Original Article

Celiac autoimmunity in autoimmune thyroid disease is highly prevalent with a questionable impact

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ABSTRACT

Introduction: The prevalence of autoimmune thyroid disease (AITD) is 10–12% in the general population worldwide. Among various disorders co-existing with AITD, the concomitance of celiac disease (CD) with AITD results in poor absorption of thyroid medications and results in higher doses of the same. Institution of gluten-free diet (GFD) in this cohort helps reduce medication doses. **Aim:** To screen patients with AITD for the presence of celiac autoimmunity (CA). **Materials and Methods:** A total of 280 consecutive patients with AITD attending the thyroid Out-patient Department of a tertiary care hospital were screened for the presence of tissue transglutaminase antibodies (immunoglobulin A tissue transglutaminase). Those with a positive titer (but < 10 times the upper limit of normal) underwent upper gastrointestinal endoscopy and duodenal mucosal biopsy for the diagnosis of CD, followed by institution of GFD in confirmed cases. **Results:** Of a total of 280 (182 females and 98 males) patients with AITD screened, 24 (8.6%) turned out to be positive for CA. Of 24 (8.6%), 15 (8.24%) females and 9 (9.18%) males were positive for CA. There was no statistically significant difference in the thyroxine doses required for normalization of thyroid function and the weight of the patients in CA positive and CA negative patients. **Conclusions:** The prevalence of CD in patients with AITD is much greater than in the general population. This forms the basis for screening patients with AITD for presence of CD.

Key words: Autoimmunity, celiac disease, thyroid disease

Introduction

The prevalence of autoimmune thyroid disease (AITD) worldwide in the general population is 10–12%.[1] Thyroid antibodies are present in 8–27% of the general population.[2] Its reported prevalence in India is 18–24%. Association of other autoimmune diseases with AITD as part of polyglandular autoimmune syndromes is well known. The prevalence of celiac disease (CD) in general population is only 1%, even though it has increased fourfold in the last three decades.[3]

The prevalence of celiac autoimmunity (CA) in the setting of AITD is 2–5%[4] with a prevalence of 4.1% in adults[4] and 7.8% in children.[5] Also, the largest longitudinal study to date of the condition showed that adults with CD had 4.4 times the relative risk of hypothyroidism and 2.9 times the risk of hyperthyroidism compared with the general population. In children, the rates were higher

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still at 6 times and 4.8 times the risk, respectively.[6] The co-existence of these two conditions is clinically significant with far-reaching implications in the management of thyroid disease. CD not only affects the absorption of several essential nutrients but also that of thyroxine used in the treatment of hypothyroidism. The time honored management of CD with institution of gluten-free diet (GFD) tends to prevent progression of histological changes in the intestine and may as well reverse them, thereby improving absorption parameters. A growing amount of research suggests that when people with CD and AITD adopt a GFD, not only do their celiac related antibody levels improve but also their thyroid antibody levels decrease.[7]

In view of the close association of the two conditions and the possible influence of GFD on the disease course of both, we undertook a study to determine the prevalence of CA in patients with AITD. To our knowledge, this is the first study of its kind in India.

Aims

The aim of our study was to screen patients with AITD for the presence of CA.

Materials and Methods

The study was conducted at a large tertiary care center hospital in accordance with the code of ethics of World Medical Association (Declaration of Helsinki). After obtaining written informed consent, a total of 280 consecutive patients with AITD (hypothyroid/hyperthyroid) attending the Out-patient Department of the hospital were recruited. The baseline characteristics of the patients (age, sex, history, anthropometry, goiter, and general physical examination) were noted down for future reference by a single examiner. Hypothyroidism was defined as a TSH value above 5.5 μIU/ml by chemiluminometry (CLIA) with values between 5.5 and 10 μIU/ml categorized as subclinical hypothyroidism and those over 10 as overt hypothyroidism. Hyperthyroidism was defined as a TSH below 0.4 μIU/ml with categorization into subclinical toxicosis and overt toxicosis based on T4, T3 estimation by CLIA. AITD was confirmed by measuring anti-thyroid peroxidise (anti-TPO) antibody levels in patients with thyroid dysfunction by CLIA. Levels above 60 U/L were taken as positive.

Exclusion criteria

Patients with thyrotoxicosis secondary to solitary thyroid nodule, thyroiditis and multinodular goiter, and all patients with negative TPO antibody status were excluded from the study. Patients with critical illnesses were also excluded from the study.

The above patients then underwent screening for CA through estimation of Immunoglobulin A tissue transglutaminase (IgA tTG) antibody levels. This was done using Bio-Rad enzyme-linked immunosorbent assay system. Those patients with IgA tTG levels above 15 U/L were considered positive for CA.

In accordance with the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines for the diagnosis of CD, unless the IgA tTG levels were more than 10 times the upper limit of normal, consenting patients underwent gastrointestinal endoscopy and duodenal biopsy for confirmation of CD. The diagnosis of CD was made pathologically using Marsh staging [Appendix 1]. Following confirmation of CD histologically, patients were advised regarding initiation of GFD by a registered dietitian.

Results

Of a total of 280 (182 females and 98 males) patients with AITD screened, 24 (8.6%) turned out to be positive for CA. Fifteen (8.24%) females and nine (9.18%) males were positive for CA. Of 24 (33.33%), 8 patients had titers more than 10 times the upper limit of normal and so were directly initiated on GFD. Due to certain limitations, only 3 of the other 16 patients could undergo gastrointestinal endoscopy and duodenal biopsy. Of these three, only one patient had unequivocal changes of CD (Marsh stage three), while the other two had some degree of duodenitis (Marsh stage one). None of our patients had been screened for CA despite being diagnosed with AITD previously. Eighty percent of patients on retrospective probing agreed to be having some symptoms suggestive of CD, most notably gastritis (60%), abdominal pains (50%), and occasional loose motions (30%). The dose of thyroxine was 1.82 μg/kg in CA positive group and 1.79 μg/kg in CA negative group, the difference being not significant ($P = 0.72$). Also, the average weight was 62.15 and 64.22 kg in the CA positive and negative groups, respectively, which again was not statistically significant ($P = 0.52$). Fifteen of 24 (62%) patients with CA had thyroid stimulating hormone levels in the therapeutic range as compared to 201 of 256 (78%) patients without CA ($P = 0.08$). Statistical analysis was carried out using Statistical Package for Social Sciences (Internationial Business Machines (IBM)). Z-test was applied, as required, for comparing the means of the two groups (CA positive and CA negative).

Discussion

Among autoimmune disorders, increased prevalence of CD has been found in patients with AITD, type 1 diabetes

mellitus, autoimmune liver diseases, and inflammatory bowel disease. Conversely, CD patients themselves are prone to a number of other autoimmune disorders.

It has been hypothesized that the exposure to gluten in patients with CD triggers off autoimmunity against other tissues in the body. In an elaborate study by Ventura *et al*., it was observed that the prevalence of autoimmune disorders in CD is related to the duration of exposure to gluten. With progressively increasing age at diagnosis, the likelihood of the patient having concomitant autoimmune disorders was higher in this study.[8]

The association of CD with AITD is especially important as management of the former also affects that of the later as explained earlier. In addition to the gluten exposure hypothesis described above, CD and AITD also share common genetic predisposition. Human leukocyte antigen DQ2 and DQ8 are over-represented in CD and Graves' disease and to some extent in Hashimoto's thyroiditis.[9] Also, both CD and AITD are reported to be associated with the gene encoding cytotoxic T lymphocyte-associated antigen 4.[10,11]

The prevalence of CA in AITD was found to be 8.6% in our study population. Our figures are comparable to some of the other studies done around the world. Collin *et al*., while screening 83 Finnish patients with AITD, found a CD prevalence of 4.8%.[12] Sategna-Guidetti *et al*. found 3.3% prevalence of CD in their 152 patients cohort of AITD using IgA anti-endomysial antibodies. Only one patient presented with gastrointestinal complaints.[13] Valentino *et al*. found 3.3% prevalence of CD in their cohort too.[14] Patients in the Valentino *et al*. study improved on a GFD with amelioration of hypothyroidism and thyroxine dose reduction. These studies confirm that the frequency of subclinical CD is increased in patients with AITD. IgA class antibody tests are suitable for screening.

There is also a group of patients referred to as "latent" CD, who have the requisite antibodies, but no mucosal abnormality to begin with. These patients may go on to develop overt CD as age progresses with progressive exposure to gluten.[15] In this context, the ESPGHAN has laid down guidelines for the management of CD. Those with antibody levels 10 times the upper limit of the assay used do not need a duodenal biopsy to confirm the diagnosis; while others do.

Limitations

Due to high attrition rates, it was not possible to obtain confirmatory tissue diagnosis in all CA positive patients.

Future prospects

Nutrient absorption (Vit B12, folate) and hemoglobin levels in AITD patients with and without CD, when compared, would be able to further establish the effects of CD on the same. With institution of GFD, both nutrient and thyroid medication absorptions should improve. Also, larger studies looking at differences in biopsy-confirmed CD cases to study impact of CA on AITD would be of interest.

Conclusions

The prevalence of CD in patients with AITD is much greater than in the general population. This forms the basis for screening patients with AITD for the presence of CD. Though our population did not show any difference in the doses of thyroxine needed as well as the weight and thyronormalcy, further large-scale studies of a similar nature are needed as the literature is divided about the impact of CA in AITD.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Modified Marsh classification for gluten-induced small intestinal damage

Stage	Histopathology
Stage 0	Preinfiltrative mucosa; up to 30% of patients with DH or gluten ataxia have small-intestinal biopsy specimens that appear normal
Stage 1	Increase in the number of IELs to more than 30 per 100 enterocytes
Stage 2	Crypt hyperplasia. Increased IELs, increased crypt depth, reduction in villus height. Gluten challenge can induce these changes, which can also be seen in 20% of untreated patients with DH and celiac disease
Stage 3	Villous atrophy: A - partial; B - subtotal; C - total. This is the classic celiac lesion. It is found in 40% of DH patients. Despite marked mucosal changes, many individuals are asymptomatic and classified as silent or subclinical cases. This lesion is characteristic of, but not diagnostic of, celiac disease and can also be seen with severe giardiasis, infantile food sensitivities, graft versus host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies, and other immune deficiencies and allograft rejection

Courtesy: World Gastroenterology Organization Global Guidelines on Celiac Disease, April 2012, Pg. 9. IELs: Intraepithelial lymphocytes; DH: Dermatitis herpetiformis