

Autoimmune Thyroid Diseases in Celiac Disease: If and When to Screen?

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Abstract Prevalence of autoimmune thyroiditis is increased in patients with celiac disease and vice versa. Both diseases are frequent autoimmune diseases sharing multiple aspects lodging at the two ends of the gut-thyroid axis where the cross-talks' pathways are still unrivalled. Many authors recommend screening patients with thyroid autoimmunity for celiac disease associated antibodies. However, routine screening of celiac patients for anti-thyroid antibodies is less clear. Despite the fact that the latter screening fulfills most of the criteria for screening a disease, the timing and cost-effectiveness remains undetermined. For now, in face of celiac disease, the increased prevalence of autoimmune thyroid diseases needs to be taken in account and the accurate diagnosis should not be delayed.

Keywords: celiac disease, thyroid, autoimmunity, Hashimoto's thyroiditis, screening

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1. Introduction

1.1. Hashimoto's Thyroiditis

Since the current journal is much more a gastrointestinal and nutritional journal, concentrating on celiac disease (CD) and not on endocrinopathies, a brief introduction on Hashimoto's thyroiditis (HT) is warranted. HT, which is also known as autoimmune thyroiditis, is one of the most common autoimmune endocrine diseases, characterized by an autoimmune-mediated destruction of the thyroid gland, predominantly affecting women. The incidence of HT is approximately 3.5 cases per 1000 people per year in woman and 0.8 per 1000 in men, with a prevalence of 2-3% of the population. Due to its age dependency, the prevalence can reach 40% in elderly women. It may also be characterized by an enlarged thyroid gland and is identified histologically by lymphocytic thyroid infiltration and positive antibody tests for anti-thyroglobulin (TG) and/or anti-thyroid peroxidase (TPO) antibodies. The disease is a common cause of hypothyroidism. However, some cases

exhibit normal thyroid hormone levels, whereas other cases exhibit subclinical hypothyroidism in the presence of increased TSH levels. The diagnosis relies on the demonstration of the above mentioned circulating autoantibodies and reduced echogenicity on the sonography of patients with proper clinical features [1,2]. Interestingly, symptoms of HT and CD often overlap, and both share pathological, immunogenic, serological and genetic aspects.

1.2. Screening Criteria for Human Diseases

Almost 40 years ago, WHO commissioned a report on screening diseases from Wilson and Jungner. The report, published in 1968, was entitled: Principles and practice of screening for disease since than it become a public health classic [1]. Even by using the same criteria, these have at times been criticized for being too vague or theoretical and difficult to assess in a consistent manner. Those are the reasons for several adaptations made to the classic criteria, and several new criteria have also been emerged [2].

Following are the emerging screening criteria proposed over the past 40 years and their fulfillment in HT (Table 1, modified from 2):

Table 1. The emerging screening criteria proposed over the past 40 years and their fulfillment in HT (modified from ref. [2])

Criteria for screening	fulfillment in HT
should respond to a recognized need	+
objectives should be defined at the outset	+
should be a defined target population	+
should be scientific evidence of screening program effectiveness	+
should integrate education, testing, clinical services and program management	+
should include quality assurance, with mechanisms to minimize potential risks of screening	+
should ensure informed choice, confidentiality and respect for autonomy	+
should promote equity and access to screening for the entire target population	+
should be planned from the outset	+
overall benefits should outweigh the harm	+/-

2. Screening for CD in Children with Autoimmune Thyroid Disease (ATD)

Thyroid disorders commonly impact on the gastrointestinal tract and gut disorders can affect the thyroid functions [3]. CD is associated with a number of autoimmune conditions, including autoimmune thyroiditis disease (ATD), be HT or Grave's disease (GD). In fact, multiple epidemiological, clinical, serological, pathological, pathophysiological, genetic and immunological aspects are shared between CD and HT [3-10]. Increased prevalence of CD associated antibodies is well described in ATD. In India anti-tissue transglutaminase (tTg) autoantibodies were present in 6.9% subjects with ATD compared to 3.5 % in a control population [11], and much more, 14.79%, in the Czech Republic [12]. The plethora of studies, showing this high prevalence in ATD, resulted in cross the board recommendation to screen HT populations for celiac autoimmunity [6,9,13-21]. Exceptions were the recent Brazilian [22] and Turkish [23] studies that found a much lower prevalence (1.2, 1.25%, respectively) of CD in ATD and concluded that "much higher number of subjects are needed to justify screening of CD in subjects with HT" [23].

Even when checked in Grave's hyperthyroidism, CD screening is recommended [24]. However, in the opposite direction, the routine screening of CD for ATD is less established, and the timing of the screen is debatable [25]. When checked in the same area in Brazil, the authors noticed that ATD patients are less commonly affected with CD than CD patients in ATD [22].

3. Screening for ATD in Patients with CD

Fewer investigators alluded to the prevalence of ATD autoantibodies in CD populations. The prevalence of hypothyroidism and subclinical hypothyroidism in CD patients was 19.2% and 21.2%, respectively, at least in Brazil, even on GFD [26]. In Italy, thyroid disease was 3-times higher in untreated CD adults, compared to controls [27]. When CD children were screened, ATD was detected in 26.2% (10% in controls), justifying thyroid status assessment at diagnosis and at follow up (even on GFD) evaluation of CD children [28].

A bidirectional approach, studying HT and CD for CD and HT associated serology, respectively, found 21% positive thyroid autoantibodies in confirmed CD [20]. Furthermore, the authors concluded that "screening patients with HT for CD and vice versa is recommended". In the same direction, two editorials, based on current immunological and histological observations, recommended screening CD patients for autoimmune thyroiditis [29,30].

The main clinical arguments to screen CD patients for ATD are:

1. ATD might be a/hypo symptomatic and can be easily missed if not screened for.
2. Quality of life, cardiac morphology and functions may be affected in adult's subclinical hyperthyroidism.
3. Adolescents with HT are at high risk for thyroid failure.

4. Having the two conditions might encourage patients to adhere to the corresponding therapies.
5. Strict GFD might improve thyroid replacement drug absorption.

Two major questions arise concerning screening for ATD in diagnosed CD:

1. Will GFD affect the natural history of ATD?

The impact of GFD in CD patients upon subsequent emergence of ATD is unclear for now. In an Italian study, most patients who strictly followed a 1- y gluten withdrawal, showed normalization of subclinical hypothyroidism [27]. This suggests that in distinct cases, gluten withdrawal may single-handedly reverse the thyroidal abnormality. More recent studies could not substantiate those conclusions [31,32]. It seems that facing thyroid-associated orbitopathy, CD is the only autoimmune disease where complaints and autoantibodies to tTg usually resolve on a GFD [33]. Evaluating the importance of gluten in the induction of endocrine autoantibodies and organ dysfunction in adolescent celiac patients it was found that at least one antibody was positive in 10 of 19 untreated patients but only in five of 25 gluten restricted patients [10]. Once again it shows that gluten withdrawal may change thyroid autoimmunity, mainly when associated with CD.

2. What is the time to screen CD patients for ATD?

Several studies reported on the lag period between CD diagnosis and ATD detections. In a recent study, none of the CD patients had anti-thyroid antibodies at diagnosis. Anti-thyroid antibodies became positive in 16.4% of the patients 2 to 3 years after the diagnosis of CD, once again alluding to the age dependence of the thyroid autoimmunity. Interestingly enough, clinical hypothyroidism was observed only in 27.2% of CD patients with positive anti-thyroid antibodies [34]. Wessels et al, concluded that in their Dutch CD population after 5-y follow up period, empiric surveillance for thyroid dysfunction was not warranted [35]. On the same line, in Canova's study, there was a 5-y difference in the median age of developing CD and thyroid disease [32]. A median of a 9-y period from CD detection until the first diagnosis of thyroid diseases was reported in a Swedish study [36]. At the end of the day, it seems that thyroid autoimmune surveillance is justified after more than 5-y post CD diagnosis. A more precise recommendation has to wait for longer-term and controlled studies. For now, no North American nor European guidelines clearly delineate ATD screening times after CD diagnosis [37,38,39].

4. Conclusions

CD and ATD share multiple aspects and increased prevalence exists among each other. Most of the current literatures recommend to screen ATD with CD associated antibodies. The opposite screening of CD for ATD is less obvious. Despite the fact that the latter screening fulfills most of the criteria for screening a condition, the timing and cost-effectiveness remains undetermined. For now, in face of CD, the increased prevalence of ATD needs to be taken in account and the accurate diagnosis should not be delayed.

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