

Review Article

Hypothyroidism and celiac disease: correlations and therapeutic implications*Hipotireoidismo e doença celíaca: correlações e implicações terapêuticas***Ruana Farias Novaes¹, Lauro José Ribeiro Viana²**

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ABSTRACT: Hypothyroidism represents a thyroid hypofunction, mainly caused by autoimmune diseases of the gland, characterized by a local thyroid immune response that reduces the production of thyroid hormones. Celiac disease (CD), on the other hand, is a permanent autoimmune enteropathy triggered by gluten, causing the production of several autoantibodies. A significant percentage of individuals with hypothyroidism requires higher doses of T4 to achieve optimal TSH levels, among which are celiac patients. Also, considering different causes that diversify the clinical presentation of CD, one of the most common is hypothyroidism. Thus, focusing on establishing associations between both diseases, a review based on MEDLINE and SciELO's was developed. Results show that autoimmune diseases are commonly associated and represent risk factors for each other. However, the indiscriminate screening of these diseases is still impracticable and has little benefit. Therefore, knowing when to suspect clinically and how to investigate hypothyroidism and/or CD is extremely important.

Keywords: Hypothyroidism; Celiac disease; Autoimmune diseases.

INTRODUCTION

Hypothyroidism is a deficiency in the production of thyroid hormones (TH). With a vast clinical presentation, laboratory tests define it as a low dosage of thyroid hormones and a high dosage of thyroid-stimulating hormone (TSH). In terms of etiology, countries with adequate iodine intake, such as Brazil, have a high autoimmune recurrence. In autoimmune disorders, antibodies attack the thyroid gland and develop

RESUMO: O hipotireoidismo é definido como uma hipofunção da tireoide, tendo como principal causa, atualmente, as doenças autoimunes da glândula, caracterizadas por uma resposta imune local e redução da produção dos hormônios tireoidianos. A doença celíaca (DC), por sua vez, é definida como uma enteropatia autoimune permanente desencadeada pelo glúten, na qual há produção de diversos autoanticorpos. Uma parcela significativa de pacientes com hipotireoidismo requer doses maiores de T4 para alcançar os níveis ideais de TSH, incluindo os pacientes celíacos. Ademais, dentre as causas que diversificam a apresentação clínica da DC destaca-se o hipotireoidismo. Com o objetivo de estabelecer associações entre ambas as doenças foi realizada uma revisão embasada nos bancos de dados MEDLINE e SciELO. Os resultados mostram que as doenças autoimunes comumente se associam e representam fatores de risco entre si. Porém, o rastreamento indiscriminado dessas ainda é inviável e pouco benéfico. Por isso, saber quando suspeitar clinicamente e como investigar o hipotireoidismo e/ou a DC é de extrema importância.

Descritores: Hipotireoidismo; Doença celíaca; Doenças autoimunes.

a hypofunctional state¹.

Celiac disease (CD), on the other hand, is a permanent autoimmune enteropathy triggered by gluten, a protein that can be found in wheat, rye, and barley, causing the production of several autoantibodies. In genetically predisposed individuals, the disease causes inflammatory responses in the small intestine mucosa, culminating in villous atrophy, T lymphocyte infiltration, and intestinal crypt hyperplasia².

There is an increased prevalence of autoimmune

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diseases in patients who already have other illnesses of the same sort. In celiac patients, for instance, this association may be based on the fact that CD and such autoimmunities share similar pathogenic mechanisms or perhaps a defect in the same genes. There is still a lack of data on the association of these pathologies, but it is possible to find higher correlations with hypothyroidism, type 1 diabetes mellitus, autoimmune liver diseases, inflammatory bowel diseases, rheumatoid arthritis, chromosomal syndromes, pemphigus, and several others, as it has already been documented. It is common knowledge that individuals with celiac disease have a greater risk of developing hypothyroidism, and the opposite is also true^{3,4}.

With that setting, the goal of the study was to establish associations between hypothyroidism and celiac disease, especially in refractory cases to treatment with levothyroxine, and to estimate the influence of one pathology on the effective treatment of the other. Specifically, there was an interest in: (1) amplifying the knowledge that these conditions are linked and, therefore, may be identified earlier; (2) establishing genetic and environmental factors that predispose the presentation of the two pathologies in the same person; (3) identifying celiac disease and hypothyroidism as risk factors for other pathologies; (4) emphasizing the importance of gluten restriction to avoid negative consequences; (5) disseminating, in Portuguese language, the knowledge acquired about both diseases; and, finally, (6) stimulating the elaboration of studies that correlate the two diseases in Brazilian patients.

Chart 1: Articles distribution

Topic	Author/Year		
Hypothyroidism general aspects and refractoriness to levothyroxine treatment	Alexander et al., 2004 Cellini et al., 2014 Centanni et al., 2006 Chaker et al., 2017 Deiana et al., 2012 Eligar et al., 2016	Garber et al., 2012 Hoermann et al., 2017 Jonklaas et al., 2014 Kahaly et al., 2015 Lips et al., 2004 Lobasso et al., 2017	Lundin et al., 2015 Mehrdad et al., 2012 Neumann et al., 2013 Venneman et al., 2018 Virili et al., 2018
Celiac disease overview	Abadie et al., 2011 Emilsson et al., 2015 Fasano et al., 2003 Freeman, 2009 Freeman, 2016 Hill et al., 2005 Husby et al., 2012	Lionetti et al., 2015 Liu et al., 2014 Lohdi et al., 2018 Ludvigsson et al., 2014 Nejad et al., 2011 Passos et al., 2017 Sdepanian et al., 2001	Silano et al., 2007 Silva et al., 2006 Sollid et al., 2013 Tursi et al., 2006 Volta et al., 2001 Zubarik et al., 2015
Etiology and epidemiology of hypothyroidism and celiac disease association	Collin et al., 2002 Emilsson et al., 2015 Harpreet et al., 2016	Kahaly et al., 2015 Kahaly et al., 2018 Lundin et al., 2015	Neuhausen et al., 2008 Nijhawan et al., 2013 Zhao et al., 2016
Refractory hypothyroidism in celiac patients	Bayless et al., 2017 Cellini et al., 2014 Ch'ng et al., 2007 Collins et al., 2012	Hadit et al., 2007 Virili et al., 2012 Jiskra et al., 2003 Lebwohl et al., 2018	Liwanpo et al., 2009 Virili et al., 2018 Ward, 2010
Other implications about the simultaneous pathologies	Collin et al., 2002 Freeman, 2016 Goddard et al., 2006 Hakanan et al., 2001	Lundin et al., 2015 Metso et al., 2012 Nenna et al., 2013 Rua et al., 2017	Sategna et al., 2001 Williamson et al., 2002

MATERIALS AND METHODS

This study is a narrative literature review. To develop it, the Health Sciences Descriptors (DeCS) “hypothyroidism” and “celiac disease” were applied through the Boolean operator AND, restricting the search in the MEDLINE and SciELO’s databases. Afterward, there was a selection, organization, and bibliographic analysis of the data. As a result, articles in Portuguese and English, published between 2000 and 2018, were selected. Finally, after reading the title and abstract of each article, the studies were distributed in one or more of the following categories: (1) hypothyroidism general aspects and refractoriness to levothyroxine treatment; (2) celiac disease overview; (3) etiology and epidemiology of hypothyroidism and celiac disease association; (4) refractory hypothyroidism in celiac patients; and (5) other implications about the simultaneous pathologies.

RESULTS

We found 201 articles in MEDLINE’s database and eight in SciELO’s. Excluding the ones that did not match the established topics, 59 articles remained to compose this paper (Chart 1). It is worth mentioning that, out of the chosen databases, a ministerial decree concerning CD was consulted, totaling the 60 cited bibliographic references.

DISCUSSION

Next, we will discuss the main aspects of refractoriness to hypothyroidism, its association with celiac disease, and the implications of this overlap.

Hypothyroidism: general aspects and levothyroxine treatment refractoriness

Nowadays, autoimmune disorders are the main cause of thyroid hypofunction. Diseases in this spectrum have a local immune response that reduces the production of the thyroid hormones T3 (triiodothyronine) and T4 (thyroxine), phenomena seen in Hashimoto's thyroiditis and Graves' disease. Hashimoto's thyroiditis is the most prevalent thyroid disease, and also the most associated with other endocrinopathies. It is defined by the presence of antithyroid peroxidase (antiTPO) or antithyroglobulin antibodies, with normal or high levels of TSH in the absence of medications^{5,6}.

The lower basal metabolism and the reduction in adrenergic activity characterize the clinical course of hypothyroidism. There may be weight gain, dyslipidemia, dysglycemia, disturbances in children's growth and development, menstrual alterations, and miscarriages. Regarding its complications, although it is rare, the risk of thyroid lymphoma is 67 times greater in patients with Hashimoto's disease⁵.

The treatment for hypothyroidism is levothyroxine supplementation, aiming for normal TSH levels. Levothyroxine is a synthetic T4 hormone that, when orally administered, is absorbed in the small intestine after the action of gastric juice. The consensual dose is 1.6 to 1.8 µg/kg/day, a value capable of restoring TSH to normal levels in most patients with hypothyroidism⁷.

However, several factors may affect this standard dosage, culminating in complete biochemical or clinical response failure in approximately 20 to 50% of patients. Thus, these patients will need greater doses, care, monitoring, and repetition of diagnosis methods, representing an additional cost to health systems⁸.

In drugs with a narrow therapeutic index, such as levothyroxine, the medication effectiveness depends on many factors, including appropriate dosage, mode of ingestion, absorption, and associated conditions. Therefore, this indicates that there can be wide variations in the responses to the drug. In this context, hypothyroidism is said to be refractory to levothyroxine when there is clinical or biochemical evidence of the condition, with lower than the reference value-free T4 after the last dose, and/or unresolved symptoms of hypothyroidism, even with administration of high levothyroxine doses, usually above 1.9 µg/kg/day^{9,10}.

According to our findings, levothyroxine pseudo-

malabsorption is the primary and first cause to be excluded in refractory patients to hypothyroidism treatment as the condition consists of poor therapeutic adherence when the drug is not adequately ingested; or the fasting for its administration is not respected. In that case, TSH remains persistently increased regardless of the administration of high T4 doses, so patients must receive proper instructions and, if possible, be observed during the medication intake period to exclude this hypothesis¹¹.

About fasting, it is established that levothyroxine requires the action of acidic pH for adequate dissolution and subsequent intestinal assimilation. When administered after a meal, especially with foods containing dietary fiber (e.g., dairy and soy products, coffee, and papaya), its degradation reduces due to changes in pH. Consequently, there is a change in intestinal absorption, affecting motility and deconjugation of bacterial enzymes, biliary excretion, decreased enterohepatic circulation of thyroid hormones, and increased fecal loss of replaced T4¹².

Therefore, non-fasting T4 administration is associated with a higher variation in serum TSH levels, so the recommendation is to postpone breakfast for 30 minutes to 1 hour after taking T4. In recent studies, the daily dose of T4 during fasting to obtain TSH levels between 0.5 and 2.5 mU/L was 1.3 µg/kg, a much lower dosage than the previously mentioned, adopted by the American Thyroid Association – 1.6 to 1.8 µg/kg. These findings may be justified, as said, by the modification of gastric acidity promoted by the food bolus, which can reduce the hormone bioavailability^{9,13}.

Once pseudo-malabsorption is excluded, using other drugs should be extensively investigated in patients with refractory hypothyroidism. While many medicines can bind T4 and form insoluble complexes, others act at different stages of its absorption, altering the pharmacokinetics of levothyroxine for several reasons: proton pump inhibitors, aluminum hydroxide, ferrous sulfate, cholestyramine resins, orlistat, simethicone, and raloxifene¹⁴.

In cases of refractory hypothyroidism in women of reproductive age, hypothetical pregnancy should be ruled out. Pregnant women demand higher doses of levothyroxine for different reasons, and, during pregnancy, the dosage of T4 required for TSH regulation is high. It is caused by the reduction in TSH levels, as human chorionic gonadotropin (hCG) stimulates its receptors and raises overall T4 levels – whose peak occurs around the 16th gestational week – developing a negative feedback mechanism. At the same time, a carrier protein, called thyroxine-binding globulin (TBG), which reduces the bioavailability of free T4, starts increasing. Additionally, there is a change in levothyroxine's pharmacokinetics because gastrointestinal peristalsis decreases in pregnant women since the increase in progesterone levels is capable of delaying gastric emptying, also prolonging transit in the small intestine^{15,16}.

Finally, after excluding pseudo-malabsorption, applying a detailed pharmacological and nutritional anamnesis, and ruling out the possibility of pregnancy, pathologies capable of causing T4 malabsorption should be considered. Here, we categorize the probable conditions in gastric, intestinal, and others. Examples of gastric conditions include *Helicobacter pylori* infection, autoimmune gastritis, and gastroparesis, with *H. pylori* infection being the most prevalent disorder capable of interfering with the stomach's pH. For the last case, pathogen investigation via urea breath test or fecal antigen test is recommended, in addition to testing for antibodies against the bacteria. If the result is positive, specific treatment should be initiated with an evaluation of gastric mucosa via serial biopsies¹⁷.

In negative cases of *H. pylori* infection, anti-parietal cells autoantibodies (antiPCA) and fasting gastrinemia are investigated to look for autoimmune atrophic gastritis. If gastrin levels are high and antiPCA is confirmed, endoscopy with biopsies should be performed to evaluate the involvement of the body and gastric antrum¹⁸.

Regarding gastroparesis, there is delayed gastric emptying in the absence of mechanical obstruction. In addition, there is a strong correlation between gastroparesis and T4 malabsorption with different etiologies, such as idiopathic, post-surgical, or diabetes-related. An erratic exposure to gastric hydrochloric acid keeps the food bolus in the patient's stomach for a longer time, changing the luminal pH and, consequently, the chemical reactions suffered by the drug. In these cases, weekly intramuscular T4 injections can improve thyroid hormone profile^{1,9}.

At last, regarding intestinal conditions that cause levothyroxine malabsorption, the main one is celiac disease, discussed below. Other hypotheses can be considered, such as giardiasis, which causes intense intestinal mucosa inflammatory response and epithelial apoptosis, and also short bowel syndrome, characterized by a shortening of the absorptive surface. After gastric and intestinal conditions, we mention pancreatic insufficiency and cystic fibrosis as examples of other malabsorption etiologies, which cause steatorrhea due to the absence of lipases and the ability to increase T4 fecal loss; and liver cirrhosis which, as a result of reduced bile secretion, decreases T4 binding to intraluminal proteins¹⁴.

Celiac disease

Celiac disease is an autoimmune disorder triggered by dietary gluten – composed of gliadin and glutenin – in genetically susceptible patients, causing histopathological changes in small intestine proximal portions. Among these changes, we highlight epithelial infiltration, with rich plasma cells and lymphocytes lamina propria; intestinal mucosa villi atrophy; more cuboidal and less columnar epithelium appearance; crypt hyperplasia; and high mitotic index²⁰.

Subcellular alterations, such as increased epithelial vacuolization and glycocalyx changes, also occur, resulting in significant malabsorption clinically expressed as diarrhea, abdominal discomfort, and weight loss – the classic CD triad. Among other disorders caused by malabsorption, there are also clinical findings of iron deficiency, anemia, and hypocalcemia².

It is also important to highlight that genetic factors are strongly associated to the emergence of celiac disease. There is a 75% concordance in monozygotic twins and 10% in first-degree relatives.²¹ The haplotype most associated with immune and non-immune cell effects is a variant of HLA-DQ2, found in 90 to 95% of celiac patients. Consequently, the remaining patients were associated with HLA-DQ8. The HLA-DQ molecules present gluten peptides to T cells, and, after this point, T cells produce IFN- α , IFN- γ , TNF, IL-4, IL-5, and IL-2122. The immune system also produces autoantibodies, especially of the IgA class, capable of affecting different body tissues. The most common autoantibody is the anti-tissue transglutaminase²³.

Gluten exposure is a crucial environmental factor to initiate disease in genetically predisposed individuals, but others factors are under investigation. Thus, it is still unknown if intestinal microbiota, antibiotics and other drugs usage, and intrauterine and perinatal exposures, among many others, affect CD genesis²⁴. More work is needed to clarify celiac disease etiology, genes involved in pathology, other environmental factors capable of triggering the condition, and the role of gut responses to these stimuli²⁵.

Nowadays, the disease is considered much more common than previously thought. With a universal prevalence of one in 150 people, it is the most common autoimmune disease of the small intestine, affecting 1-2% of individuals with Caucasian ancestries, such as Europeans, North and South Americans, Arabs, Indians, Pakistanis, and Northern Chinese. Although typically described in children, more and more adults express the disease, with diverse intestinal and/or extraintestinal manifestations^{21,23}.

In Brazil, one in 474 adults and one in 184 children develop undiagnosed CD. The incidence of celiac disease in individuals aged 1 to 14 years is 5.44 per 1,000 people, while in adults, the number is 2.11 per 1,000, showing that CD is not a rare disease in our country and has similarities with European rates²⁶.

The symptoms diversity is the biggest diagnostic challenge of this enteropathy, making its clinical suspicion difficult. CD presents itself differently, and less characteristic or later-onset patterns may include absent or unimportant digestive manifestations. In these situations, clinical cases differ from the commonly associated model, resulting in a significant obstacle to pathology diagnosis^{21,27}.

Clinically, CD has three categories: classic (or typical), non-classical (or atypical), and asymptomatic (or silent). The classic form includes signs and symptoms of

the gastrointestinal tract, such as chronic diarrhea, bloating, weight loss, nutritional deficits, and steatorrhea. The non-classical form adds extraintestinal manifestations and may have subtle or absent gastrointestinal symptoms, such as short stature, dental enamel hypoplasia, changes in bones mineral density, pubertal delay, infertility, refractory iron deficiency anemia, megaloblastic anemia, arthralgia and arthritis, liver disease, neurological disease, and behavioral changes. At last, asymptomatic patients have positive serology for CD and possible changes in the biopsy but discrete clinical manifestations that may progress to other forms after continuous gluten exposure²⁸.

Although the most recurrent CD presentation in adults is the one called classic, with clear signs of intestinal malabsorption, it is important to understand that these manifestations may vary in different patients²⁹.

Sdepanian et al.³⁰ analyzed 289 questionnaires from patients registered in the *Associação dos Celiacos do Brasil* (Celiac's Brazilian Association), investigating diagnosis methods, and signs and symptoms presented by the time of CD's confirmation. After the evaluation, it was found that 88.9% of patients had the classic form of celiac disease, while 11.1% had the non-classical form. Although the classical form continues to be more common, according to the authors, there was an increase in the proportion of non-classical cases compared to records from the 1980s.

Therefore, as the increasing number of signs and symptoms make it difficult to identify CD, especially in adolescents and adults, this disease should be remembered even when the classic symptoms are not present^{27,31}. The heterogeneity of celiac disease must be recognized, and the classic intestinal form should be seen as one of its phenotypic presentations.

Because of that, extraintestinal presentations became attributed as consequences of enteropathy, including endocrine manifestations³². It is known that up to half of the patients have systemic presentations³³.

The first step in diagnosing celiac disease is laboratory investigation of tissue or endomysial transglutaminase antibodies. Although these tests do not confirm CD, they work as screening tools. Considering that, individuals who benefit from antibodies screening are the ones that: (1) have signs or symptoms of classic CD; (2) are at risk, among whom the prevalence of CD is expected to be considerably higher than the general population – first-degree relatives of CD patients; (3) have non-classical CD findings, such as refractory to oral replacement iron anemia, reduced bone mineral density, pubertal delay or short stature with no apparent cause, among others; (4) carry autoimmune diseases such as insulin-dependent diabetes mellitus, autoimmune thyroiditis, selective IgA deficiency, Sjögren's syndrome, autoimmune cholestasis, autoimmune myocarditis, Down syndrome, Turner syndrome, Williams syndrome, infertility, history of spontaneous miscarriage and/or dermatitis herpetiformis³⁴.

After the screening, in case of diagnosis of celiac disease, two sequentially adopted criteria are required. The first criterion is typical histopathological change on proximal small intestine biopsy before treatment. Then, with a gluten-free diet, regression of the biopsy changes should take place. The only therapy for this disorder is to eliminate the type of cereals we previously mentioned from the diet, which is capable of reversing most of intestinal changes presented²⁹.

A worrying fact: 19% of 289 Brazilians investigated did not undergo a biopsy for CD diagnosis, which signals the need to clarify to the medical population that the histopathological small intestine study is an essential criterion³⁰. More recent studies with a similar focus were not found in Brazilian celiac patients.

The biopsy can only be ruled out in two situations: if anti-tissue transglutaminase autoantibodies are 10 times higher than the upper reference limit by the time of screening, with HLA and anti-endomysial tests also positive; or if there is a significant clinical improvement after gluten consumption restriction, solving diarrhea and weight loss (in situations of difficult access to the histopathological study)³⁵.

Early diagnosis and treatment of CD are essential because any delay can lead to complications. Celiac disease has a strong association with neoplasms, a case in which the greatest risk is represented by non-Hodgkin's lymphoma, but other malignancies such as small intestine adenocarcinoma, colon carcinoma, Hodgkin's lymphoma, and stomach carcinoma can also be identified². Therefore, early identification of CD is extremely important, avoiding the exposure time to gluten and intestinal epithelium aggression².

Most celiac patients remain undiagnosed and the risk of complications increases³⁶. In addition to neoplasms (and the autoimmune conditions discussed below), there are other common conditions in celiac patients, especially in those who are not diagnosed or who do not adopt a gluten-free diet. Among them, we can mention: Crohn's disease, also associated with increased Th1 response and chronic inflammation, although Crohn's patients have much less association with HLA genes³⁷; hepatitis B, since patients with HLA haplotypes, such as celiac patients, tend to be unresponsive to vaccination against this disease due to genetic mechanisms that are still under investigation³⁸; and calcium, copper, folate, and zinc deficiencies, given the absorptive importance of the small intestine³⁹.

Etiology and epidemiology of hypothyroidism and celiac disease association

Hypothyroidism occurs in 5 to 15% of patients with celiac disease, a risk 4 times greater than in control groups. Celiac disease, on the other hand, occurs in 2 to 5% of patients diagnosed with autoimmune thyroiditis, also

more prevalent than in control groups. It is suggested that patients with autoimmune thyroiditis should be investigated for celiac disease and vice versa, but the pathogenesis of this association still requires further investigation⁴⁰.

The link between the two diseases can be attributed to genetic reasons, especially when considering the finding of HLA haplotypes in both conditions. This connection can also be explained by the hypothesis that the thyroid and the small intestine share the same embryological origin – the pharyngeal intestine – facilitating simultaneous diseases. In addition, the change in intestinal permeability resultant from celiac disease may explain the circulation of various antigens in the body that begin to react with tissues such as the thyroid⁴¹.

The existence or future development of other autoimmune diseases must be considered in all patients with celiac disease, autoimmune endocrinopathies, or both⁵. In a cohort²¹ that evaluated the risk of other autoimmune diseases in first-degree relatives and spouses of celiac patients, there was a higher prevalence in both cases, proving the mixture of genetic and environmental factors in their etiology. Hypothyroidism was one of the diseases described, therefore reinforcing the need to study this combination.

Studying individuals with autoimmune diseases or those who, from a genetic point of view, have a higher chance of developing them is a prevention act. Since such conditions can coexist in a subclinical way for many years, some authors suggest evaluating newborns with high chances of developing celiac disease, such as children of parents with CD, recommending prospective studies that allow greater control of variables for long-term analysis^{6,42}.

Polymorphisms of several immune response genes (IRG) overlap to generate susceptibility to celiac disease and glandular autoimmune diseases, including hypothyroidism. Consequently, CD should be screened in patients with autoimmune thyroid disease in the same way that these patients should be screened for celiac disease⁴³.

Refractory hypothyroidism in celiac patients

It is necessary to keep an eye out for the development of other autoimmune diseases in patients who have already been diagnosed with one of them. Besides predisposition, the treatment of these diseases is highly influenced by the concomitance of pathologies^{29,44}, one of the main consequences of the coexistence of the two conditions. The proximal intestine, typically damaged in celiac disease, is where the greatest absorption of levothyroxine occurs, and where 62 to 82% of the administered levothyroxine is absorbed. Possible reasons for incomplete absorption include the different effects of hypothyroidism, drug and food interactions, individual characteristics (age and body mass index), bioequivalence between formulations, and concomitant diseases. CD is one of these reasons, requiring

higher levels of levothyroxine^{45,46}.

The CD mechanisms that affect T4 absorption originate from the progressive reduction of intestinal surface – with shortening and effacement of the intestinal villi – due to apoptosis of enterocytes and inadequate cell regeneration in the crypts, and intense lymphocytic infiltration. Celiac patients also have an increase in intestinal permeability, changes in gastrointestinal transit time, and changes in luminal pH. Delayed gastric emptying has also been described, as well as increased bacterial growth in the small intestine, all factors implicated in T4 absorptive change¹⁴.

Besides, there is protein and enzyme loss in the intestinal brush border, impairing the absorption of various nutrients. Together with celiac disease, there may be concomitance with lactose intolerance, a condition caused by a decreased activity of lactase, the enzyme responsible for sugar hydrolysis. This other condition is called secondary when caused by the destruction of the small intestine lining, as it occurs in CD. If the process of carbohydrate hydrolysis does not occur properly, the compound accumulates and exerts an osmotic effect in the intestinal lumen, which can also decrease T4 absorption and increase intestinal motility, further reducing the exposure of the hormone to the absorptive surface. Lactose intolerance is also associated with bacterial overgrowth, which influences T4 recycling via enteropathic circulation^{9,47}.

Thus, patients with hypothyroidism and CD need higher doses of T4 than those with hypothyroidism only. These patients, when receiving treatment, require constant monitoring and dose adjustment. Failure to follow up on these patients can even result in overdose hyperthyroidism⁴⁸.

The prevalence of celiac disease in patients with hypothyroidism and the benefits of early detection of the enteropathy in these individuals should be evaluated to recommend screening. Patients who require higher doses to maintain the euthyroid state may represent an indicated research population. In the presence of abdominal bloating and pain, chronic diarrhea and/or refractory iron deficiency anemia in patients with refractory hypothyroidism, there should be high suspicion of CD⁴⁹.

Detecting and treating celiac disease in hypothyroid patients, as well as avoiding the symptoms and complications of untreated enteropathy, is possibly key to success in levothyroxine treatment. However, although screening for CD may be useful to increase the effectiveness of T4 treatment in patients with thyroiditis, the cost-effectiveness of the process still requires further studies^{50,51}.

There is a chance to reduce the doses of T4 administration after starting the gluten-free diet. An American retrospective study⁵² evaluated individuals with celiac disease and hypothyroidism, comparing them to the control group, with only hypothyroidism. The cases in this study required doses of at least 1.5µg/kg to

maintain the euthyroid state, postulating that patients with equal or greater doses than this should undergo serology for celiac disease. According to the findings, the doses of levothyroxine needed to maintain normal thyroid function in patients with untreated celiac disease and hypothyroidism are higher than those needed for patients who do not have CD. Furthermore, it is relevant that the required dose of the synthetic hormone decreases after dietary treatment in celiac patients, possibly due to the reversal of drug malabsorption.

Virili et al.⁵³ evaluated 35 patients with hypothyroidism and celiac disease of atypical manifestation. Among these, 21 received the same dosage of T4 and were investigated for their ability to reach the TSH target before and during the gluten-free diet, while 14 celiacs did not change their eating habits. They were compared to a group of 68 patients with isolated hypothyroidism and without evidence of celiac enteropathy. All three groups reached the TSH target, however, the two celiac groups needed more time, and those who did not adopt the gluten-free diet needed superior dosages of T4, almost 50 percent higher than average. The study reinforced the greater need for T4 in celiac patients, especially in the absence of a gluten-free diet.

Other implications about the simultaneous occurrence of the pathologies

The high prevalence of autoimmune thyroiditis in adults can make the identification of celiac disease more difficult. The severity of diarrhea or weight loss, some of the previously mentioned standard symptoms of celiac enteropathy, is limited by lower action of thyroid hormones, while on the other hand, there is an increase in intestinal transit time, fluid retention, myxedema, and consequent weight gain³¹.

Patients with classic indicators such as weight loss, chronic diarrhea, and malabsorption represent a decreasing proportion of the total celiac population, endorsing the heterogeneous character of the disease and the need to perform constant updates about its symptoms. The clinical course of the two diseases combined is, as said, even more eccentric. Considering that the more atypical the presentation of celiac disease, the later the diagnosis tends to be given⁵⁴, it is essential for its early identification to know the different clinical manifestations of the association between CD and hypothyroidism⁵⁵.

About 60% of celiac patients are undiagnosed and do not adopt a gluten-free diet. The gluten-free diet has organ-specific effects on the thyroid of celiac patients, although limited. In addition to the exogenous T4 reduced dose, as mentioned, in some cases there is a clinical or subclinical recovery of thyroid function after gluten exemption^{44,56,57}.

An Italian multicenter study⁵⁷ evaluated 128 newly

diagnosed celiac patients a year after they began a gluten-free diet. At the time of CD diagnosis, measurements of TSH, free T3, free T4, and thyroperoxidase were performed, which showed that 91 of them had normal thyroid function and 37 had some clinical or subclinical alteration of the gland. After one year, an intestinal biopsy was repeated in 75 of the 128 patients (58.6%) and showed recovery of the intestinal mucosa in 43 of them (57.3%) and partial or total persistence of mucosal atrophy in 32 (42.7%). The study emphasizes the improvement of thyroid function in celiac patients after gluten withdrawal and shows that most patients who strictly followed the diet – confirmed by intestinal biopsy with mucosal recovery – had their thyroid changes normalized. However, 25% of patients with antibodies to the disease in the euthyroid state evolved with subclinical hyperthyroidism or subclinical hypothyroidism. In these individuals, intestinal biopsy findings showed that the adherence to the diet was poor.

On the other hand, a Finnish study⁵⁸ separated 27 patients recently diagnosed with CD (7 with overt hypothyroidism and 3 with subclinical hypothyroidism) submitted to a year of a gluten-free diet, opposed to 27 non-celiac individuals (3 of them with hypothyroidism). After this first stage, the thyroid volume and echogenicity were evaluated via ultrasound. Next, anti-TPO and anti-transglutaminase antibodies, as well as thyroid function tests, were also performed. Thyroid volume decreased in control patients regardless of their gluten-free status, indicating the evolution of gland atrophy independently of diet changes. Therefore, the study showed no influence of the one year gluten-free diet on clinical – or even radiological – changes in the course of Hashimoto's thyroiditis.

The most frequent clinical finding in hypothyroid patients is symmetrical and painless goiter. However, the thyroid has a smaller volume in celiac patients when compared to control groups. As the atrophy of the gland tends to be bigger and less goiter in patients with both diseases, this indicates a possible barrier for diagnosing hypothyroidism, with physical examination of the thyroid showing innocent or little change on palpation⁵⁹.

Finally, a less known consequence of the simultaneity of the diseases, but still of extreme importance, concerns the patients' quality of life and health-disease perception of patients. A cross-sectional study⁶⁰ investigated celiac patients on, among other variables, adoption of a gluten-free diet and presence or absence of concomitant diseases. Participants were asked to rate, on a scale from 0 to 10, their perception of themselves as "healthy or sick". Analyzing the responses, it was found that approximately 87% of celiac respondents felt healthy. This number was influenced by the low prevalence of associated conditions and the longer duration of gluten exclusion from the diet. On the other hand, individuals with more associated conditions and shorter CD treatment time declared themselves less

healthy. It is worth highlighting that patients diagnosed hypothyroidism only did not have worse indices of well-being; however, when hypothyroidism was added to diabetes, arthrosis, osteoporosis, vitiligo, anemia, asthma, osteopenia, or hypercholesterolemia, the rate dropped.

Few scientific studies have described the implications of celiac disease on health systems, and even fewer have evaluated these aspects arising from the association between celiac disease and hypothyroidism, a topic that still needs research⁶.

CONCLUSION

Genetic and environmental aspects, many of which are still unknown, make hypothyroid individuals more likely to develop CD, and the opposite is also true. Autoimmune diseases can commonly associate and represent risk factors for each other. However, indiscriminate screening of these diseases is still impracticable and little beneficial. As shown, it is of utmost importance knowing when to clinically suspect and how to investigate autoimmune hypothyroidism and CD.

We also pointed out that, in patients with hypothyroidism, celiac disease is a proven cause of levothyroxine malabsorption. When faced with a patient who requires a higher dosage of T4 to achieve optimal

TSH levels, the physician must consider poor adherence to treatment and even pregnancy before starting a specific investigation for CD. Thus, it is essential to know which hypothyroid patients should be screened for enteropathy.

In patients with celiac disease, hypothyroidism should be suspected, especially in the presence of atypical symptoms. The studies confirm CD presentation changes when associated with hypothyroidism. Facing celiac disease no longer as an exclusive cause of gastrointestinal tract symptoms and thinking about it as a diagnostic hypothesis, when applicable, is fundamental for the early diagnosis of pathologies.

Thinking about the association of the two diseases described here brings benefits such as: (1) possibility of administration of smaller doses of levothyroxine to hypothyroid patients when celiac disease is discovered and treated; (2) early diagnosis of hypothyroidism, especially in non-classical CD clinics; and (3) an increase in life quality of patients and caretakers regarding physical, mental, psychosocial, and economic reasons, since the need for assistance or complications of diseases decreases due to adequate treatment. More studies must be conducted to accurately point out the factors that determine the isolated and associated emergence of these diseases, as well as the individual, family, and health systems impacts arising from this junction, especially in Brazilians.

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