Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults

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INTRODUCTION

Celiac disease, also known as gluten-sensitive enteropathy, is a common immune-mediated inflammatory disease of the small intestine caused by sensitivity to dietary gluten and related proteins in genetically predisposed individuals. The epidemiology, pathogenesis, and clinical manifestations of celiac disease will be reviewed here. Its management and the use of antibodies for diagnosis are presented separately. (See "Management of celiac disease in adults" and "Diagnosis of celiac disease in adults".)

PATHOGENESIS

Genetic factors — Celiac disease is an immune disorder triggered by an environmental agent (the gluten component of wheat and related cereals) in genetically predisposed individuals [1,2]. The genetic basis of celiac disease is supported by the frequent intrafamilial occurrence and the remarkably close association with the human leukocyte antigen (HLA) DR3-DQ2 and/or DR4-DQ8 gene locus. More than 99 percent of individuals with celiac disease have HLA DR3-DQ2 and/or DR4-DQ8, compared with 30 to 40 percent of the general population of most countries. Homozygosity for HLA DQ2 has been associated with an increased risk for celiac disease and enteropathy-associated T-cell lymphoma (table 1) [3-5]. It has been estimated that the HLA contribution to the development of celiac disease among siblings is 36 percent [6]. Thus,

another gene or genes at an HLA-unlinked locus must also participate [7-11]. Moreover, novel genetic and especially epigenetic factors that increase the risk or severity of celiac disease have been identified [12]. Celiac disease is associated with a number of autoimmune disorders, including type 1 diabetes mellitus and autoimmune thyroid disease [13,14]. A particular association was found with chromosome 15q26, which contains a type 1 diabetes susceptibility locus [8,9,13], and with chromosome 5q and possibly 11q [9]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children", section on 'Genetic factors'.)

Several non-HLA locus genes conferring risk for celiac disease have also been identified and an increasing number of non-HLA risk alleles have been associated with an increased risk of celiac disease [10,11,15]. Non-HLA genes that may influence susceptibility to the disease have been identified, but their influence has not been confirmed. However, these polymorphisms, even when taken together, contribute only 3 to 4 percent to the genetic risk for celiac disease, as compared with 30 to 40 percent for HLA-DQ2 or -DQ8.

Mucosal immune response — In patients with celiac disease, immune responses to gliadin fractions promote an inflammatory reaction, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy. This response is mediated by both the innate and adaptive immune systems.

- **Adaptive immune response**

  - **Gliadin reactive T cells** – The adaptive response is mediated by gliadin (gluten)-reactive T-cells in the lamina propria that recognize gliadin peptides bound to HLA-DQ2 or -DQ8 on antigen-presenting cells.

    Tissue transglutaminase, a ubiquitous intracellular enzyme, deamidates gluten peptides, increasing their immunogenicity. Tissue transglutaminase is released by inflammatory and endothelial cells and fibroblasts in response to mechanical irritation or inflammation. Once it has been secreted, it crosslinks glutamine-rich proteins such as the gluten proteins from wheat. However, it can also deamidate glutamine residues in gluten to glutamic acid. Deamidation produces a negative charge in gluten peptides that increases their binding to HLA-DQ2 and -DQ8, which potentiates their capacity to stimulate T-cells [16-18].

    A 33 amino acid peptide (A-gliadin, peptide 56-89) that is particularly resistant to gastrointestinal peptidases may be the primary initiator of the inflammatory response to gluten in patients with celiac disease [19]. This peptide can be completely degraded by enterocytes in controls but only partly in celiac patients [20]. Enterocytes from patients with celiac disease show only limited digestion of peptide 31-49 of A-gliadin, a

peptide that is not recognized by HLA-DQ2/DQ8. The high stability against proteolysis or the incomplete degradation of these gliadin peptides favors them as important initiators of the inflammatory response and toxic effects [20]. The key role of tissue transglutaminase in celiac disease pathogenesis has been confirmed in a phase 2 clinical study of 160 volunteers with celiac disease in remission who were challenged with 3 g daily of gluten, where an oral inhibitor of this enzyme largely prevented intestinal damage [21].

Gluten peptide receptor(s) on intestinal epithelial cells may mediate the transport of gluten peptides to the lamina propria where T-cell activation occurs. A study found that CD71 (the transferrin receptor) was increased in patients with celiac disease and was also expressed at the apical pole of enterocytes, in contrast to its usual location at the basolateral pole of enterocytes [22]. CD71 colocalized with secretory IgA and seemed to be responsible for the apical to basal retro-transport of secretory IgA. Gluten peptides that are bound to secretory IgA (ie, IgA anti-gliadin antibodies) may be protected from degradation by the enterocytes, leading to accumulation in the lamina propria where T-cell stimulation occurs [22]. Gluten may also induce an increase in intestinal permeability in patients with celiac disease by binding to chemokine receptor CXCR3 found on enterocytes [23]. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children".)

- **Autoantibodies and intraepithelial lymphocytes** – The relative pathogenic importance of humoral versus the established role of cellular immunity in the pathogenesis of celiac disease is uncertain. In a cell culture system, autoantibodies to tissue transglutaminase blocked intestinal epithelial differentiation [17,24]. Tissue transglutaminase may support the bioactivation of transforming growth factor beta 1, which is required for epithelial differentiation, a process that is impaired in celiac disease. Some inhibitory effect of isolated autoantibodies on tissue transglutaminase activity was also demonstrated in vitro [25]. However, residual enzymatic activity appears to be sufficient for protein crosslinking and (gluten) deamidation reactions [26]. Therefore, the mucosal tissue transglutaminase activity in celiac disease, which cannot be completely blocked by the locally produced autoantibodies, may have a role in the pathogenesis of celiac disease [16,27].

  The number of intraepithelial lymphocytes, which mainly bear the otherwise infrequent gamma-delta T-cell receptor, is increased in patients with active, gluten-sensitive celiac disease compared with normal subjects, while patients with refractory celiac disease also have aberrant lymphocytes with restricted gene rearrangements. The intraepithelial T lymphocytes show increased expression of interferon gamma and IL-10 [28]. However, the

pathogenetic role of these lymphocytes, compared with the lamina propria lymphocytes, is controversial [29], and several inflammatory conditions, such as enteric infections and drug and food allergies that are unrelated to celiac disease, can cause intraepithelial lymphocytosis [30,31].

- **Innate immune response** – Innate responses promote adaptive (T-cell-mediated) immunity in most autoimmune diseases and also in celiac disease. Triggers can be microbial but also chemicals, small molecules, or even food derived. Innate responses are usually sensed by pattern recognition receptors that are prominently expressed on myeloid immune cells, such as monocytes, macrophages, or dendritic cells. They usually lead to immediate immune responses to foreign invaders but can also exacerbate T-cell responses. Interleukin-15 is a prominent innate cytokine that promotes celiac disease [32], serving as a target for nondietary therapies [33]. Moreover, innate immunity elicited by non-gluten wheat proteins (in addition to gluten-mediated activation of pathogenic T-cells) is involved in and perhaps even necessary to trigger the gliadin-specific (adaptive) T-cell response in genetically predisposed individuals [34].

  In celiac disease, gluten peptides have been implicated as triggers of innate immune responses not only in intestinal epithelial cells but also in mononuclear cells [34-40]. However, this was not confirmed in a study that identified a family of non-gluten proteins, the wheat amylase-trypsin inhibitors (ATIs), as activators of innate immunity in macrophages, monocytes, and dendritic cells via toll-like receptor 4, the receptor for bacterial lipopolysaccharide [41]. Notably, the ATIs regulate storage proteins and carbohydrates of the grain kernel and serve as pest-resistance proteins of gluten-containing cereals [42-45]. ATIs are highly resistant to intestinal digestion and induce low-level intestinal inflammation as well as intestinal dysbiosis after oral ingestion. They are possibly the major cause of non-celiac "gluten sensitivity" (more correctly "non-celiac wheat" sensitivity), which is defined as dose-dependent intolerance to gluten-containing cereals, with intestinal and extraintestinal manifestations, after exclusion of celiac disease or classical wheat allergy [46,47]. (See "Diagnosis of celiac disease in adults", section on 'Differential diagnosis'.)

EPIDEMIOLOGY

Prevalence — Celiac disease is not limited to individuals ethnically derived from European populations and has increasingly been found in populations of Northern Africa, the Middle East, India, and Northern China [48]. The estimated global prevalence of celiac disease based on serologic studies is approximately 1 percent [49,50]. Epidemiologic studies using serologic tests

with biopsy verification have reported prevalences of 1:70 to 1:300 in most countries [51]. Even higher worldwide prevalences were reported by a systemic review and meta-analysis, with a prevalence of 1.4 percent based on serologic results and 0.7 percent found by biopsy results [52]. Overall, the global distribution of the disease seems to parallel the distribution of human leukocyte antigen (HLA) genotypes that predispose to celiac disease, provided that the population is also exposed to gluten [53].

Population-based studies have suggested that recognized cases of celiac disease may only represent the tip of the celiac iceberg. As an example, a study from Italy reported that asymptomatic cases outnumbered symptomatic cases by a ratio of 7:1 [54]. Screening programs based upon antibody testing have demonstrated a high prevalence of celiac disease [48,54-60]. In European and United States cohorts, prevalence estimates range from 1:96 to 1:252 [48,54,56-62]. A large serologic screening study in the United States suggested a prevalence of 1:133 among patients with no risk factors or symptoms [59]. Analysis of self-reported data from the National Health and Nutrition Examination Surveys suggest that prevalence of individuals with celiac disease in the United States has remained stable between 2009 and 2014 [63]. In contrast, a study with Italian school-age children showed a significantly increased prevalence ranging from 0.88 percent when assessed between 1993 and 1995 up to 1.58 percent when assessed between 2015 and 2016 [64].

High risk groups — First- and second-degree relatives of patients with celiac disease are at increased risk [59,65]. In a meta-analysis, the pooled prevalence of celiac disease was 8.9 percent (1:11) for siblings, 7.9 percent (1:13) for offspring, and 3 percent (1:33) for parents of the celiac patient [65].

Other individuals at increased risk for celiac disease include (among several other autoimmune diseases):

- Type 1 diabetes
- Autoimmune thyroiditis
- Down and Turner syndromes
- Pulmonary hemosiderosis (moderate risk)

TERMINOLOGY

Symptomatic disease

Classic celiac disease — The classic celiac disease or gluten-sensitive enteropathy is characterized by diarrhea or signs and symptoms of malabsorption (eg, steatorrhea, weight

loss, or other signs of nutrient or vitamin deficiency) or both; villous atrophy; and resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months [66]. Patients with classic disease possess antibodies against tissue transglutaminase. (See "Diagnosis of celiac disease in adults", section on 'Serologic evaluation'.)

Atypical celiac disease — Patients with atypical celiac disease lack classic symptoms of malabsorption but may exhibit minor gastrointestinal complaints. They usually have extraintestinal manifestations of celiac disease including anemia, dental enamel defects, osteoporosis, arthritis, increased aminotransferases, neurological symptoms, infertility, and several associated autoimmune diseases. These patients usually have villous atrophy in duodenal biopsies and display positive celiac antibodies, prominently against tissue transglutaminase. (See "Diagnosis of celiac disease in adults", section on 'Serologic evaluation'.)

Subclinical or asymptomatic disease — Patients are asymptomatic and are identified incidentally during endoscopy performed for other indications (picture 1) or by serologic screening of high-risk groups for antibodies against tissue transglutaminase. The term "silent" may be a misnomer; after treatment with a gluten-free diet, many of these patients retrospectively recognize subclinical symptoms that they had not previously considered to be abnormal. Although these patients usually display the characteristic architectural remodeling of the intestinal mucosa, mainly villous atrophy, seen in classic celiac disease, they do not show classic clinical symptoms.

Establishing the diagnosis of subclinical or asymptomatic celiac disease is of potential importance due to the risk of malignancy, the presence of unsuspected nutritional deficiencies, and the association with low-birth weight infants in affected mothers. (See "Management of celiac disease in adults".)

Potential celiac disease — The term is used for patients with positive celiac-specific serum antibodies but normal duodenal mucosal biopsy. Potential celiac disease is also used for patients with positive serology and increased intraepithelial lymphocytes (Marsh 1 lesion) (figure 1). These patients have no symptoms or laboratory signs of malabsorption. However, patients are at risk of developing classic celiac disease, and must be made aware of this possibility and should be monitored.

Latent celiac disease — Latent celiac disease was a previously used term for patients that presented with celiac disease in the past, usually diagnosed in childhood, but who recovered completely with a gluten-free diet and remained "silent" even once a normal diet was resumed [67]. Approximately 20 percent of such patients continued to be in remission (asymptomatic with normal villous architecture) into adulthood and were therefore classified as latent, while

the others redeveloped variable degrees of villous atrophy [68]. Latency may be transient and thus regular follow-up of such patients is warranted. Moreover, diagnostic errors such as incorrect orientation and reading of duodenal biopsies may have obscured an otherwise positive histologic finding [69].

Refractory disease — Refractory disease is defined by the persistence of symptoms and villous atrophy despite adherence to a gluten-free diet. Failure to improve on a gluten-free diet is mostly due to poor dietary compliance or other underlying malabsorptive disorders. However, in rare cases, diet-refractory celiac disease may be related to one of the following:

- Non-malignant inflammation of the small intestine, possibly due to a high sensitivity towards minimal amounts of gluten (refractory celiac disease type 1 [RCD1]).
- Semi-malignant inflammatory condition (RCD2).
- Overt enteropathy-associated T-cell lymphoma (EATL).
- Collagenous sprue, a very rare, little understood disorder, which is characterized by subepithelial collagen deposition [70].
- Alternative diagnosis including autoimmune enteropathy, common variable immunodeficiency (CVID; IgG deficiency) or drug-induced villous atrophy.

Patients with refractory celiac disease type 2 or EATL have aberrant intraepithelial lymphocytes with restricted gene rearrangements; the relation of this finding to the resistance to gluten restriction is not known [29].

CLINICAL MANIFESTATIONS

Although classically a disease of infants, celiac disease now often presents later, between the ages of 10 and 40 years. Thus, the impressive clinical picture of a child with life-threatening malabsorption is often replaced by the mostly atypical presentation of adult celiac disease. This is in part due to longer periods of breast-feeding and the later introduction of gluten in the infant diet.

Thus, celiac disease represents a continuum with variable degrees of severity. The severity of symptoms appears to correlate with both histologic severity and tissue transglutaminase titers [71,72].

Gastrointestinal manifestations — Patients may present with classic signs, including diarrhea with bulky, foul-smelling, floating stools due to steatorrhea and flatulence. These symptoms are paralleled by the consequences of malabsorption, such as weight loss, severe anemia, neurologic disorders from deficiencies of B vitamins, and osteopenia from deficiency of vitamin D and calcium.

Adult patients with undiagnosed celiac disease rarely present with profuse diarrhea and severe metabolic disturbances (celiac crisis) [73].

The severity of histologic changes in the small bowel does not necessarily correlate with the severity of clinical manifestations [74]. Although there is a gradient of decreasing severity from the proximal to the distal small intestine, correlating with the higher proximal concentration of dietary gluten, sampling error can occur due to spotty features of mucosal inflammation, or individual differences in gluten digestion and, therefore, a more proximal or distal maximal mucosal exposure to immunogenic gluten peptides. The histologic severity ranges from a mild alteration characterized by increased intraepithelial lymphocytes (type 1 lesion) to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia (type 3 lesion) (picture 2 and figure 1) [66,67,75-78]. (See "Diagnosis of celiac disease in adults", section on 'Endoscopy with small bowel biopsy'.)

Extraintestinal manifestations — A number of nongastrointestinal manifestations of celiac disease have been described. (See "Diagnosis of celiac disease in adults".)

Mucocutaneous

- **Dermatitis herpetiformis** – Dermatitis herpetiformis is common among patients with celiac disease. The classic clinical finding in dermatitis herpetiformis is the development of multiple intensely pruritic papules and vesicles that occur in grouped ("herpetiform") arrangements. The elbows, dorsal forearms, knees, scalp, back, and buttocks are among the most common sites for lesion development (picture 3A-F). The clinical manifestations, diagnosis, and management of dermatitis herpetiformis are discussed in detail separately. (See "Dermatitis herpetiformis", section on 'Treatment'.)

- **Atrophic glossitis** – Oral lesions (erythema or atrophy) and a soreness or burning sensation of the tongue have been described in association with celiac disease and respond to a gluten-free diet [79]. Oral symptoms are frequent in patients with classical celiac disease, thus the involvement of the oral cavity is a helpful tool in diagnosis of celiac disease [80].

Metabolic bone disorders — Metabolic bone disease is common in celiac disease and can occur in patients without gastrointestinal symptoms [81-84]. Patients with celiac disease may have bone loss due to secondary hyperparathyroidism from vitamin D deficiency [85]. Osteomalacia due to vitamin D deficiency is also sometimes seen, although its prevalence is unknown [86]. In adults, loss of bone density in the peripheral skeleton may persist despite apparent normalization at axial skeletal sites after patients are on a gluten-free diet [85,87].

The risk of fractures is slightly increased in patients with celiac disease [88]. In a population-based cohort study in which 4732 patients with celiac disease were compared with 23,620 age- and sex-matched controls, the overall hazard ratio for any fracture was 1.3 (95% CI 1.16-1.46). The absolute difference in the overall fracture rate was 3.2 per 1000 person-years.

A higher prevalence of osteoarthritis has also been described in celiac disease, but whether there is a causal relationship is unclear [89].

Hematologic

- **Iron deficiency anemia** – Celiac disease may be a surprisingly frequent cause of iron deficiency anemia [90-92]. One study of 93 patients presenting for evaluation of iron deficiency anemia found 11 (12 percent) with small bowel biopsy findings compatible with celiac disease [93]. Some had other mucosal abnormalities, such as esophagitis and gastritis, which could have been taken as the cause of the anemia and delayed the discovery of celiac disease. Similar findings were noted in another report in which 6 percent of 85 patients with iron deficiency anemia had celiac disease [90]. The incidence was 20 percent in the subgroup of nonresponders to supplemental iron.

- **Hyposplenism** – Several case reports have described hyposplenism in association with celiac disease [94-97], the pathogenesis of which is unknown. (See "Management of celiac disease in adults", section on 'Pneumococcal vaccination'.)

Neuropsychiatric — Several reports have described an association between celiac disease and neurologic or psychiatric symptoms including headache, peripheral neuropathy, ataxia, epilepsy, depression, dysthymia, and anxiety [98-113]. However, these studies are limited by a small sample size, retrospective acquisition of data, tertiary referral bias, and potential misclassification of celiac disease, as the diagnosis in some studies was based on the presence of gliadin antibodies rather than duodenal histology or more specific autoantibodies. The association of celiac disease with depression and epilepsy is still unclear as studies have been conflicting [114,115].

Peripheral neuropathies, characterized by burning, tingling, and numbness in hands and feet, have been described in up to 50 percent of patients with celiac disease and may precede its diagnosis [99]. In a large population-based study from Sweden that included 14,000 celiac patients and 70,000 controls, celiac disease was associated with an increased risk of polyneuropathy (hazard ratio 3.4), but not with other neurologic outcomes [116].

In patients with celiac disease, neuropathies may also be associated with lymphoma and deficiencies of vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B12 (cobalamine), and E. However, vitamin deficiency syndromes are uncommon in the absence of severe and extensive small bowel involvement.

While a gluten-free diet has been shown to have a favorable effect on headache and dysthymia, it has not been demonstrated to improve peripheral neuropathies [98,117]. (See "Overview of water-soluble vitamins" and "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency" and "Overview of vitamin E".)

ASSOCIATED CONDITIONS

Selective IgA deficiency — Selective IgA deficiency has been associated with celiac disease and has been detected in up to 8 percent of patients with celiac disease in some studies [118,119]. Screening for celiac disease in patients with IgA deficiency is discussed in detail separately. (See "Diagnosis of celiac disease in adults".)

Autoimmune disease

- **Diabetes mellitus** – Celiac disease is closely associated with type 1 diabetes mellitus and polyglandular autoimmune syndrome type III characterized by autoimmune thyroiditis combined with immune-mediated diabetes [120-123]. In several reports, between 2.6 and 7.8 percent of adults with type 1 diabetes had IgA autoantibodies to endomysium or to tissue transglutaminase; most such patients were proven to have celiac disease with small bowel biopsy [124,125]. Many such patients had no overt clinical manifestations of celiac disease [124]. Other reports have demonstrated that as many as 3.5 percent of children of parents with type 1 diabetes have celiac disease, the prevalence of which increases with age [126].

  Type 1 diabetes and celiac disease share multiple genetic loci such as HLA-DR3, HLA-DQ2 (HLA-DQ8), and several genetic variations [8,127,128]. This suggests that type 1 diabetes and celiac disease have common features in their pathogenesis, such as tissue damage from autoimmunity or intolerance to dietary antigens. Approximately one-third of patients

with type 1 diabetes who have the celiac disease-predisposing haplotype HLA-DQ2 (which is found in 20 to 25 percent of the general Western population) have raised IgA autoantibodies to tissue transglutaminase and are therefore likely to have celiac disease [129]. This is in comparison to a prevalence of tissue transglutaminase autoantibodies in only 2 percent of those without HLA-DQ2.

The age of onset and the severity of diabetes do not appear to be influenced by the presence of celiac disease [124]. Furthermore, celiac disease does not appear to trigger autoimmunity leading to diabetes as suggested in one report [130], since celiac autoantibodies usually develop after the onset of diabetes [131].

Whether a gluten-free diet improves diabetes in patients with both diabetes and celiac disease is unclear. Only two small studies, one retrospective [132] and one short-term [121], investigated the effect of a strict gluten-free diet in patients with type 1 diabetes and silent celiac disease. Patients showed at best a trend toward an increased body mass index, but no change in folate or hemoglobin levels or insulin requirements. However, animal studies suggest that the interplay between gluten exposure and the intestinal immune system can modulate the development of type 1 diabetes. Substitutions of hydrolyzed casein instead of gluten in the diet delayed the onset of type 1 diabetes in BB rats, which spontaneously develop diabetes [133], and a gluten-free diet reduced the incidence of type 1 diabetes in non-obese diabetic mice from 64 to 15 percent [134]. Furthermore, the very early supplementation of newborns' diet with gluten (<3 months) showed an increased risk for islet autoantibodies, which precede type 1 diabetes mellitus [135]. Thus, larger and prospective clinical studies are required to clarify the relationship between celiac disease, type 1 diabetes, and other secondary autoimmunities.

- **Thyroid disease** – There is an increased incidence of autoimmune thyroid disease among patients with celiac disease [136,137]. Hypothyroidism is more frequent than hyperthyroidism.

- **Atopic dermatitis** – Patients with celiac disease (and their families) may also be more likely to have atopic dermatitis compared with the general population, although the prevalence of other allergies is not increased [138].

Gastrointestinal disease

Gastroesophageal reflux disease — An association of celiac disease with gastroesophageal reflux disease (GERD) has been reported. In a study of 133 patients with celiac disease and 70 healthy controls, patients with celiac disease had significantly higher GERD symptom scores when compared with controls [139]. Prior to treatment, 30 percent of patients with celiac

disease reported moderate to severe symptoms compared with 6 percent of controls. Fifteen percent of patients with atypical or silent cases of celiac disease reported moderate to severe GERD. Three months after initiating a gluten-free diet, GERD symptom scores in patients with celiac disease were comparable to those in the healthy controls.

Eosinophilic esophagitis — The incidence of eosinophilic esophagitis is increased in both children and adults with celiac disease (age-adjusted and sex-adjusted standardized incidence ratio [SIR] 16.0, 95% CI 8.7-25.5) [140-144].

Inflammatory bowel disease — Several case series have demonstrated an association between celiac disease and inflammatory bowel disease (IBD), more frequently with ulcerative colitis than Crohn disease [145,146]. In one case-control study, the risk of IBD in patients with celiac disease was elevated 10-fold, while the risk of celiac disease in patients with IBD was comparable to controls [147]. Of note, two independent studies have found a common proinflammatory polymorphism of the IL-23 receptor gene in both ulcerative colitis and celiac disease [148,149]. First-degree relatives of patients with celiac disease may also be at a fivefold increased risk of developing ulcerative colitis as compared with the general population [150]. In one case-control study that included 51 patients with coexisting IBD and celiac disease and 102 IBD controls, patients with ulcerative colitis and coexisting celiac disease were more likely to have pancolitis as compared with patients with ulcerative colitis alone (odds ratio [OR] 3.3, 95% CI 1.05-21.5) [151]. However, among patients with Crohn disease, there were no phenotypic differences based on the presence of coexisting celiac disease.

Microscopic colitis — Patients with celiac disease have an increased risk of microscopic colitis. In a large cohort study of 1009 patients with celiac disease, 44 (4.3 percent) were diagnosed with microscopic colitis, corresponding to a 72-fold increased risk of microscopic colitis in patients with celiac disease, as compared with the general population [152]. (See "Microscopic (lymphocytic and collagenous) colitis: Clinical manifestations, diagnosis, and management", section on 'Associated conditions'.)

Liver disease

- **Elevated aminotransferase** – Celiac disease may be associated with nonspecific mild to moderate chronic elevation in serum aminotransferase levels in 15 to 55 percent of patients (alanine aminotransferase is usually slightly greater than aspartate aminotransferase [153,154]). A meta-analysis found that in patients with cryptogenic elevations in aminotransferases, celiac serologies were positive in 6 percent and duodenal biopsies suggested celiac disease in 4 percent [155]. In addition, abnormal serum transaminases were detected in 27 percent of patients with newly diagnosed celiac

disease. Serum transaminases normalized in 63 to 90 percent of patients within a year of initiating a gluten-free diet.

- **Cholestatic and autoimmune liver disease** – Celiac disease has been associated with primary biliary cirrhosis (PBC) [156]. Two large studies suggested a prevalence of 6 to 11 percent in patients with PBC, although these may be overestimates [157,158]. (See "Evaluation and treatment of low bone mass in primary biliary cholangitis (primary biliary cirrhosis)".)

Celiac disease has also been associated with other causes of liver disease [156,159,160]. One study evaluated the risk of liver disease in 13,818 patients with celiac disease from 1964 to 2003, with 66,584 age- and sex-matched controls [160]. Celiac disease was associated with an increased risk of acute hepatitis, chronic hepatitis, and primary sclerosing cholangitis. Adjustment for socioeconomic index or diabetes mellitus had no notable effect on the risk estimates. In addition, prior liver disease was associated with a statistically significant four- to six-fold increased risk of later celiac disease.

Pancreatitis — Large database studies have described an increased risk of pancreatitis (both acute and chronic) in patients with celiac disease [161,162]. Further studies are needed to clarify the strength of the association and potential mechanisms that underlie it.

Menstrual and reproductive issues — On a population basis, women with celiac disease, most of them on a gluten-free diet, have similar overall fertility to the general female population [163,164]. However, women with untreated celiac disease may have later age of menarche, earlier menopause, secondary amenorrhea, recurrent miscarriage, spontaneous abortion, preterm delivery, and low birth weight [164-174].

Male infertility, characterized by abnormalities in sperm motility and morphology as well as a biochemical picture of androgen resistance (high serum testosterone and high luteinizing hormone [LH] concentrations), has been reported in celiac disease [175,176]. In one study of 41 men with celiac disease and high testosterone and LH concentrations, dietary modification led to normalization of the biochemical abnormalities [176]. (See "Causes of male infertility".)

Idiopathic pulmonary hemosiderosis — Coexistence of celiac disease and idiopathic pulmonary hemosiderosis, also known as Lane-Hamilton syndrome, has been reported in a number of cases, and introduction of a gluten-free diet has been associated with remission of pulmonary symptoms in several patients. (See "Idiopathic pulmonary hemosiderosis".)

Cardiovascular disease — Celiac disease, which is often clinically unsuspected, accounts for as many as 5 percent of patients with autoimmune myocarditis or idiopathic dilated

cardiomyopathy [177,178]. In one study of nine such patients, none had classic gastrointestinal symptoms of celiac disease (recurrent abdominal pain, diarrhea, and weight loss), but all had iron deficiency anemia refractory to oral iron replacement [177]. Cardiac function improved following a gluten-free diet with or without immunosuppressive therapy. Patients with celiac disease may also be at increased risk for ischemic heart disease [179-183]. (See "Myocarditis: Causes and pathogenesis", section on 'Celiac disease'.)

Kidney disease — Glomerular IgA deposition is common, occurring in as many as one-third of patients. The great majority of affected patients have no clinical manifestations of kidney disease, perhaps because there is no associated activation of complement. (See "IgA nephropathy: Pathogenesis".)

PROGNOSIS

Cancer risk — Patients with celiac disease are at increased risk for lymphoma and gastrointestinal cancer. Whether the degree of compliance with a gluten-free diet influences the rates of cancers is uncertain [184,185]. The increase in cancer risk in patients with celiac disease is illustrated in the following studies:

- One of the largest population-based studies to address cancer risk in patients with celiac disease included 12,000 patients with celiac disease or dermatitis herpetiformis [186]. Cancer was diagnosed in 249 patients during follow-up (standardized incidence ratio [SIR] 1.3, 95% CI 1.2-1.5), suggesting that the overall increase in cancer risk was modest. The risk of cancer was not increased in children or adolescents. The most common malignancy was lymphoma (SIR 5.9), which accounted for 18 percent of all cancers (image 1). The risk of other digestive tract cancers was also increased, including oropharyngeal (mostly esophageal squamous cell), small intestinal adenocarcinoma, colorectal, and hepatocellular. In contrast, there was a significantly reduced risk of breast cancer. The risk declined with increasing length of follow-up. (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas".)

- In another large cohort study that evaluated the risk of gastrointestinal (GI) cancers in 28,882 patients with celiac disease (villous atrophy, Marsh score = 3), 12,860 with mild inflammation (Marsh score 1 to 2), and 3705 individuals with potential celiac disease (normal mucosa but positive serology), the risk of incident GI cancers was increased in all three groups in the first year of diagnosis (hazard ratio [HR] 5.95, 9.13, 8.10, respectively) [187]. Although the high incident cancer risk in the first year of diagnosis may be due to ascertainment bias, after the first year of diagnosis, the site-specific risk for small

intestinal cancer and hepatocellular carcinoma was increased in patients with celiac disease (HR 2.22 and 1.78) and inflammation (HR 2.49 and 2.17). There was an increased risk of lymphoproliferative malignancy in patients with villous atrophy (HR 2.82) compared with patients with intestinal inflammation without villous atrophy (HR 1.81), but not in individuals with normal mucosa but positive serology celiac disease (HR 0.97) [188]. This risk of lymphoma but not solid tumors remained increased for five years or more after diagnosis despite adherence to a gluten-free diet.

- In a retrospective study that included 48,119 individuals with celiac disease and 239,249 controls, the risk of small bowel adenomas and adenocarcinoma was increased in individuals with celiac disease (HR 5.73 [95% CI, 3.70–8.88] and 3.05 [95% CI, 1.86–4.99], respectively), however, the absolute risk of small bowel adenocarcinoma was low (5 per 10,000 celiac patients over 10 years) [189]. Individuals with celiac disease with mucosal healing had lower rates of small bowel adenocarcinoma, as compared to those with persistent villous atrophy, but the differences were not statistically significant (0.01 versus 0.18 percent, HR 0.18 [95% CI 0.02-1.61]). The risk of carcinoids was not increased in individuals with celiac disease.

Mortality — A number of observational studies have noted a small absolute increase in overall mortality in patients with celiac disease compared with the general population [127,179,184,186,190-196]. The magnitude of mortality risk and its relation to small bowel histopathology was evaluated in a retrospective cohort study that included approximately 29,000 individuals with celiac disease (Marsh stage 3: villous atrophy), 13,000 individuals with only inflammation on biopsy (Marsh stage 1 to 2), and 3700 individuals with normal mucosal histology (Marsh 0), but positive celiac disease serology [179]. There was a significant absolute increase in mortality in all three groups (2.9, 10.8, and 1.7 per 1000 person-years, respectively). The higher absolute mortality among patients with inflammation is partly explained by their older age at study entry. The increase in mortality was largely due to cardiovascular disease and malignancy.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Celiac disease" and "Society guideline links: Dermatitis herpetiformis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Celiac disease (The Basics)")
- Beyond the Basics topics (see "Patient education: Celiac disease in adults (Beyond the Basics)")

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: Celiac disease".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Celiac disease is not limited to individuals ethnically derived from European populations and has increasingly been found in populations of Northern Africa, the Middle East, India, and Northern China. The estimated global prevalence of celiac disease based on serologic studies is approximately 1 percent, and locally can be well above 1 percent. (See 'Prevalence' above.)
- **High-risk groups** – First- and second-degree relatives of patients with celiac disease are at increased risk for celiac disease. Other high-risk groups include patients with one of the following (see 'High risk groups' above):
  - Type 1 diabetes

- Autoimmune thyroiditis
- Several other autoimmune diseases
- Down and Turner syndromes

- **Pathogenesis** – Celiac disease is an immune disorder triggered by an environmental agent (the gluten component of wheat or related cereals) in genetically predisposed individuals. The genetic basis of celiac disease is supported by the frequent intrafamilial occurrence and the remarkably close association with the human leukocyte antigen (HLA) DR3-DQ2 and/or DR4-DQ8 gene locus. (See 'Pathogenesis' above.)

- **Clinical manifestations** – Patients with celiac disease may present with classic symptoms related to malabsorption, including diarrhea, steatorrhea, weight loss, and nutrient or vitamin deficiencies. However, the majority of patients with celiac disease exhibit only minor gastrointestinal complaints, have extraintestinal manifestations, or are asymptomatic. (See 'Gastrointestinal manifestations' above and 'Clinical manifestations' above and 'Symptomatic disease' above.)

- **Associated conditions** – Celiac disease is frequently associated with dermatitis herpetiformis, selective IgA deficiency, and other conditions which have autoimmune features such as type 1 diabetes mellitus, thyroid disease, and other autoimmune diseases. (See 'Associated conditions' above.)

- **Cancer risk** – Patients with untreated celiac disease are at increased risk for lymphoma and gastrointestinal cancer. It remains unclear if early detection of celiac disease, the prior duration and severity of active celiac disease, or the degree of compliance with a gluten-free diet influence the rates of the associated cancers. (See 'Prognosis' above.)

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Topic 4774 Version 36.0

GRAPHICS

Cumulative risk of developing celiac autoimmunity or celiac disease by five years of age by HLA haplotype

HLA DR-DQ genotype	Celiac disease autoimmunity*	Celiac disease¶	Adjusted hazard ratio for celiac disease autoimmunityΔ	Adjusted hazard ratio for celiac diseaseΔ
DR3–DQ2/DR3-DQ2 (n = 1374, 21%)	26%	11%	5.70 (95% CI 4.66-6.97)	6.08 (95% CI 4.43-8.36)
DR3-DQ2/DR4-DQ8 (n = 2612, 41%)	11%	3%	2.09 (95% CI 1.7-2.56)	1.66 (95% CI 1.18-2.33)
DR4-DQ8/DR4-DQ8 (n = 1303, 20%)	9%	3%	1.00	1.00
DR4-DQ8/DR8-DQ4 (n = 1114, 17%)	2%	<1%	1.00	1.00

Results from a prospective study of 6403 children with HLA haplotype DR3-DQ2 or DR4-DQ8, living in the United States, Finland, Germany, or Sweden, which evaluated the risk of celiac disease by haplotype (TEDDY study).

HLA: human leukocyte antigen.

* Celiac disease autoimmunity was defined as the presence of tissue transglutaminase (tTG) antibodies on two consecutive tests at least three months apart.

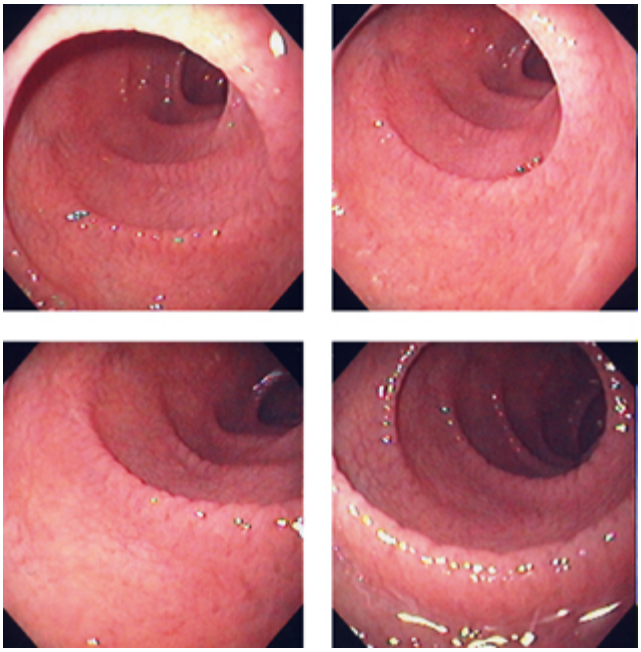
¶ Celiac disease was defined as abnormal results of an intestinal biopsy (Marsh score ≥2) in 291 subjects. For patients with celiac autoimmunity who did not undergo biopsy, celiac disease was diagnosed if tTG was ≥100 units on two consecutive tests (21 subjects).

Δ Adjusted for sex, family history of celiac disease, and country of origin, with the two lowest-risk haplotypes as the reference group.

Based on data from: Liu E, Lee HS, Aronsson CA, et al. Risk of pediatric celiac disease according to HLA haplotype and country. N Engl J Med 2014; 371:42.

Graphic 96365 Version 2.0

Celiac disease

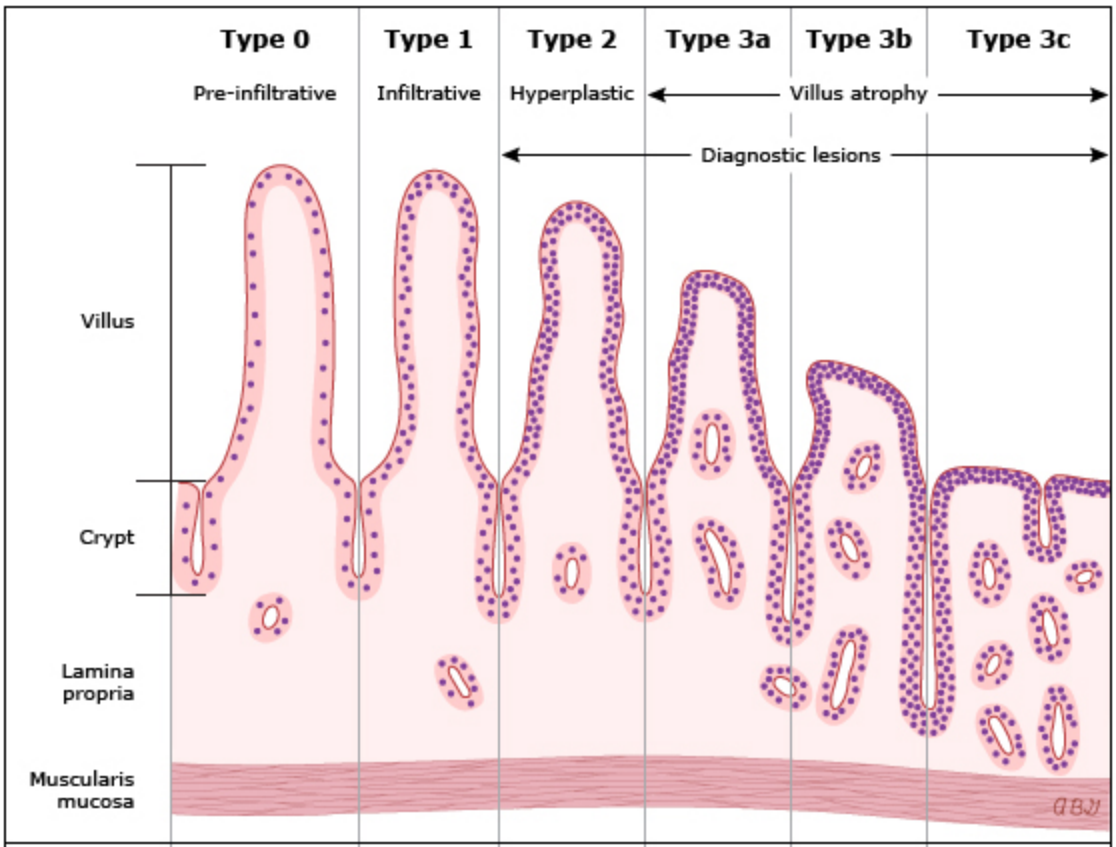


Scalloped duodenal folds seen on endoscopy in a patient with celiac disease.

Courtesy of Eric D Libby, MD.

Graphic 65969 Version 1.0

Intestinal lesions in celiac disease



Villus	Normal	Normal	Normal	Mild atrophy	Moderate atrophy	Severe atrophy
Crypt	Normal	Normal	Hyperplasia	Hyperplasia	Hyperplasia	Hyperplasia
Ratio, villus height: crypt depth	3:1	3:1	<3:1	<2:1	1:1	<1:1
IEL/ 100 EC	<40	>40	>40	>40	>40	>40

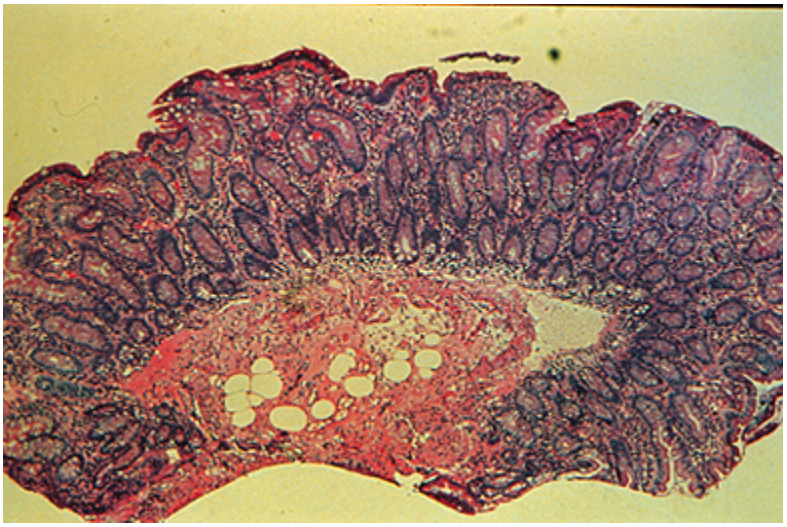
Schematic drawing of the characteristic histologic changes seen in celiac disease as described by Marsh. The lesions range in severity from only increased numbers of intraepithelial lymphocytes in the early stages (Type I) to elongation of the crypts (Type II) and progressive villus atrophy (Type 3a to 3c).

IEL: intraepithelial lymphocytes; EC: epithelial cells (in villus).

Modified from: Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102:330.

Graphic 60343 Version 6.0

Celiac disease

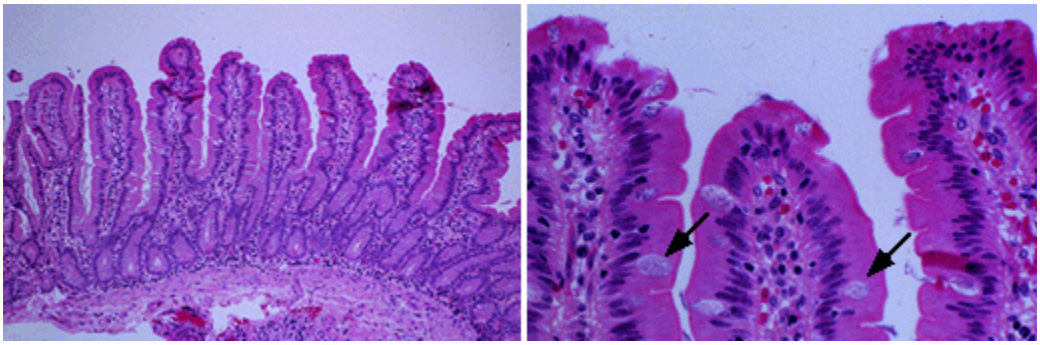


Low-power view of a small bowel biopsy from a patient with celiac disease. The mucosa is flat with complete loss of the normal villous architecture.

Courtesy of Robert Odze, MD.

Graphic 76680 Version 3.0

Normal small intestine

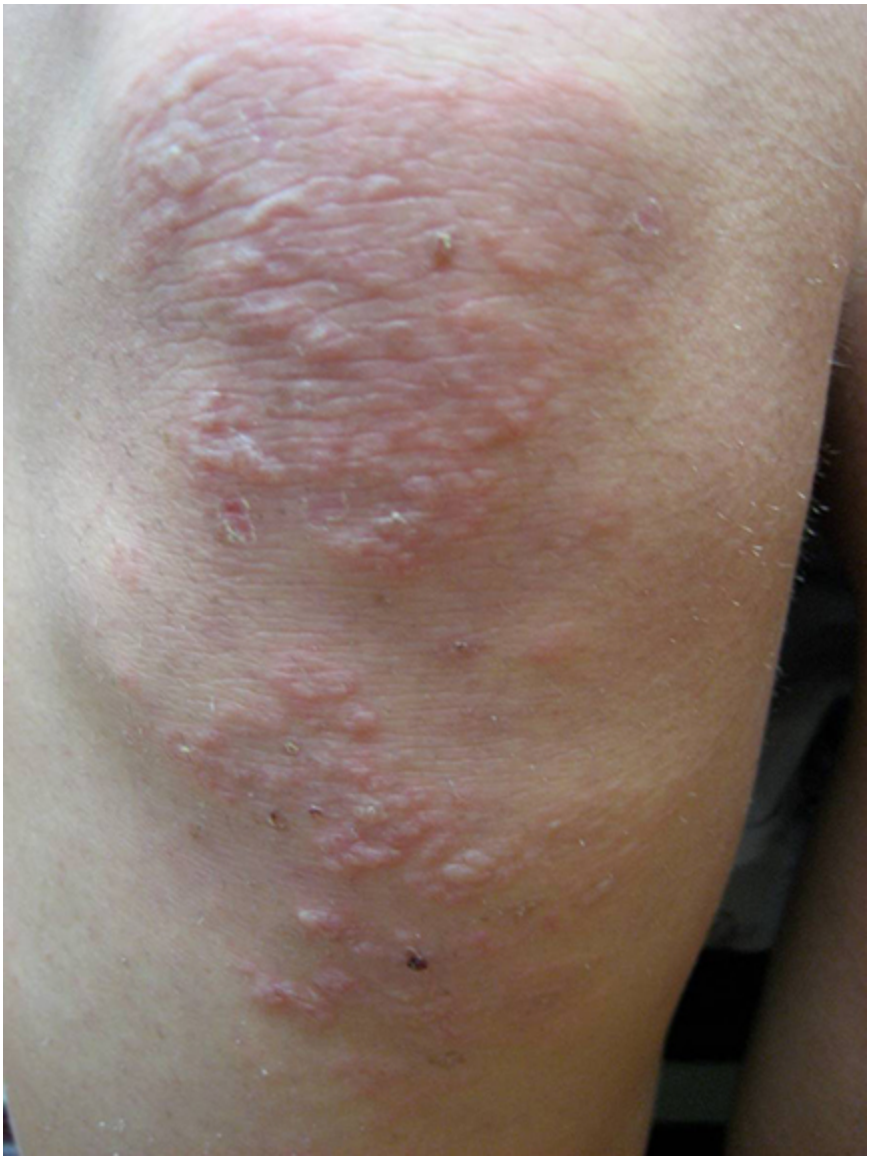


Low-power (left) and high-power (right) views of the normal villous architecture of the small intestine. The high-power view shows the enterocytes and interspersed goblet cells (arrows).

Courtesy of Robert Odze, MD.

Graphic 63225 Version 2.0

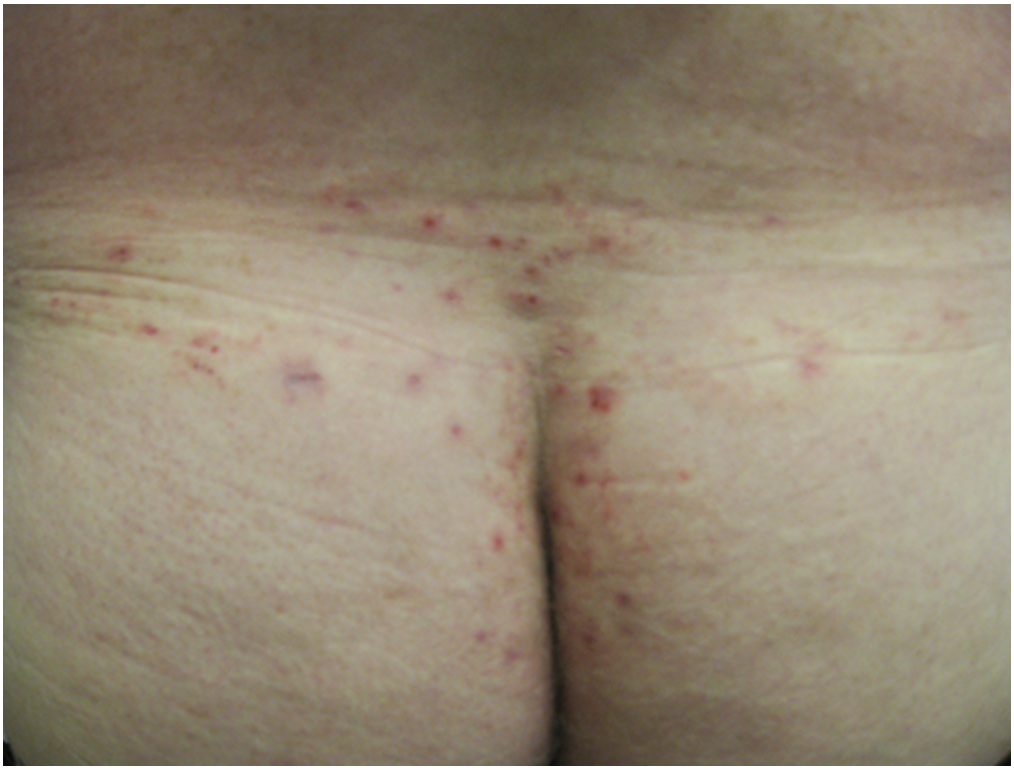
Dermatitis herpetiformis



Erythematous papules and vesicles are present on the knee.

Graphic 86749 Version 2.0

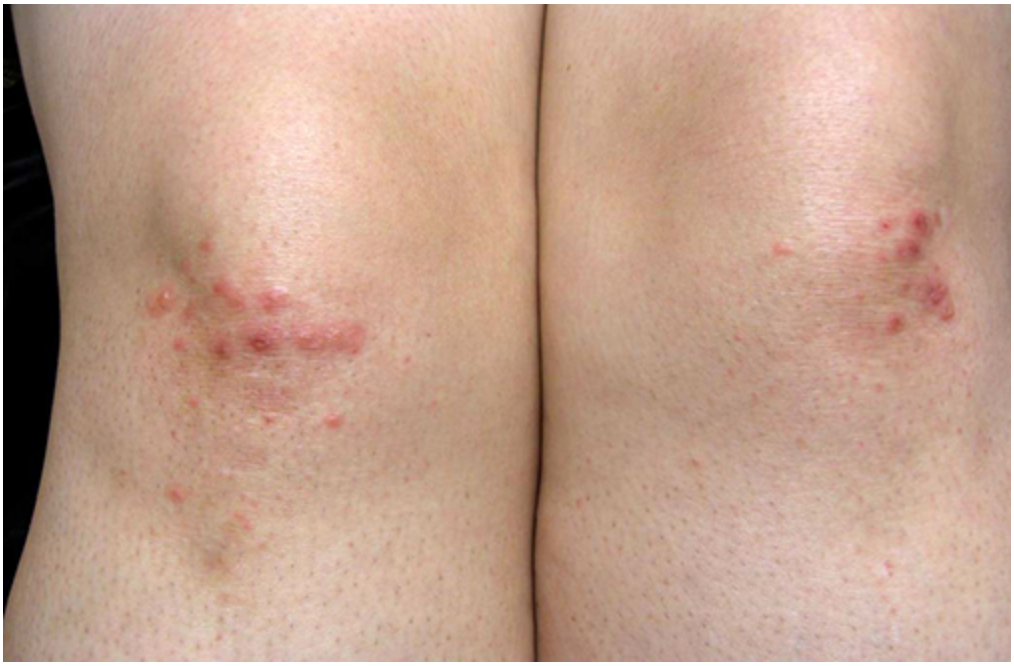
Dermatitis herpetiformis



Multiple excoriated, erythematous papules are present on the buttocks.

Graphic 86750 Version 2.0

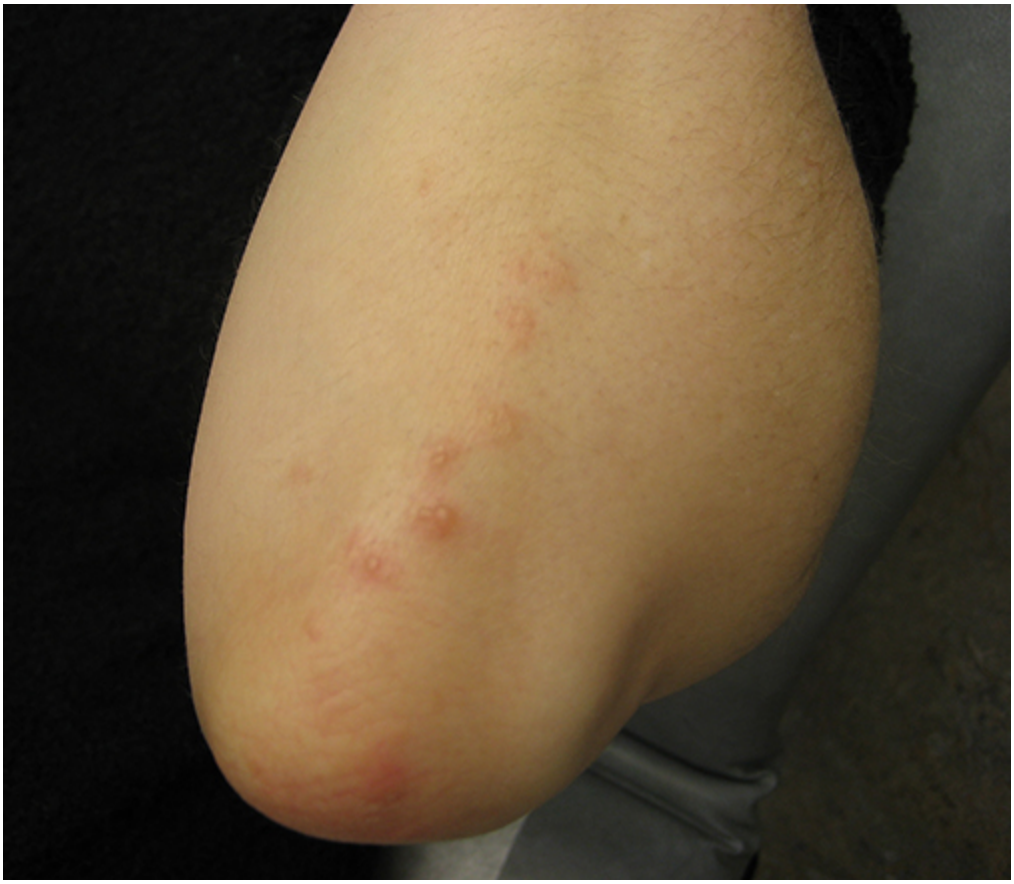
Dermatitis herpetiformis



Multiple erythematous papules and vesicles are present on the knees.

Graphic 86751 Version 2.0

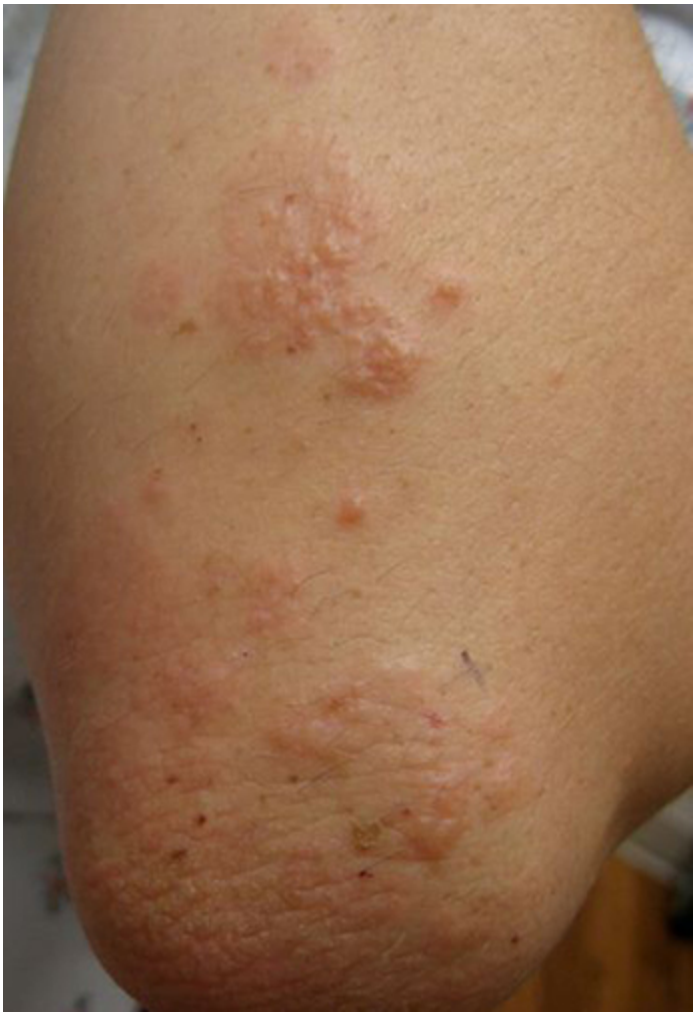
Dermatitis herpetiformis



A few vesicles are present near the elbow.

Graphic 86752 Version 1.0

Dermatitis herpetiformis

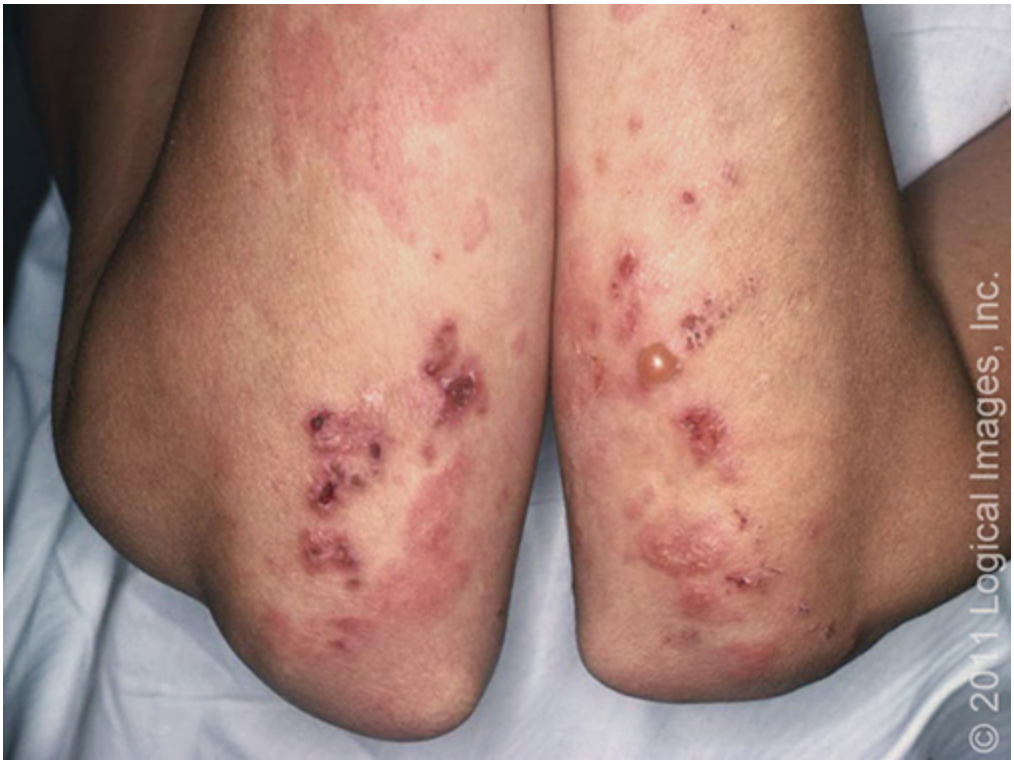


Multiple inflammatory papules and vesicles are present near the elbow.

Courtesy of Scott Florell, MD, Department of Dermatology, University of Utah.

Graphic 86768 Version 3.0

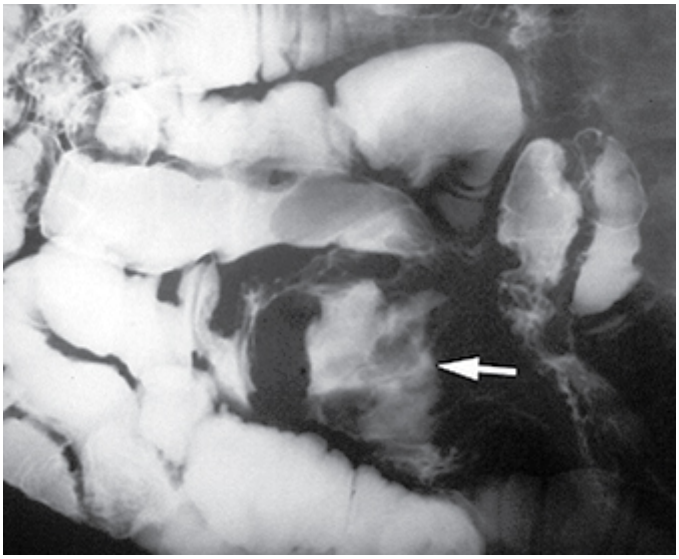
Dermatitis herpetiformis



Vesicles, bullae, erosions, and crusts on elbow skin.

Graphic 78315 Version 6.0

Lymphoma arising in celiac disease



Small bowel follow through examination shows a large ulcerating extrinsic mass (white arrow) arising between and displacing loops of jejunum in a patient with celiac disease. Note the distended, featureless loops of jejunum, which have lost their normal fold pattern; these features are characteristic of celiac disease.

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 67338 Version 2.0

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Conflict of interest policy

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