



Published in final edited form as:

*Clin Gastroenterol Hepatol.* 2008 July ; 6(7): 722–723. doi:10.1016/j.cgh.2008.03.017.

## Celiac Disease Beyond the Gut

Alberto Rubio-Tapia and Joseph A. Murray

Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN 55905

Celiac disease (CD) is a common immune-mediated disorder that affects approximately 1% of Caucasians and develops in genetically susceptible subjects after the ingestion of gluten proteins present in wheat, barley, and rye.<sup>1</sup> Although historically CD was defined by small-bowel damage and subsequent malabsorption, more recently it has been recognized as a multisystem disorder that may affect other extraintestinal organs, such as the skin, heart, nervous system, and liver.<sup>2</sup> CD has some characteristics that have been described in typical autoimmune disorders but CD is unique among the autoimmune diseases because the autoantigen (tissue transglutaminase) and environmental trigger (gluten) are known (Table 1).<sup>3</sup>

### Autoimmune Diseases Associated With Celiac Disease

CD frequently may co-exist with organ-specific or systemic autoimmune diseases, such as type 1 diabetes mellitus, thyroiditis, connective tissue diseases, and many other autoimmune diseases.<sup>4</sup> Several hepatic disorders have been described in association with CD. CD itself may injure the liver (the so-called *celiac hepatitis*) or may co-exist with chronic liver diseases, especially those of autoimmune etiology.<sup>5</sup> In this issue of *Clinical Gastroenterology and Hepatology*, Caprai et al<sup>6</sup> reported a multicenter retrospective experience that showed that more than 16% of 140 pediatric patients followed up because of chronic autoimmune liver disease had CD. Indeed, CD has been found consistently to be associated with autoimmune liver disorders.<sup>7</sup>

Co-existent liver disease in CD must be considered especially if any of the following occurs: (1) persistence of abnormal liver tests after at least 1 year on a gluten-free diet (GFD) in patients with known CD, (2) abnormal liver tests after GFD in patient with CD and normal pre-GFD liver chemistries, and (3) symptomatic liver disease with abnormal physical examination.<sup>5</sup> Conversely, CD needs to be actively investigated in patients with cryptogenic hypertransaminasemia and/or cirrhosis.<sup>5</sup> and <sup>8</sup>

There are anecdotal reports that have suggested reversal of liver failure after gluten exclusion in patients with both CD and severe liver disease.<sup>9</sup> It is unknown, however, if the prognosis of the autoimmune liver disease associated to CD is different than in those patients with autoimmune liver disease alone, as well as the impact of the GFD on the natural history of the liver disorder (ie, rates of biochemical or histologic remission, need of liver transplantation). A GFD is indicated, however, to treat CD-related symptoms and to decrease the risk of serious CD long-term complications (ie, lymphoma). Thus, it has been suggested that patients with autoimmune liver disease and CD may receive both the specific treatment for the liver disorder and a GFD.<sup>5</sup> Although Capri et al<sup>6</sup> showed that most biochemical relapses of the liver disease were related to interruption or discontinuation of

immunosuppressive therapy, some patients relapsed after voluntary gluten contamination. The possible effect (if any) of gluten withdrawal to modify the natural history of autoimmune liver diseases co-existent with CD remains to be shown.

## Celiac Disease as a Risk Factor for Autoimmunity and the Effect of Gluten Withdrawal

Are those patients with previously diagnosed CD at risk for autoimmune-mediated disorders? Can the strict adherence to a GFD decrease the risk of autoimmunity?

In this issue of *Clinical Gastroenterology and Hepatology*, Cosnes et al<sup>10</sup> showed an increased risk of autoimmune disorders (19.3% prevalence) in patients with CD, especially those diagnosed early in life and having a family history of autoimmunity. Interestingly, the risk at 10 years of a subsequent autoimmune disorder was lower in patients diagnosed with CD in adulthood who were compliant with a GFD versus those who were noncompliant, suggesting that the GFD has a protective effect.

The duration of gluten exposure as a risk factor for autoimmunity and the protective effect of a GFD are, however, controversial. A large Italian study that included 909 children or adolescents with CD showed a higher prevalence (14%) of autoimmune disorders in patients with CD as compared with healthy controls. Age at diagnosis (duration of exposure to gluten) was the only significant predictor variable of the risk of developing an autoimmune disorder thus, the longer at-risk individuals had consumed a gluten-containing diet before the diagnosis of CD, the higher the prevalence of autoimmune disorders later in life. The effect of a GFD was not investigated.<sup>11</sup> A subsequent report suggested an increased risk of autoimmune diseases in first-degree relatives of CD children (4.8% prevalence) as compared with relatives of healthy children; the risk of autoimmune diseases increased with age and was even higher (20% prevalence) in those relatives with screen-detected positive endomysial and/or tissue transglutaminase autoantibodies (undiagnosed and untreated CD).<sup>12</sup> On the contrary, in adults from Finland and Italy, although the increased risk of autoimmune diseases (21.8% and 30% prevalence, respectively) was confirmed in patients with CD, gluten withdrawal did not protect them from autoimmune diseases.<sup>13 and 14</sup> A GFD did not modify the risk of autoimmunity in 170 Italian children with CD (27% prevalence of clinical, subclinical, and potential autoimmune disease) after a median follow-up period of 4 years, but may have had a favorable disease-specific effect.<sup>15</sup>

Thus, CD is associated with other autoimmune diseases but it is not clear whether the early diagnosis and treatment of CD will lead to either a decreased incidence or a better clinical outcome of other autoimmune disorders.<sup>16 and 17</sup> The mechanisms underlying the increased risk of autoimmunity in CD are poorly understood. Hypotheses that have been proposed and that are partially supported by clinical or experimental evidence include the following. First, shared genes (eg, at-risk HLA haplotypes), which also may partially explain the higher prevalence of CD in patients with some autoimmune disorders, such as type 1 diabetes mellitus or primary sclerosing cholangitis. Recently, a large genome-wide association study showed a strong association among CD and a single nucleotide polymorphism (rs6822844) located close to the interleukin-2 and interleukin-21 genes.<sup>18</sup> Seven additional loci associated with CD were identified in a follow-up study of markers showing association signals in the previous study; most of the regions contain immune-related genes such as CCR3, IL-12A, IL-18RAP, RGS1, SH2B3, and TAGAP, which have been implicated in other immune-mediated diseases.<sup>19</sup> Second, intestinal barrier dysfunction associated with undiagnosed or untreated CD that may increase the permeability to undefined triggers of other autoimmune diseases.<sup>4 and 20</sup>

Healing of the intestinal damage in CD patients compliant with a GFD might normalize intestinal permeability and thus decrease exposure to triggers of autoimmunity. Alternatively, it is possible that autoimmune diseases may develop after strict adherence to a GFD if the following occurred: (1) the autoimmune process already was fully developed (irreversible) before gluten exclusion, or (2) as a consequence of shared genetic susceptibility that is not modifiable by decreasing the exposure to gluten.

The studies by Caprai et al<sup>6</sup> and Cosnes et al<sup>10</sup> included in this issue of *Clinical Gastroenterology and Hepatology* support the association between CD and other autoimmune disorders. Ultimately, proof of the association would require the finding of an increased frequency of autoimmune diseases in covert CD that has gone untreated for a long period of time as compared with CD that has been diagnosed and treated.

## Acknowledgments

Supported by the National Institutes of Health Training Grant in Gastrointestinal Allergy and Immunology Research T32 AI-07047 (to A.R.T.) and the National Institutes of Health grants DK-57892 and DK-070031 (to J.A.M.).

## References

1. Green PH, Cellier C. Celiac disease. *N Engl J Med*. 2007; 357:1731–1743. [PubMed: 17960014]
2. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology*. 2006; 131:1981–2002. [PubMed: 17087937]
3. Jabri B, Sollid LM. Mechanisms of disease: immunopathogenesis of celiac disease. *Nat Clin Pract Gastroenterol Hepatol*. 2006; 3:516–525. [PubMed: 16951668]
4. Fasano A. Systemic autoimmune disorders in celiac disease. *Curr Opin Gastroenterol*. 2006; 22:674–679. [PubMed: 17053448]
5. Rubio-Tapia A, Murray JA. The liver in celiac disease. *Hepatology*. 2007; 46:1650–1658. [PubMed: 17969053]
6. Caprai S, Vajro P, Ventura A, SIGENP study group for autoimmune liver disorders in celiac disease. et al. Autoimmune liver disease associated with celiac disease in childhood: a multicenter study. *Clin Gastroenterol Hepatol*. 2008; 6:803–806. [PubMed: 18258488]
7. Ludvigsson JF, Elfstrom P, Broome U, et al. Celiac disease and risk of liver disease: a general population-based study. *Clin Gastroenterol Hepatol*. 2007; 5:63–69. [PubMed: 17161656]
8. Volta U, De Franceschi L, Lari F, et al. Celiac disease hidden by cryptogenic hypertransaminasemia. *Lancet*. 1998; 352:26–29. [PubMed: 9800742]
9. Kaukinen K, Halme L, Collin P, et al. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. *Gastroenterology*. 2002; 122:881–888. [PubMed: 11910339]
10. Cosnes J, Cellier C, Viola S, Groupe D'Etude et de Recherche sur la Maladie Coeliaque. et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. *Clin Gastroenterol Hepatol*. 2008
11. Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. *Gastroenterology*. 1999; 117:297–303. [PubMed: 10419909]
12. Cataldo F, Marino V. Increased prevalence of autoimmune diseases in first-degree relatives of patients with celiac disease. *J Pediatr Gastroenterol Nutr*. 2003; 36:470–473. [PubMed: 12658037]
13. Viljamaa M, Kaukinen K, Huhtala H, et al. Coeliac disease, autoimmune diseases and gluten exposure. *Scand J Gastroenterol*. 2005; 40:437–443. [PubMed: 16028438]
14. Satenga Guidetti GC, Solerio E, Scaglione N, et al. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. *Gut*. 2001; 49:502–505. [PubMed: 11559646]

- A. Satenga Guidetti, Solerio E, Scaglione N, et al. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. *Gut*. 2001; 49:502–505. [PubMed: 11559646]
15. Guariso G, Conte S, Presotto F, et al. Clinical, subclinical and potential autoimmune diseases in an Italian population of children with celiac disease. *Aliment Pharmacol Ther*. 2007; 26:1409–1417. [PubMed: 17892522]
16. Ziegler AG, Schmid S, Huber D, et al. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA*. 2003; 290:1721–1728. [PubMed: 14519706]
17. Michaelsson G, Gerden B, Hagforsen E, et al. Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet. *Br J Dermatol*. 2000; 142:44–51. [PubMed: 10651693]
18. van Heel DA, Franke L, Hunt KA, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. *Nat Genet*. 2007; 39:827–829. [PubMed: 17558408]
19. Hunt KA, Zhernakova A, Turner G, et al. Newly identified genetic risk variants for celiac disease related to the immune response. *Nat Genet*. 2008; 40:395–402. [PubMed: 18311140]
20. Frisk G, Hansson T, Dahlbom I. A unifying hypothesis on the development of type 1 diabetes and celiac disease: gluten consumption may be a shared causative factor. *Med Hypotheses*. 2008 doi: 10.1016/j.mehy.2007.05.058.

**Table 1****Common Characteristics Between Typical Autoimmune Disease and CD**

---

Complex immunogenetics
Production of disease-specific autoantibodies (ie, endomysial antibodies)
Strong association with HLA molecules (DQ2 and/or DQ8 in CD)
Comorbidity with other autoimmune diseases (shared autoimmunity)
Multi-organ involvement
Familial aggregation of both CD and other autoimmune disorders
Innate and adaptive immune system dysregulation

---