Clinical Medicine & Research
Volume 5, Number 3: 184-192

http://www.clinmedres.org

Review

Celiac Disease and Autoimmune Thyroid Disease

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Celiac disease (CD) or gluten sensitive enteropathy is relatively common in western populations with prevalence around 1%. With the recent availability of sensitive and specific serological testing, many patients who are either asymptomatic or have subtle symptoms can be shown to have CD. Patients with CD have modest increases in risks of malignancy and mortality compared to controls. The mortality among CD patients who comply poorly with a gluten-free diet is greater than in compliant patients. The pattern of presentation of CD has altered over the past three decades. Many cases are now detected in adulthood during investigation of problems as diverse as anemia, osteoporosis, autoimmune disorders, unexplained neurological syndromes, infertility and chronic hypertransaminasemia of uncertain cause.

Among autoimmune disorders, increased prevalence of CD has been found in patients with autoimmune thyroid disease, type 1 diabetes mellitus, autoimmune liver diseases and inflammatory bowel disease. Prevalence of CD was noted to be 1% to 19% in patients with type 1 diabetes mellitus, 2% to 5% in autoimmune thyroid disorders and 3% to 7% in primary biliary cirrhosis in prospective studies. Conversely, there is also an increased prevalence of immune based disorders among patients with CD. The pathogenesis of co-existent autoimmune thyroid disease and CD is not known, but these conditions share similar HLA haplotypes and are associated with the gene encoding cytotoxic T-lymphocyte-associated antigen-4.

Screening high risk patients for CD, such as those with autoimmune diseases, is a reasonable strategy given the increased prevalence. Treatment of CD with a gluten-free diet should reduce the recognized complications of this disease and provide benefits in both general health and perhaps life expectancy. It also improves glycemic control in patients with type 1 diabetes mellitus and enhances the absorption of medications for associated hypothyroidism and osteoporosis. It probably does not change the natural history of associated autoimmune disorders.

Keywords: Autoimmune thyroid disease; Celiac disease; Prevalence; Screening

Celiac disease (CD) or gluten sensitive enteropathy is a permanent intolerance of dietary gluten leading to mucosal damage in the proximal small bowel in genetically susceptible individuals, characterized by inflammation, crypt hyperplasia and villous atrophy which regress on withdrawal of gluten from the diet. Recent population screening studies have shown the prevalence of CD in Western countries approaches 1%[1-3] but the condition is greatly under-diagnosed, partly because many cases are subclinical, but also because of its previously perceived rarity.

CD should be considered in many clinical settings and detected early to prevent complications in later life. In a 6-year prospective study, Corrao et al[4] followed 1,072 consecutive CD patients and found a standard mortality ratio of 0.5 in those who complied with a strict gluten-free diet but a standard mortality ratio of 6.0 in the poor compliers. Using the general practice research database, West et al[5] identified 4,732 CD patients and found a modest increase in overall risks of malignancy and mortality compared to matched controls.

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Received: December 5, 2006 Revised: April 2, 2007 Accepted: May 4, 2007

doi:10.3121/cmr.2007.738

Table 1. Manifestations of silent celiac disease (predominantly extra-intestinal).

Dermatitis herpetiformis
Anemia
Autoimmune disorders
Osteoporosis
Neurological disorders
Epilepsy with cerebral calcification
Neuropathy
Cerebellar ataxia
Chorea
Infertility/subfertility
Non-alcoholic fatty liver disease
Unexplained chronic hypertransaminasemia

Manifestation of CD

Classically CD, as originally described in the 19th century, was characterized by steatorrhea, vomiting and cachexia in early childhood.[6] Over the past 30 years, the clinical presentation of CD has moved from overt malabsorption in childhood towards milder symptoms or atypical features in adult life.[7-11] It is increasingly recognized, however, that symptomatic cases represent only the tip of a celiac iceberg. Many patients with CD have either no or very subtle symptoms (silent CD)[12] and are diagnosed through family or occasional screening.

Diagnosis of and Screening Tools for CD

The revised diagnostic criteria for CD by the working group of the European Society of Paediatric Gastroenterology and Nutrition[13] take into account the usefulness of the serological tests. However, identification of the histological changes in proximal small bowel mucosa remains the gold standard.

Both IgA anti-endomysial antibody (EmA) and IgA anti-tissue transglutaminase (anti-tTG) antibody are highly sensitive when used in screening.[14-16] As these are IgA-class antibodies, false-negative results occur in IgA-deficiency which itself is associated with CD.[17] Patients with IgA-deficiency should be tested with IgG-class anti-tTG[17] or EmA,[18] or be offered distal duodenal biopsy.

HLA typing may have a role in the diagnostic algorithm, especially in excluding the diagnosis. Negative HLA-DQ2 heterodimer or DQ8 or one-half of the DQ2 heterodimer virtually excludes susceptibility to CD with negative predictive values approaching 100%.[19,20]

Why Should Non-Gastroenterologists Recognize CD?

Gastroenterologists are already familiar with the association of CD with several immune and non-immune based diseases in the digestive system, including ulcerative colitis,[21,22] Crohn's disease,[23] microscopic colitis,[24] autoimmune liver diseases,[25-27] fatty liver[28] and elevated liver transaminase levels.[29-32] However, many diseases outside the digestive system have also been linked with CD, both in its overt and silent forms.

The association of dermatitis herpetiformis[33-36] with gluten sensitive enteropathy is widely recognized. Diseases most typically associated with silent CD are immune-based disorders, such as type 1 diabetes mellitus,[21,37-40] autoimmune thyroid diseases,[21,38,39,41,42] Sjögren's syndrome[37,38] and Addison's disease.[43,44] An association with atopy has also been described,[21,45,46] but this has been disputed.[47] Other disease associations of uncertain pathogenesis include dental enamel defects,[48-50] epilepsy with cerebral calcification,[51] neuropathy,[52,53] cerebellar ataxia,[54,55] chorea[56] and infertility[57,58] (table 1).

It is possible that some previously suggested disease associations may simply be chance findings. Nonetheless, recent screening studies in patients with type 1 diabetes mellitus,[59-63] autoimmune thyroid disease (table 2), primary biliary cirrhosis [25-27,64] and Crohn's disease[23] suggest that these relationships are real, making screening worthwhile (table 3).

CD satisfies the World Health Organization (WHO) criteria for general population screening[65] but this proposal remains controversial.[66] The most practical approach may be to screen subjects at increased risk, such as family members of an index case or patients with disorders known to be associated with CD. Diagnosis in this latter group is particularly important because of the increased morbidity of one disease superimposed on the other.

Table 2. Prevalence of celiac disease (CD) in autoimmune thyroid disorders.

Author (year of publication)	Population screened	Prevalence of CD
Collin et al (1994)[41]	83 autoimmune thyroid disease	4.8%
Sategna-Guidetti et al (1998)[76]	152 autoimmune thyroid disease	3.3%
Cuoco et al (1999)[78]	22 Hashimoto's disease 23 Graves' disease	4.3%
Valentino et al (1999)[77]	150 autoimmune thyroid disease	3.3%
Berti et al (2000)[79]	172 autoimmune thyroid disease	3.5%
Volta et al (2001)[80]	220 autoimmune thyroid disease	3.2%
Larizza et al (2001)[81]	90 Pediatric autoimmune thyroid disease	7.8%
Meloni et al (2001)[82]	297 autoimmune thyroid disease	4.4%
Mainardi et al (2002)[83]	100 autoimmune thyroid disease	2%
Ch'ng et al (2005)[42]	115 Graves' disease	4.5%

Table 3. Autoimmune disorders associated with celiac disease through screening.

Conditions	Prevalence of celiac disease
Type 1 diabetes mellitus	1% to 16%[59-63,104,105]
Autoimmune thyroid disease (adult)	2% to 4.8%[41,42,76-83]
Pediatric autoimmune thyroid disease	7.8%[81]
Primary biliary cirrhosis	3% to 7%[25-27]
Crohn's disease	19%[23]

Thyroid Dysfunction in CD and Dermatitis Herpetiformis (table 4)

An increased prevalence of thyroid dysfunction has been reported in patients with CD. In a study from Sweden where the prevalence of CD was 95.5 per 10,000, Midhagen et al[67] found that thyrotoxicosis occurred in 5.0% and spontaneous hypothyroidism in 5.8% of the celiac patients. These thyroid disorders were sometimes diagnosed before, and sometimes after, the diagnosis of CD and instigation of the gluten-free diet. The duration of the gluten-free diet in relation to the diagnosis of thyroid disease was not stated. In a cohort of 70 celiac patients, Volta et al[68] noted four with hypothyroidism and one with thyrotoxicosis. They concluded that the finding of autoantibodies in celiac patients suggested the coexistence of a wide spectrum of immunological diseases including type 1 diabetes mellitus, autoimmune hepatitis, dermatomyositis and thyroid disorders. Reunala and Collin[38] followed 305 patients with dermatitis herpetiformis and 383 with CD for a mean of 10 years and found 4.3% and 6.0% had autoimmune thyroid disease, respectively. These patients were all on a gluten-free diet and were also taking dapsone if suffering from dermatitis herpetiformis. Four patients with dermatitis herpetiformis developed hypothyroidism and three patients with CD developed thyroid disorders (two hypothyroidism and one hyperthyroidism) during follow-up, while on a gluten-free diet. Cooper et al[21] reported 11 patients with thyroid disorders among 314 patients with CD; three of these 11 patients (two with thyrotoxicosis and one myxoedema) were diagnosed while on a gluten-free diet. Collin et al[69] found 5.4% of 335 adult celiac patients, of whom 83% complied with a gluten-free diet, had autoimmune thyroid disease (autoimmune hypothyroidism or Graves' disease). Counsell et al[70] found that 14% (15 out of 107) of celiac patients had thyroid disorders (3.7% hyperthyroid and 10.3% hypothyroid). Eleven of these 15 patients were known to have prior autoimmune thyroid disease (8 autoimmune hypothyroidism and 3 Graves' disease), three were found to have thyroid disease at the time when CD was diagnosed and one developed hypothyroidism 5 months after the diagnosis of CD and introduction of a gluten-free diet. The same authors also noted a high prevalence of thyroglobulin antibodies (11%) and thyroid microsomal antibodies (15%) in their CD patients. Likewise, Velluzzi et al[71] found the prevalence of thyroid peroxidase antibodies to be higher in CD (29.7%, 14 out of 47 patients) than in healthy controls (9.6%). In five of these 14 patients, two had mild hypothyroidism and three subclinical hypothyroidism. They did not find any difference between celiac patients with or without serological or ultrasonographic evidence of thyroid disease in relation to age, disease duration, histological abnormalities and titer of immunological markers of CD. In a prospective cohort of 90 children with CD, Ventura et al[39] reported 14.4% to have thyroid autoantibodies at the time of CD diagnosis. Kowalska et al[72] observed elevated titers of antithyroid antibodies in 34 poorly compliant IgA-EmA positive children with CD (41%) compared to controls (3.6%) who were seen because of dyspepsia.

In a prospective study of 241 untreated celiac patients, Sategna-Guidetti et al[73] found hypothyroidism in 12.9% which was 3-fold higher than in controls (4.2%). Autoimmune thyroid disease with euthyroidism was found in 39 patients (16.2%) and 8 controls (3.8%). There was no increase in hyperthyroidism. In 128 patients, intestinal biopsy and thyroid function were repeated within a year. Among those who followed a strict gluten-free diet, there was an apparent normalization of subclinical hypothyroidism. Four of 16 patients with autoimmune thyroid disease with euthyroidism were found to have subclinical thyroid disease (three hypothyroidism and one hyperthyroidism). Five out of 91 celiac patients with normal thyroid function developed thyroid disease (two hypothyroidism, one subclinical hyperthyroidism and two autoimmune thyroid disease with euthyroidism). Hakanen et al[74] found clinical autoimmune thyroid disease in 13.9% of 79 celiac patients in contrast to 2.1% of 184 controls, and subclinical thyroid disease in 10.1% and 3.3%, respectively. There was no difference in the presence of circulating thyroid antibodies (thyroid peroxidase and microsomal antibodies) in relation to the duration of gluten withdrawal (20% in patients on a gluten-free diet >4 years vs. 17% in patients on a gluten-free diet <4 years). Carta et al[75] found an increased prevalence of thyroid peroxidase antibodies among 36 adult celiac patients (30.5% in CD vs. 9.7% in controls) and suggested subclinical thyroid disease might pose a risk for psychiatric illness, such as panic attacks and major depressive disorders. In patients with major depressive disorders, gastrointestinal symptoms had started earlier (before age 5) than those without. They also concluded that a gluten-free diet did not protect against development of major depressive and panic disorders.

CD in Autoimmune Thyroid Disease (table 2)

Screening 83 Finnish patients with autoimmune thyroid disease for CD using IgA-class reticulin and endomysium antibody, IgA- and IgG-class gliadin antibody tests and various biochemical tests for malabsorption, Collin et al[41]

Table 4. Thyroid dysfunction in celiac disease (CD) and dermatitis herpetiformis (DH).

Author (year of publication)	Population studied	Prevalence of thyroid antibodies (number of patients)	Prevalence of thyroid dysfunction (number of patients)	Thyroid disease following GFD (number of patients)
Midhagen et al (1988)[67]	139 CD (27 with DH)	N/A	Thyrotoxicosis (7) 5.0% Hypothyroidism (8) 5.8%	N/A
Volta et al (1997)[68]	70 CD	TMA (15) 21%	Thyrotoxicosis (1) Hypothyroidism (4)	N/A
Reunala and Collin (1997)[38]	305 DH	N/A	Hypothyroidism (10) 3.3% Hyperthyroidism (3) 1.0%	Hypothyroid (4)
	383 CD	N/A	Hypothyroidism (14) 3.7% Hyperthyroidism (9) 2.3%	Hypothyroid (4) Hyperthyroid (1)
Cooper et al (1978)[21]	314 CD (83% compliant with GFD)	N/A	Thyroid disorders (11) Thyrotoxicosis (4) Thypothyroid (7)	 Thyrotoxicosis (2) Myxoedema (1)
Collin et al (1994)[69]	355 CD	N/A	AITD 5.4% Autoimmune hypothyroidism (11) Graves' disease (7)	N/A
Counsell et al (1994)[70]	107 CD	TGA (12) 11.2% TMA (16) 15%	Hyperthyroid (4) 3.7% Hypothyroid (11) 10.3%	Hypothyroid (1)
Velluzzi et al (1998)[71]	47 CD	TPO (14) 29.7%	Hypothyroid (2) Subclinical hypothyroid (3)	N/A
Ventura et al (2000)[39]	90 CD (children)	TPO (13) 14.4%	N/A	N/A (There was reduction in TPO positivity)
Kowalska et al (2000)[72]	34 CD (children) Poorly compliant	Thyroid antibodies 41% TMA (5) TGA (11) TPO (4)	N/A	N/A
Sategna-Guidetti et al (2001)[73]	241 untreated CD	TMA and TPO (no. not given)	Hypothyroid (31) 12.9% Hyperthyroid (3) 1.2% Euthyroid AITD (39) 16.2%	Normalization of subclinical hypothyroidism on GFD (13) Hypothyroid (2) Subclinical hyperthyroid (2)
Hakanan et al (2001)[74]	79 CD	N/A	AITD (11) 13.9% Graves' disease (3) 3.8% Hypothyroid (8) 10.1% Subclinical thyroid disease (8)10.1%	N/A (GFD did not influence thyroid antibodies positivity)
Carta et al (2002)[75]	36 CD	TPO (11) 30.5%	Subclinical hypothyroid (3)	N/A

AITD, autoimmune thyroid disease; GFD, gluten-free diet; N/A = not available; TGA, thyroglobulin antibodies; TMA, thyroid microsomal antibodies; TPO, thyroid peroxidise antibodies.

found three asymptomatic celiac patients which, with one previously diagnosed CD patient, gave an overall frequency of 4.8%. In addition, 25 patients with a solitary thyroid nodule were examined and one (4%) was found to have CD. In contrast, one (0.4%) out of 249 age- and sex-matched blood donors was found to have CD. All newly detected celiac patients had IgA-class gliadin, reticulin and endomysium antibodies, but none had gastrointestinal symptoms or abnormal biochemical findings suggestive of CD. Sategna-Guidetti et al[76] found that 3.3% (5 of 152) of patients with autoimmune thyroid disease also had CD using IgA-EmA and confirmed on duodenal histology. Only one patient presented with gastrointestinal complaints, but iron deficiency was found in three and alterations in bone mineral density in all five. Valentino et al[77] screened 150 newly diagnosed patients with autoimmune thyroid disease using EmA and found five (3.3%) to have CD. Patients improved on a gluten-free diet with amelioration in hypothyroidism and thyroxine dose reduction. Cuoco et al[78] studied 92 patients with autoimmune thyroid disease (47 chronic autoimmune thyroiditis of which 22 were Hashimoto's thyroiditis and 23 Graves' disease) and looked for serological evidence of CD with anti-gliadin antibody (AGA) and EmA. Four patients (5.4%) were found to have CD confirmed by endoscopic duodenal biopsy in contrast to 1.1% of those with non-autoimmune thyroid disease and 0.4% of healthy blood donors. They also found AGA to be less specific than EmA. Berti et al[79] found six of their 172 (3.4%) patients with autoimmune thyroid disease to be EmA positive; five of these underwent small bowel biopsies and all showed total villous atrophy in contrast to 0.75% of 396 patients with non-gastrointestinal malignancies and 0.25% of 4,000 blood donors. Volta et al[80] analyzed sera from 220 patients with autoimmune thyroiditis, 50 euthyroid subjects with thyroid nodules and 250 healthy blood donors for AGA and EmA. Among those with autoimmune thyroiditis, seven had positive serology and villous atrophy. None of the euthyroid patients with thyroid nodules and only one blood donor were found to have CD. Larizza et al[81] screened 90 children and adolescents with autoimmune thyroid disease and showed seven to have CD (prevalence of 1 in 13) and recommended that children with autoimmune thyroid disease be screened. Meloni et al[82] screened 297 Sardinian patients with autoimmune thyroid disease with IgA-class and IgG-class AGA. Those found to be positive with either antibody were further tested for EmA. If any two markers were positive, hematinics were determined and the patients offered a jejunal biopsy. Thirteen of 14 patients who showed at least two positive markers underwent jejunal biopsy and all showed histological features of CD. The prevalence of CD was found to be 4.4% among patients with autoimmune thyroid disease. No patients had gastrointestinal symptoms, although half had hematinic deficiencies. Six had iron deficiency, two were deficient in vitamin B_{12} but none was folate deficient. Mainardi et al[83] found the prevalence of CD among their cohort of 100 patients with autoimmune thyroid disease to be 2%. These studies confirm that the frequency of subclinical CD is increased in patients with autoimmune thyroid disease. IgA-class antibody tests are suitable for screening, as long as selective IgA-deficiency is excluded.

CD in Graves' Hyperthyroidism

None of the previous studies looked at the prevalence of CD solely in patients with Graves' hyperthyroidism. Ch'ng et al[42] evaluated the role of screening for CD prospectively in a consecutive cohort of 115 patients with Graves' hyperthyroidism attending a secondary care thyroid clinic using AGA and IgA-class anti-tTG antibodies. Two patients were already known to have CD and were asymptomatic on a gluten-free diet. Three new celiac patients were found during screening which, with the two existing celiac patients, gave a CD prevalence of 4.5% compared to 0.9% (1 of 115) of sex- and age-matched blood donor controls. All five patients had silent CD with no gastrointestinal symptoms. In the two existing celiac patients, the diagnosis of Graves' hyperthyroidism preceded that of CD by 3 and 26 years. The latter patient had a long history of unexplained neurological disease. On the basis of this study, serological screening for CD was recommended for patients with Graves' hyperthyroidism.

Pathogenesis of Co-Existent Autoimmune Thyroid Disease and CD

The coexistence of CD and autoimmune disease is thought to be partly due to a common genetic predisposition. HLA-DQ2 and DQ8 haplotypes are over-represented in many autoimmune diseases[84-87] and the inheritance of these haplotypes[88] and the associated immunological phenotype may explain the link. Sharing similar HLA genotypes may also explain the strong association between IgA-deficiency and CD. HLA-DQ2 and DQ8 show a weak association with Hashimoto's thyroiditis, although HLA-DQ2 association is less clear in Graves' disease.[89,90]

Outside the HLA region, both CD and autoimmune thyroid disease are reported to be associated with the gene encoding cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), a candidate gene for conferring susceptibility to thyroid autoimmunity.[91-93] More recently, a study showed that 10 of 14 patients with Hashimoto's thyroiditis had genotypes compatible with CD (three patients had DQ heterodimer A1*0501, B1*0201, four had DRB1*04 and one had A1*0101, B1*0501). Six of these 14 patients showed an increased density of $\gamma\delta^+$ T-cell receptor-bearing intra-epithelial lymphocytes and signs of mucosal T-cell activation, both typical of CD.[94] Also among 4 of these 6 patients, HLA genotypes associated with CD (three with DRB1*04, DQB1*03 and one with DQA1*0501, DQB1*02) were described.

Can Treatment of CD Change the Course/ Development of Associated Autoimmune Disorders?

Identifying and treating CD in high-risk patients should confer benefit in reducing complications such as

malabsorption, infertility, osteoporosis and lymphoma.[95,96] Treatment also improves the absorption of medications for the associated conditions such as hypothyroidism[77,97] and osteoporosis.[98] It is not known whether treatment of CD reduces the likelihood of developing autoimmune disorders, or changes their natural history. Cooper et al[21] considered that a gluten-free diet did not prevent development of autoimmune disorders and had little ameliorating effect on their course, apart from an occasional improvement in atopy. Sategna-Guidetti et al,[73,99] however, noted that a gluten-free diet may reverse the abnormality in those with subclinical hypothyroidism although, like Viljamaa et al,[100] found no correlation between duration of gluten exposure in adult CD and risk of autoimmune disorders. Ventura et al[39] found that diabetes- and thyroid-related antibodies tended to disappear following a gluten-free diet (11.1% at diagnosis, 5.6% at 6 months and none at 12 or 24 months follow-up for diabetes related antibodies and 14.4%, 11.1%, 6.6% and 2.2% for thyroid related antibodies, respectively) while Mainardi et al[83] found no correlation between thyroid antibodies and the introduction of a gluten-free diet. Among their cohort of 9 CD patients with autoimmune cholestatic liver diseases (seven primary biliary cirrhosis, one primary sclerosing cholangitis and one autoimmune cholangiopathy) detected through screening, Volta et al[27] did not observe any clinical or biochemical improvement in cholestasis following a gluten-free diet. A gluten-free diet probably should be started early, before autoimmune disorders are well established, to affect their course. Rami et al,[101] studying diabetic children, found that silent CD had no obvious effect on metabolic control but negatively influenced weight gain. Sanchez-Albisua et al,[102] on the other hand, showed an increase in height and weight and a trend towards improved glycemic control in diet-compliant celiac patients diagnosed through screening type 1 diabetic children. Acerini et al[59] also showed improvement in weight and glycemic control in those treated with a gluten-free diet. Kaspers et al[103] found that children with type 1 diabetes and CD were characterized by earlier onset of diabetes and decreased growth and weight gain. These findings emphasize the clinical relevance of CD in patients with autoimmune diabetes.

Conclusion

Patients with CD may present with diverse clinical manifestations, or without symptoms, to specialists other than gastroenterologists. There is ample evidence of a strong association between CD and several immune mediated diseases, including autoimmune thyroid disorders, type 1 diabetes mellitus, primary biliary cirrhosis, inflammatory bowel diseases and autoimmune adrenal failure. Some of these conditions share HLA haplotypes and non-HLA alleles, e.g., CTLA-4, which may underlie their pathogenesis. Thyroid function should be assessed in all CD patients at diagnosis and follow-up if clinically indicated. Relatively cheap serological testing kits for anti-tTG and EmA are available to screen for CD. Screening of high-risk groups such as those with autoimmune thyroid disease is a reasonable strategy. Currently there is little evidence to support a role for a gluten-free diet in reducing the development of associated autoimmune disorders in patients with CD, but early diagnosis and dietary treatment reduces complications such as malabsorption, osteoporosis and lymphoma, and improves the absorption of drugs.

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