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REVIEW

# Epidemiology and clinical presentations of celiac disease

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**Abstract** Evidence of the prevalence of celiac disease comes from serological screening studies. These have revealed that celiac disease is common, occurring in about 1 % of the population worldwide. There are some countries with higher prevalence rates such as Finland and others with lower rates, for example Germany. The disease is found in most continents and appears to be increasing. Most people with the disease are not currently diagnosed though women are diagnosed more frequently than men. The mode of presentation has changed both in children and adults with diarrhea and a malabsorption syndrome becoming less common. Abdominal pain and growth issues are major modes of presentation in children, while anemia, osteoporosis, and recognition at endoscopy performed for GERD are seen as modes of presentation in adults. Screening of at risk groups is a major mode of presentation for both adults and children.

## Epidemiology

Many studies have addressed the prevalence of celiac disease. Most have used seroprevalence data, typically serum tissue transglutaminase IgA antibody levels, often confirmed by positivity of endomysial antibody and in some studies biopsy. These studies have revealed that celiac disease occurs in adults and children at rates approaching 1 % of the population in Europe and the USA [1–6]. The disease is recognized not only throughout Europe and in countries populated by those of European ancestry such as Australia and New Zealand, [7, 8] and South America [9–11].

The disease occurs mainly in Caucasians, though in Chile celiac disease is also seen in those of Amerindian heritage [12], and a Canadian study demonstrated celiac disease in patients of Asian origin [13]. While the disease is considered rare in people in Central Africa, it is seen in African-Americans in New York [14] and those from Caribbean nations [15, 16].

Celiac disease is increasingly recognized in the Middle East and North Africa [3, 17–20], wherein it is becoming an increasing economic health burden [21]. The highest rate is reported in North Africa in Saharawi children [19]. In this study the prevalence of antiendomysial antibody positivity in 989 Saharawi children was 5.6 %. In addition the disease occurs in South Asia [22] where presentations include both the typical and atypical [23, 24].

A population-based duodenal biopsy and serology study from northern Sweden revealed a prevalence rate approaching 2 % [25]. This high rate is similar to findings in Mexico and Finland [26, 27]. However, an international serological screening study revealed differences in populations across Europe with high values in Finland (2.4 %) and low in Germany (0.3 %) while the prevalence in Italy was 0.7 % [28].

Females are diagnosed two to three times more frequently than men [29], except in the young and elderly when there is a more equal sex distribution [30]. However in population-based screening studies, males and females appear more evenly affected [4, 6], suggesting either

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differences in severity of symptoms or acquisition of health care between genders. Though in one study, at presentation, men had greater evidence of severe illness than women [29].

Serologic screening studies have shown a dramatic increase in celiac disease serology positivity over time [27, 31–33]. In the study by Rubio-Tapia, there was a four- to fivefold increase over 50 years. In addition the prevalence of the disease increases with age for 2.45 % of an elderly cohort in Finland had celiac disease [32], compared to 1 % of children [2].

The bulk of those with celiac disease are undiagnosed [1, 34], though the rate of diagnosis varies in different countries with a high in Finland in which about 70 % of those with celiac disease are diagnosed [35], compared to the USA in which only 5 % were diagnosed [34]. Within the USA the rate of diagnosis is increasing in both adults [36] and children [37].

## Presentation of celiac disease

Celiac disease was originally considered a pediatric disorder characterized by malabsorption and steatorrhea [38–40]. Subsequently it was recognized that children did not grow out of the disease [41], and it could affect adults at any age [42, 43]. Most adults with celiac disease diagnosed prior to 1980 presented with diarrhea [44]. With the advent of serological tests in the 1980s, the wide spectrum of clinical manifestations became apparent.

Among children celiac disease has a varied presentation, impacted by factors such as age at presentation and duration of disease. Very young children present more often with "classical" celiac disease, marked by diarrhea, abdominal distension, and failure to thrive [37, 45]. Older children and adolescents are more likely to present with atypical gastrointestinal complaints such as pain, vomiting, or constipation; extraintestinal symptoms such as arthritis, neurologic symptoms, and anemia or may have silent disease without any apparent symptoms [46, 47]. Younger patients are more likely to present with diarrheal or malabsorptive manifestations of the disease [48]. Our experience shows that currently, the bulk of children have one of three major presentations [49]: firstly, growth issues that may be failure to thrive in the youngest children or short stature among older children [50]; secondly, recurrent abdominal pain; and thirdly, via serological screening of at risk children either because they were relatives of people with celiac disease or they had one or more autoimmune disorders [49]. Only 9 % of children presented with diarrhea [49]. In fact, diarrhea and the malabsorption syndrome were mainly evident in the very young, less than 2 years of age [51]. Our experience differs from a series of pediatric patients from Spain in which 62 % of the children presented with diarrhea [45].

In addition to the diverse spectrum of disease presentations and age-related variability of the manifestations of celiac disease in children, the shifting presentation of the disease over time should be recognized. An overall decrease in the prevalence of diarrheal presentations over the past two decades, accompanied by an increase in atypical manifestations of the disease, has been well described in both adults and children [37, 44, 52, 53]. More widespread use of serologic markers has facilitated diagnosis of celiac disease in children [52]; this alone does not entirely explain the decrease in diarrheal manifestations, as many long-term studies of adult and pediatric patients predating the use of these markers have documented this shift in clinical presentation [44, 54]. Of note, since the initial availability of sensitive and specific serological assays over the past two decades, the gap between initial presentation and diagnosis in symptomatic children has been gradually fading [55, 56]. This reduction in duration of symptoms has also been documented in adults [44].

The major mode of presentation for adults is diarrhea, though this presentation occurs in less than 50 % of patients [44]. Other presentations include anemia that is mainly due to iron deficiency, though anemia due to nutritional factors and chronic disease may also be present at diagnosis of celiac disease [57, 58]. Anemia is more frequently seen at presentation in adults compared to children [59].

Osteoporosis is another presentation of celiac disease in adults. Reduced bone density is common in patients with celiac disease [60, 61], and there is increased fracture risk [62, 63]. Research from Argentina demonstrated a high prevalence of bone fractures in the peripheral skeleton, mostly occurring before diagnosis or in noncompliant patients [62]. Interestingly a population-based study from Sweden showed both adults and children with celiac disease were at increased fracture risk [64]. A study from the USA demonstrated an increased prevalence of celiac disease among osteoporotic patients [65], though this was not seen in other studies from France and among postmenopausal women in Turkey [66, 67].

Another mode of presentation is the incidental recognition of signs of villous atrophy due to celiac disease during endoscopy performed for any reason [68]. Most upper endoscopy in adults is performed for gastroesophageal reflux disease (GERD). When celiac disease is recognized and treated in people with GERD, improvement in the reflux is frequently noted [69]. There is a reasonable argument for routine duodenal biopsies during endoscopy for adults as is the usual practice for pediatric gastroenterologists [70].

Other presentations in adults include dermatitis herpetiformis, IBS, bloating, and chronic fatigue as well as a variety of neurological presentations [71]. Many of the symptoms of celiac disease are common, frequently seen among patients attending primary care physicians [72]. In a

multicenter North American primary care screening study involving patients with a variety of symptoms including bloating, fatigue, recurrent abdominal pain, and IBS, screening for celiac disease resulted in a 40-fold increase in the rate of celiac disease diagnosis [73]. Recurrent episodes of abdominal pain are seen prior to diagnosis in adults and children [49, 74], and may be due to small intestinal intussusceptions that appear commonly in celiac disease [75, 76].

Serological screening of at risk groups is undoubtedly responsible for increased detection of celiac disease in children, some of whom are asymptomatic. Screening was the mode of presentation of about 25 % of children seen in our center [49]. This includes those identified due to serological screening of family members and those with associated autoimmune conditions [52]. Similarly for adults there has been an increase in those diagnosed due to screening at risk groups [53]. Currently about 10 % of those adults diagnosed with celiac disease seen in the Celiac Disease Center at Columbia University in New York presented through screening of at risk groups. Not all detected by screening are in fact asymptomatic [4, 77].

Several high-risk groups are commonly screened. The most frequently screened group are family members of individuals with celiac disease [4]. Several studies have shown that about 4 to 10 % of first-degree relatives have the disease [78]. The greatest risk is among siblings of affected individuals [79], but the risk extends to second degree relatives as well [4, 79]. Other frequently screened groups include those with type I diabetes (3–7 %) [78] and autoimmune liver disease [80, 81].

The reason that some patients present with diarrhea and others are asymptomatic is not clear, for there is no correlation of a diarrheal presentation with severity of villous atrophy [82], nor length of bowel involved as assessed by video capsule endoscopy [83]. Neurohumoral mechanisms may be important in determining the presence of symptoms, for patients with celiac disease had increased mucosal 5-hydroxytryptamine content and enhanced release from the upper small bowel which correlated with postprandial dyspepsia [84].

## Associated conditions

While the list of associated conditions associated with celiac disease is quite extensive, there are several groups that are frequently tested for celiac disease. The association between celiac disease and type 1 diabetes in children is well described [85]. The coexistence of both diseases also occurs in adults [86, 87]. The presentation of diabetes generally precedes that of celiac disease. While an increased prevalence of celiac disease has been described in adults with autoimmune thyroid disease [88, 89], this association may not exist in children [90].

Children and adolescents with autoimmune liver disease, including biliary disease, have a high prevalence of celiac disease [91, 92]. An increased prevalence of celiac disease has additionally been identified in children with Down syndrome (7 %) [93], Turner syndrome (6.4 %) [94], and Williams syndrome (9.5 %) [95].

There are several other conditions that have been associated with celiac disease. They include: autoimmune myocarditis, idiopathic dilated cardiomyopathy, Sjogren's syndrome, IgA deficiency, Addison's disease, IgA nephropathy, sarcoidosis, primary hyperparathyroidism, alopecia areata, neurological abnormalities including epilepsy, ataxia and neuropathy, atopy, inflammatory bowel disease, psoriasis, and chronic urticaria.

The association with celiac disease and autoimmune disorders is great. About 30 % of adult patients with celiac disease have one or more autoimmune disorders [29, 96], compared to about 3 % in the general population. The mechanism of this is prominent association is unclear. It has been suggested that the increase is associated with the duration of exposure to gluten [96], however this was not confirmed by other studies [97, 98]. In a study from France, however, after the diagnosis of celiac disease, those that were strictly adherent to the gluten-free diet acquired fewer autoimmune disorders than those who were not compliant with the diet [99]; this indicates that the diet is protective against the development of autoimmune diseases. However, the institution of a gluten-free diet did not prevent progression of established autoimmune thyroid disease after the diagnosis of celiac disease [100].

Celiac disease is also associated with infertility, in both women [101–103] and men [104]. Screening infertile women detects undiagnosed celiac disease [105]. The fertility improves after diagnosis of celiac disease [106].

## Terminology and definitions

There have been several terms used to classify the presentations of celiac disease in both childhood and adulthood. Such terms as typical, atypical, classical, nonclassical, silent, asymptomatic, latent, and potential celiac disease have added confusion to the topic. Recently a consensus document has attempted to bring clarity to the field [107].

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