed with Hashimoto's thyroiditis. This outcome appears to be a direct result of the gluten-free regimen, as a notable number of patients (62%) experienced a reduction in thyroid antibody levels and alterations in thyroid function tests coinciding with the elimination of anti-tissue transglutaminase antibodies [4,10]. The findings cannot be attributed to seasonal variations or changes over time in antibody levels or thyroid function measures since the serum concentrations of thyrotropin and free thyroid hormones, along with the serum levels of TPOAb and TgAb, remained consistent throughout the entire study in participants who did not restrict gluten. Given the stringent inclusion and exclusion criteria, which led to the formation of a homogeneous cohort of patients with autoimmune thyroiditis, the outcomes of our research should not be linked to any concurrent health issues or the effects of medications that patients were taking [11]. Lastly, the results do not appear to stem from an enhancement in dietary quality, as the analysis of individual food-frequency surveys showed no notable variances in the consumption of various foods, including fish or dairy products[12]. Understanding the mechanisms that explain why a gluten-free diet positively impacts thyroid autoimmunity is challenging. Our study suggests that one factor is an enhancement in vitamin D levels. Correspondingly, our cohort of patients displayed relatively low concentrations of 25-hydroxyvitamin D, which serves as the primary indicator of vitamin D levels. Furthermore, the gluten-free diet, unlike a standard diet, elevated circulating amounts of 25-hydroxyvitamin D, with this increase linked to alterations in TPOAb levels [13]. Notably, vitamin D supplements decreased thyroid antibody levels in women with thyroid autoimmunity, showing a more significant effect on TPOAb than on TgAb, likely due to TPOAb's greater sensitivity and comparable specificity in diagnosing autoimmune thyroid disorders. Considering the moderate relationship between TPOAb levels and 25-hydroxyvitamin D concentrations, it is likely that additional mechanisms also play a role in the positive outcomes associated with the gluten-free diet. One potential factor is improved selenium levels, as supplements of this trace element have been shown to mitigate thyroid autoimmunity, at least partly by inhibiting the secretory activity of human T cells [14,15,16]. Coeliac disease, regardless of its severity, is marked by a deficiency of selenium, which is more evident in individuals who do not adhere strictly to a gluten-

free diet compared to those who follow it diligently. We chose not to assess serum or whole-blood selenium concentrations as they do not show a strong relationship with the intake of this micronutrient in adults, indicating a greater consumption of selenomethionine and selenium-rich yeast supplements rather than other forms of selenium [2,8,17,18]. Nonetheless, the relatively low initial readings of the SPINA-GD index in both patient groups imply potential selenium deficiency within the studied demographic. The gluten-free diet could also directly suppress the activity of inflammatory cells. Supporting this notion, research indicated that dietary gluten impacts the ratio of pro-inflammatory to anti-inflammatory cytokines in mouse T cells [9], shifting it towards a more inflammatory state, while following a gluten-free diet led to decreased levels of pro-inflammatory cytokines in circulation. The gluten-free regimen resulted in an enhancement of the SPINA-GT index, which serves as an indicator of the peak secretion rate when stimulated. The impact on thyroid function was minimal because throughout the entire follow-up period, the SPINA-GT index values stayed within normal limits. Notably, changes in the SPINA-GT induced by treatment showed a correlation with both initial serum levels of TPOAb and TgAb, as well as with the decrease in thyroid antibody levels[11,12]. This observation leads us to two main inferences. First, the reducing influence of a gluten-free diet on thyroid autoimmunity might aid in enhancing the thyroid's secretory abilities. Second, the most significant effects on antibody levels were observed in patients exhibiting the highest titers. Given that thyroid antibodies and their levels could predict the risk of developing hypothyroidism, a gluten-free diet has the potential to postpone the onset of thyroid hypofunction in euthyroid women diagnosed with Hashimoto's thyroiditis [8,15]. While the gluten-free diet was found to elevate the SPINA-GT index, it did not influence other evaluated markers of thyroid homeostasis. The lack of impact on the SPINA-GD index, which assesses the overall activity of peripheral deiodinases, suggests that the gluten-free diet does not alter the peripheral metabolism of thyroid hormones. Lastly, the consistency of Jostel's thyrotropin index, which quantitatively measures pituitary thyrotropic activity, signals that the gluten-free diet does not have a direct impact on thyrotropic cells. Several limitations of our research need to be highlighted. The most significant drawback is that the study was not randomized, involved a small participant group, and had a short duration of treatment. Additionally, the participants exhibited low levels of selenium status and adequate iodine consumption. It remains unclear if the effects of a gluten-free diet are comparable in areas with sufficient selenium or those lacking iodine[5]. Moreover, since only euthyroid women were part of the study, it is still unknown whether the gluten-free diet influences antibody levels and thyroid function assessments in individuals with thyroid issues. Lastly, we cannot dismiss the possibility that the effects of the gluten-free diet could vary in women taking medications that lower thyroid antibody levels, such as levothyroxine, vitamin D, and selenium, which were not represented in our study. The gluten-free diet resulted in lowered serum levels of TPOAb and TGAb in euthyroid women diagnosed with Hashimoto's thyroiditis, alongside an increase in the SPINA-GT index[7]. This result suggests that adopting a gluten-free diet may provide clinical advantages for euthyroid women with Hashimoto's thyroiditis, who are at a heightened risk for hypothyroidism due to significantly elevated thyroid antibody levels. Given the study's constraints, it should be viewed as preliminary, indicating that further, more extensive prospective studies are needed to validate our results.

References

1. Lorini R, Gastaldi R, Traggiai C et al. Hashimoto's thyroiditis. Pediatr Endocrinol Rev 2003; 1: (Suppl 2): 205–211
2. Caturegli P, Kimura H, Rocchi R et al. Autoimmune thyroid diseases. Curr Opin Rheumatol 2007; 19: 44–48
3. Brown RS. Autoimmune thyroid disease: Unlocking a complex puzzle. Curr Opin Pediatr 2009; 21: 523–528
4. Hadithi M, de Boer H, Meijer JW et al Coeliac disease in Dutch patients with Hashimoto's thyroiditis and vice versa. World J Gastroenterol 2007; 13: 1715–1722
5. Stazi AV, Trinti B. Selenium status and over-expression of interleukin-15 in celiac disease and autoimmune thyroid disease. Ann Ist Super Sanita 2010; 46: 389–399

6. Fisher AH, Lomasky SJ, Fisher MJ et al. Celiac disease and the endocrinologist: A diagnostic opportunity. Endocr Pract 2008; 14: 381–388
7. Naiyer AJ, Shah J, Hernandez L et al. Tissue transglutaminase antibodies in individuals with celiac disease bind to thyroid follicles and extracellular matrix and may contribute to thyroid dysfunction. Thyroid 2008; 36: 1171–1178
8. Krysiak R, Okopień B. The effect of levothyroxine and selenomethio- nine on lymphocyte and monocyte cytokine release in women with Hashimoto's thyroiditis. J Clin Endocrinol Metab 2011; 96: 2206–2215
9. Jostel A, Ryder WD, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: Definition and evaluation of the TSH index. Clin Endocrinol 2009; 71: 529–568
10. Street ME, Volta C, Ziveri MA et al. Changes and relationships of IGFS and IGFBPS and cytokines in coeliac disease at diagnosis and on gluten-free diet. Clin Endocrinol (Oxf) 2008; 68: 22–28
11. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study Group. Lancet 1994; 344: 1383–1389
12. Arrigo T, Wasniewska M, Crisafulli G et al. Subclinical hypothyroidism: the state of the art. J Endocrinol Invest 2008; 31: 79–84
13. Szybiński Z.Polish council for control of iodine deficiency disorders. Work of the Polish council for control of iodine deficiency disorders, and the model of iodine prophylaxis in Poland. Endokrynol Polska 2012; 63: 156–320
14. Muller AF, Drexhage HA, Berghout A. Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: Recent insights and consequences for antenatal and postnatal care. Endocr Rev 2001; 22: 605–630
15. Kłapcińska B, Poprzecki S, Danch A et al. Selenium levels in blood of Upper Silesian population: Evidence of suboptimal selenium status in a significant percentage of the population. Biol Trace Elem Res 2005; 108: 1–15
16. Hinks LJ, Inwards KD, Lloyd B et al. Body content of selenium in coeliac disease. Br Med J (Clin Res Ed) 1984; 288: 3662–3663
17. Kalita B, Nowak P, Slimok M et al. Selenium plasma concentrations in children with celiac disease in different stages of diagnosis. Pol Merkur Lekarski 2002; 12: 43–44
18. Hurst R, Collings R, Harvey LJ et al. EURRECA-estimating selenium requirements for deriving dietary reference values. Crit Rev Food Sci Nutr 2012; 53: 1077–1096