

# Autoimmune Thyroid Disease with Hypothyroidism in Adult Celiac Disease

Hugh J Freeman \*

Department of Medicine (Gastroenterology), University of British Columbia, Vancouver, BC, Canada

\*Corresponding author: [hugfree@shaw.ca](mailto:hugfree@shaw.ca)

**Abstract** Evidence largely from earlier prevalence studies and recent population-based studies indicate that there is a strong clinical association between autoimmune thyroid disease and adult celiac disease. In part, at least, this appears to be related to common genetically-based determinants as well as a common embryonic origin since the fetal thyroid is derived from the pharyngeal gut. Specific phenotypic features have been described if both disorders are defined, including dermatitis herpetiformis, and a greater risk for a malignant complication, including lymphoma, especially if celiac disease is initially diagnosed at a late age. Some phenotypic characteristics of autoimmune thyroid disease, such as orbitopathy, may be an important clue to occult celiac disease. Similarly, a high thyroxine dose requirement for treatment of autoimmune thyroid disease may be another phenotypic characteristic of undetected celiac disease. Serological screening for celiac disease should be considered if autoimmune thyroid disease is detected.

**Keywords:** hypothyroidism, thyroiditis, hashimoto's thyroiditis, adult celiac disease

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## 1. Introduction

Celiac disease is an immune-mediated small intestinal mucosal disorder that responds to restriction of dietary gluten [1]. Celiac disease is relatively common, especially in Europe and the Americas, with screening studies of different populations showing that up to 2% may be affected, based on serological evaluation, and likely more in referred patients with endoscopic screening biopsies [2]. A number of extra-intestinal sites may display features of an associated immune-mediated inflammatory process, often with alterations in normal function. In adults with celiac disease, co-existent immune-mediated endocrine manifestations occur, particularly immune-mediated thyroiditis with reduced thyroid function, summarized elsewhere [3]. In earlier studies, it was already well recognized that specific HLA haplotypes, B8 and DR3, occurred with increased frequencies in either adults or children with autoimmune thyroid disease or celiac disease. Because of these shared haplotypes, it has been widely hypothesized that the relationship between autoimmune thyroid disease and celiac disease is genetically determined or, alternatively, this may be related to a common embryonic origin as the fetal thyroid gland is derived from the pharyngeal gut on the 17th day [3].

Physicians caring for patients with celiac disease may consider screening or case-finding for co-existent thyroid disease since (it can be argued) definition of concomitant (or later) thyroid disease could affect patient quality of life and clinical management. In some adult celiacs, other individual endocrine glands may also be affected as a

more generalized immune-mediated polyglandular clinical disorder may occur, often with reduced glandular function [3]. Here, the focus will be adults with celiac disease and thyroiditis with hypothyroidism, even though children and adolescents with celiac disease may also suffer from one or more concomitant immune-mediated endocrinopathies.

## 2. Initial Prevalence Evaluations

Immune-mediated thyroid disease, usually with reduced thyroid function, was initially described in early descriptive accounts on celiac disease from the United Kingdom, and later, in an evaluation of celiac prevalence and associated diseases from a defined geographic area in Sweden [4,5]. Moreover, the definition of lymphocytic thyroiditis in children was thought to provide added evidence of immune-mediated pathological changes in celiac disease [6]. Later studies using definition of thyroid antibodies and specific measures of thyroid function suggested that clinically overt hypothyroidism was often co-existent in adults with celiac disease [7].

A prospective evaluation of consecutive adults with biopsy-defined celiac disease demonstrated a higher than expected rate (almost 20%) with autoimmune thyroid disease [8]. Interestingly, most diagnosed with celiac disease already had a diagnosis of thyroid disease previously established, but the mean age of celiacs diagnosed with thyroid disease appeared approximately a decade later compared to the entire celiac group. Moreover, another specific immune-mediated skin disorder, dermatitis herpetiformis, was present in almost half of the celiacs diagnosed with associated thyroid

disease and a higher than usual prevalence of lymphoma or small bowel adenocarcinoma was also noted. These results have suggested that a specific celiac disease phenotype that might be more prone to develop a complicating malignancy, including lymphoma. In a subsequent prospective Italian multicenter evaluation of 242 celiacs, hypothyroidism was present in 12.9% [9]. In this study, treatment with a gluten-free diet for at least 1 year led to improved thyroid function. Finally, more recent studies showed that 13.9% of 79 [10] and 30.5% of 36 adults with celiac disease [11] developed autoimmune thyroid disease. Taken together these early studies strongly suggested that adult celiac disease and autoimmune thyroid disease often co-exist.

### 3. Modern Population-based Studies

Additional population-based studies have been recently reported. In an evaluation [12] of 25,885 Sardinians, the prevalence of celiac disease was 124 per 100,000 and autoimmune thyroiditis, 2,619 per 100,000. This study also showed a higher probability of a subsequent autoimmune disorder after diagnosis of an initial autoimmune disorder. Later, in a prospective multicenter study from the United Kingdom [13], 129 of 4089 had biopsy-defined celiac disease while thyroid disease appeared to be independently associated with increased celiac disease risk. Likewise, in a recent Chinese population study [14], serological markers (specifically, not biopsies) for celiac disease and autoimmune thyroid disease were similarly increased. In a notable Dutch study [15] of 412 patients (selected from 9468 small bowel biopsy pathology reports and financial codes), 4.1% had immune-mediated thyroid disease. Interestingly, as in a previous study [8], celiac disease first diagnosed at a higher age had a risk of concomitant immune-mediated diseases and more malignancies (12.9%), including 8 lymphomas. Moreover, in an extensive nationwide cohort study of type 1 diabetes using the Swedish National Patient Register between 1964 and 2009 [16], the presence of celiac disease was noted to increase the risk for later development of autoimmune thyroid disease. Furthermore, a subsequent meta-analysis [17] of published articles in PubMed Medline and EMBASE to September 2015 revealed that 1 in 62 patients with autoimmune thyroid disease have biopsy-defined celiac disease. Interestingly, the prevalence appeared to be higher in children than adults, and more prevalent with hyperthyroidism than hypothyroidism. The authors suggested that patients with autoimmune thyroid disease should be screened for celiac disease. Finally, in a further population-based report from Brazil with extended follow-up of 6 to 10 years, relatives of patients with celiac disease had a significant increase in different autoantibodies, including thyroid microsomal antibodies, compared to results in the general population [18]. These studies together indicate that the risk of autoimmune thyroid disease is increased in adults and their relatives with celiac disease. Finally, in an intriguing study of co-morbid autoimmune disorders associated with autoimmune thyroid disease, celiac disease was found to be the most prevalent co-morbid autoimmune condition, especially if thyroid-associated orbitopathy was present [19]. These observations suggest that the detection of

specific phenotypic features associated with autoimmune thyroid disease may be a particularly critical clinical clue to the presence of occult celiac disease.

### 4. Levothyroxine Malabsorption

An important element in management of celiac disease patients with autoimmune thyroid disease relates to a requirement for replacement therapy. Interestingly, a number of causes for a high levothyroxine dose may be evident in autoimmune thyroid disease with hypothyroidism. Although lack of medication compliance is common, other concomitantly ingested medications, such as calcium carbonate, may impair levothyroxine absorption [20]. Indeed, in one report, impaired absorption of levothyroxine if given with calcium carbonate, may be particularly pronounced with underlying malabsorption [21]. Gastroparesis may also be responsible for increased oral thyroxine needs [22]. Of particular importance, however, is underlying celiac disease. Hypothyroid patients requiring elevated daily doses of levothyroxine are more likely to have celiac disease [23]. Indeed, this may be a further clue to a need for screening for celiac disease in a patient with autoimmune thyroid disease and hypothyroidism. Some [23] have suggested that absorption of levothyroxine medication may improve after celiac disease treatment with a gluten-free diet. This improvement appears to occur in spite of the likelihood of celiac-associated lactose intolerance as an independent factor in causing an increased need for oral thyroxine [24]. Thus, increased dose requirement of levothyroxine medication in autoimmune thyroid disease may be a further "phenotypic" clue to unrecognized celiac disease.

### 5. Gluten-free Diet Effects on Thyroxine Absorption

Some studies have also explored the effects of a gluten-free diet treatment in this setting. In an Italian multicenter study [25], strict gluten withdrawal confirmed by small intestinal biopsy recovery after 1 year on a gluten-free diet revealed normalization of hypothyroidism, and some had complete reversal of their subclinical hypothyroidism. In contrast, 25 per cent of euthyroid patients that demonstrated poor dietary compliance developed changes of subclinical hypothyroidism or hyperthyroidism. In a smaller prospective Finnish study [26], treatment with a gluten-free diet did not seem to prevent progression of the autoimmune process during a follow-up period of 1 year. Recently, the suggestion was made that screen-detected celiac disease and autoimmune thyroid disease, may already have an established autoimmune process that will not be altered with a gluten-free diet [27]. Although possible, long-term follow-up studies will be particularly important to determine if this hypothesis has merit.

### 6. Conclusion

Earlier prevalence evaluations and more recent population-based studies confirm the close relationship

between autoimmune thyroid disease and adult celiac disease, possibly related to recognition of common genetic determinants or embryonic origins. In some studies, the relationship has also been extended to other phenotypic features, such as dermatitis herpetiformis, and a greater risk of malignant complication, especially if celiac disease is detected in late or elderly age groups. In addition, some phenotypic characteristics of thyroid disease, such as orbitopathy and a high dose requirement for replacement may be added clinical clues to occult or undetected celiac disease. Serological screening for adult celiac disease should be considered in autoimmune thyroid disease.

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