Gastroenterology 2024;167:64–78

Celiac Disease–Related Conditions: Who to Test?




Fabiana Zingone[1,2] Julio C. Bai[3,4] Christophe Cellier[5] Jonas F. Ludvigsson[6,7,8]

[1]Department of Surgery, Oncology, and Gastroenterology, University of Padua, Padua, Italy; [2]Gastroenterology Unit, Azienda Ospedale-Università Padova, Padua, Italy; [3]Small Bowel Section, Dr C. Bonorino Udaondo Gastroenterology Hospital, Buenos Aires, Argentina; [4]Research Institutes, Universidad del Salvador, Buenos Aires, Argentina; [5]Department of Gastroenterology and Endoscopy, Paris Cité University, European Georges Pompidou Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France; [6]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [7]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden; and [8]Division of Digestive and Liver Disease, Department of Medicine, Columbia University Medical Center, New York, New York

Celiac disease (CeD) is a chronic immune-mediated condition triggered by gluten consumption in genetically predisposed individuals. Approximately 1% of the general population is affected by the disorder. Disease presentation is heterogeneous and, despite growing awareness among physicians and the public, it continues to be underestimated. The most effective strategy for identifying undiagnosed CeD is proactive case finding through serologic testing in high-risk groups. We reviewed the most recent evidence on the association between CeD and more than 20 conditions. In light of this review, CeD screening is recommended in individuals with (1) autoimmune disease and accompanying symptoms suggestive of CeD; (2) diseases that may mimic CeD (eg, irritable bowel syndrome [IBS], inflammatory bowel disease [IBD], and microscopic colitis); and (3) among patients with conditions with a high CeD prevalence: first-degree relatives, idiopathic pancreatitis, unexplained liver enzyme abnormalities, autoimmune hepatitis, primary biliary cholangitis, hyposplenism or functional asplenia with severe bacterial infection, type 1 diabetes mellitus, Hashimoto's thyroiditis and Graves' disease, Sjögren's syndrome, dermatitis herpetiformis, recurrent aphthous syndrome and enamel defects, unexplained ataxia, peripheral neuropathy, delayed menarche or premature menopause, Down syndrome, Turner syndrome, Williams syndrome, chronic fatigue syndrome, IgA nephropathy, and IgA deficiency. CeD serology should be the initial step in the screening process. However, for patients with any of the aforementioned disorders who are undergoing upper endoscopy, biopsies should be performed to rule out CeD.

Keywords: Associated Conditions; Celiac Disease; Comorbidity; Gluten; Screening; Testing.

Celiac disease (CeD) is an immune-mediated disorder[1] that affects approximately 1% of the general population.[2] In the 1970s and 1980s, it was primarily regarded as a childhood disorder, but since then it has become clear that it occurs often in adults. The disease is characterized by enteropathy with a systemic involvement and formation of antibodies. The diagnosis is made through duodenal biopsies and positive serology.[3] The underdiagnosis of CeD can be attributed, in part, to the wide spectrum of symptoms it presents, ranging from classical signs of malabsorption (classical CeD) to asymptomatic cases.[3] Many individuals first manifest their CeD through an associated disorder. Multiple mechanisms could potentially account for these associations.

The severity of chronic inflammation and the immune-mediated damage of the small intestinal mucosa in CeD causing villous atrophy can lead to impaired nutrient absorption, causing malnutrition, fatigue, weight loss, and nutritional deficiencies. Villous atrophy impairs, for example, the absorption of calcium and vitamin D, resulting in hypocalcemia and elevated parathyroid hormone levels.[4] Bone resorption, accelerated by increased parathyroid

Abbreviations used in this paper: AIH, autoimmune hepatitis; AP, acute pancreatitis; CAPH, chronic asymptomatic pancreatic hyperenzymemia; CeD, celiac disease; EoE, eosinophilic esophagitis; GI, gastrointestinal; GFD, gluten-free diet; HR, hazard ratio; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IgAD, IgA deficiency; MC, microscopic colitis; OR, odds ratio; PBC, primary biliary cholangitis; SjS, Sjögren's syndrome; T1DM, type 1 diabetes mellitus; WHO, World Health Organization.

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2024.02.044

hormone, outpaces new bone formation, leading to net bone loss.[5] Persistent villous atrophy has been linked to an increased risk of hip fractures.[6]

Genetic predisposition, particularly involving HLA class II genes located on chromosome 6p21 (DR, DQ, and DP loci), plays a crucial role in CeD etiology. Twin studies have reported a high degree of heritability in CeD.[7] The presence of HLA molecules linked to CeD is a prerequisite for its development. However, these molecules are prevalent in the general population (30%–40%) and are not diagnostic markers for CeD.[8–10] Recent research using Mendelian randomization has established a relationship between CeD and several autoimmune diseases[11]: Crohn's disease, primary biliary cholangitis (PBC), rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes mellitus (T1DM), and asthma. Shared genetic backgrounds, particularly DQ2 and DQ8 positivity, have been documented extensively in T1DM and CeD.[12,13]

Chronic inflammation in the small intestine, an established risk factor for cancer, is a hallmark of untreated or poorly managed CeD. A Swedish study comprising 7625 patients with CeD with follow-up biopsies revealed a greater risk of lymphoproliferative malignancies in individuals with persistent villous atrophy compared with those with healed mucosa.[14] Nonadherence to a gluten-free diet (GFD) may elevate the risk of cancer and mortality.[15–19]

Certain diseases may seem more prevalent in CeD because they share symptoms and trigger CeD investigations. With the introduction of CeD serology,[20,21] physicians have a new tool allowing wider CeD screening. Diagnostics then involve clinical, serologic, genetic, and histologic factors. In clinical practice, distinct clinical scenarios warrant investigation for CeD; Table 1 summarizes the guidelines for identifying CeD in high-risk individuals and in special situations.[22–27]

This article undertakes an examination of screening for CeD in more than 30 conditions to provide evidence-based and robust recommendations for screening (Table 2, Figure 1).

Irritable Bowel Syndrome

IBS is a disorder of the gut–brain interaction that affects a significant portion of the Western population, ranging from 1.5% to 10.1%.[28] The prevalence of CeD in patients with IBS varies across studies and geographical regions, with potential surveillance bias often playing a role (one disease is often diagnosed just before the other, potentially suggesting misclassification). Conversely, many patients diagnosed with CeD encounter IBS symptoms during follow-up, which can sometimes be attributed to gluten cross-contamination, despite strict adherence to a GFD. In addition, some individuals may experience IBS symptoms independent of gluten, as these conditions can overlap.[29] Recent international guidelines[30] suggest that CeD be ruled out in all functional bowel disorders accompanied by diarrhea. Some guidelines recommend that serologic screening be performed in all patients with IBS symptoms independent of stool pattern.[31] The recommendation to conduct screening for CeD was partially grounded in a meta-analysis of 36 eligible studies (n = 15,256 individuals, with 9275 fulfilling the criteria for IBS). The odds ratio (OR) for biopsy-confirmed CeD in IBS was 4.48.[32] In general, patients presenting with IBS-like symptoms should undergo screening for CeD.[30,33–35]

Type 1 Diabetes Mellitus

Evidence suggests that the incidence of CeD has increased.[36] Recent data (2021) indicate that 8 million people have T1DM.[37] T1DM has a strong genetic component (mainly DR3-DQ2 and DR4-DQ8),[38] and Thomas et al[39] recently reported that autoantibody-positive T1DM is

Table 1. Guidelines for Identifying Populations at Risk for Celiac Disease (High-Risk Individuals) and in Special Situations

Characteristic	Patient group description	Comment on diagnostics
High-risk individuals	Individuals exhibiting symptoms related to CeD or having clinical conditions potentially linked to the disorder (eg, first-degree relatives of patients with CeD or having coexisting autoimmune disorders).	The conventional approach is testing for IgA TTG antibodies plus total IgA concentration, followed by an upper endoscopy in cases of positive serology. However, there is growing evidence supporting a nonbiopsy diagnosis. A serologic approach may be considered in cases of repeatedly high levels of IgA TTG antibodies.
Undergoing endoscopy for any reason	Typical duodenal endoscopic signs of CeD are evident.	Obtain a sufficient number of biopsies. Subsequently, CeD-specific serology may serve as a confirmatory diagnostic test.
Selective IgAD	It is estimated that ≥6% of individuals with this deficiency also have CeD.	IgG serology (IgG TTG/IgG deamidated gliadin peptide antibodies) is needed for diagnosis.
Seronegative CeD	This condition is rare among patients with CeD (1%–5%). In these cases, IgG and IgA serology results are negative, but HLA DQ2/DQ8 is positive.	Duodenal biopsies should be performed.

TTG, tissue transglutaminase.

Table 2. Disorders at High Risk of Celiac Disease

Who to screen?[a]	Yes/no	Source of evidence	Authors' comment
GI disorders			
EoE	No	Guidelines	—
Autoimmune atrophic gastritis	Yes	Guidelines	—
IBS[b]	Yes	Guidelines	—
IBD[b]	Yes	Expert opinion	Screening is not needed during follow-up of IBD if the patient responds well to treatment
MC[b]	Yes	Guidelines	—
Liver/pancreas/spleen disorders			
Unexplained pancreatic enzyme abnormalities	No	Expert opinion	Scarce and contradictory evidence on whether CeD is overrepresented in this group of patients
Idiopathic pancreatitis	Yes	Guidelines	—
Unexplained liver enzyme abnormalities	Yes	Guidelines	—
AIH	Yes	Guidelines	Screening should ideally be carried out before the patient with AIH has received steroids or immunosuppressives
PBC	Yes	Guidelines	—
Hyposplenism or functional asplenia accompanied by severe bacterial infections	Yes	Guidelines	Screening should be performed if the patient has also suffered from severe bacterial infections, in particular, those associated with encapsulated bacteria
Endocrinologic disorders			
T1DM	Yes	Guidelines	Repeat screening in CeD-negative patients with T1DM at 2 and 5 y after T1DM diagnosis
Hashimoto's thyroiditis and Graves' disease	Yes	Guidelines	—
SjS	Yes	Guidelines	—
Osteopenia and osteoporosis	No	Expert opinion	[c]
Dermatologic disorders			
Dermatitis herpetiformis	Yes	Guidelines	All patients diagnosed with dermatitis herpetiformis should undergo a duodenal biopsy before initiating GFD
Psoriasis, other dermatologic disorders	No	Expert opinion	[c]
Oral disorders			
Recurrent aphthous syndrome	Yes	Guidelines	—
Enamel defects	Yes	Guidelines	—
Neurologic disorders			
Epilepsy	No	Expert opinion	[c]
Unexplained ataxia	Yes	Guidelines	—
Peripheral neuropathy	Yes	Guidelines	—
Migraine	No	Expert opinion	[c]
Gynecologic disorders			
Infertility	No	Expert opinion	—
RSA	No	Expert opinion	—
Delayed menarche/premature menopause	Yes	Guidelines	—
Genetic conditions			
Down syndrome, Turner syndrome, Williams syndrome	Yes	Guidelines	—

Table 2. Continued

Who to screen?[a]	Yes/no	Source of evidence	Authors' comment
Other disorders			
Chronic fatigue syndrome	Yes	Guidelines	—
IgA nephropathy	Yes	Guidelines	—
IgAD	Yes	Guidelines	—
First-degree relatives, even if asymptomatic	Yes	Guidelines	—
Mass screening in the general population	No	Guidelines	—

[a]Screening includes serologic testing at diagnosis and obtaining appropriate small intestinal biopsies if a patient recommended for screening undergoes upper endoscopy for any reason.
[b]Reasons to screen for CeD not only based on associations with CeD, but also because GI symptoms in these diseases mean they may represent misclassified CeD.
[c]Consider screening only if the patient has GI symptoms or other information suggesting an increased risk of CeD.

strongly linked to DR3-DQ2. A nationwide Finnish study found 1 in 5 individuals with T1DM had at least 1 other autoimmune disease.[40] Compared with diabetes-free controls, Finnish people with T1DM were at a 4.6-fold increased risk of CeD.[40] Also, several meta-analyses have concluded that CeD is more prevalent in T1DM, with pooled prevalence rates ranging from 5.1%[41,42] to 6.0%.[43] Detecting CeD in T1DM is important because of the potential impact of celiac comorbidity on the long-term prognosis of T1DM.[44–46] Supported by a screening study of more than 1000 asymptomatic patients with TIDM,[47] treatment with a GFD adds to the burden of T1DM but seems to have no major negative effects on hemoglobin A1c levels, hypoglycemia episodes, and growth in young people.[48] However, Mahmud et al[47] failed to find a lower hemoglobin A1C in asymptomatic T1DM+ patients with CeD randomized to a GFD compared with those who continued on a normal diet. Individuals with T1DM should be screened for CeD.[23,49] Because CeD can manifest at any time and with greater frequency during the initial 5 years, conducting additional screenings in CeD-negative T1DM patients 2 and 5 years after T1DM diagnosis and those who later develop gastrointestinal (GI) symptoms may be advisable.

Autoimmune Hepatitis and Unexplained Liver Enzyme Abnormalities

Autoimmune hepatitis (AIH) is a progressive autoimmune liver disorder in which inflammation can ultimately develop into cirrhosis with liver failure.[50,51] AIH has been linked to several autoimmune conditions.[52] The CeD prevalence has ranged from just above that of the general population (approximately 1%) to 1 in 5 individuals in AIH (2%–20%).[53–55] In a recent meta-analysis, 15 relevant studies were identified, with 8 included in the main analysis. The pooled prevalence of biopsy-verified CeD in AIH was 3.5% (95% CI, 1.6–5.3%).[56]

CeD may also present through elevated liver enzymes (aminotransferases), a condition that is often asymptomatic. Two mechanisms have been proposed to explain why liver enzymes can increase in individuals with CeD. One is through cryptogenic liver disease, usually normalizing with treatment using a GFD. The other pathway involves autoimmunity (AIH, reviewed above), when both CeD and liver disease must be treated for the liver enzymes to normalize. One meta-analysis suggested that 5%–6% of patients with elevated transaminases but no other known cause have biopsy-confirmed CeD.[57] Consistent with the American Association for the Study of Liver Diseases,[50] individuals with AIH should be screened for CeD. Ideally, this testing should be performed before the patient with AIH has received steroids or immunosuppressives, as such treatment may affect the villus structure and impede CeD diagnosis. Also, patients with unexplained elevated liver enzymes should be screened.[22,23]

Inflammatory Bowel Disease

Both CeD and IBD are immune-mediated diseases. Immunologically, patients with CeD and ulcerative colitis, but not Crohn's disease, are prone to develop autoantibodies.[20,58] CeD and ulcerative colitis may also share genetic[59] risk factors.

Multiple studies have investigated the association between CeD and IBD. A meta-analysis of more than 60 studies published in 2020[60] found a risk ratio of 4.0 for CeD in patients with IBD. More recently, Mårild et al[61] conducted a large study to examine 48,551 individuals with CeD who were at a 3.9-fold increased risk of later IBD (both ulcerative colitis and Crohn's disease showed an increase). Mårild et al also reported that 2.4% of all patients with IBD in Sweden also had CeD,[61] thus providing further evidence for this association.

In their study, Kori et al[62] determined that the OR for CeD was roughly 3 in patients with IBD compared with controls. In contrast, Sonnenberg and Genta[63] recently presented data from the Inform Diagnostics database showing an inverse relationship between IBD and CeD (OR, 0.50; 95% CI, 0.38–0.64). However, this study was limited to people who underwent bidirectional endoscopy on the same day, which may have influenced the findings. Two potential causes could account for an elevated risk of CeD in IBD. An important point to note is that some individuals with IBD are being screened for CeD exclusively after their diagnosis

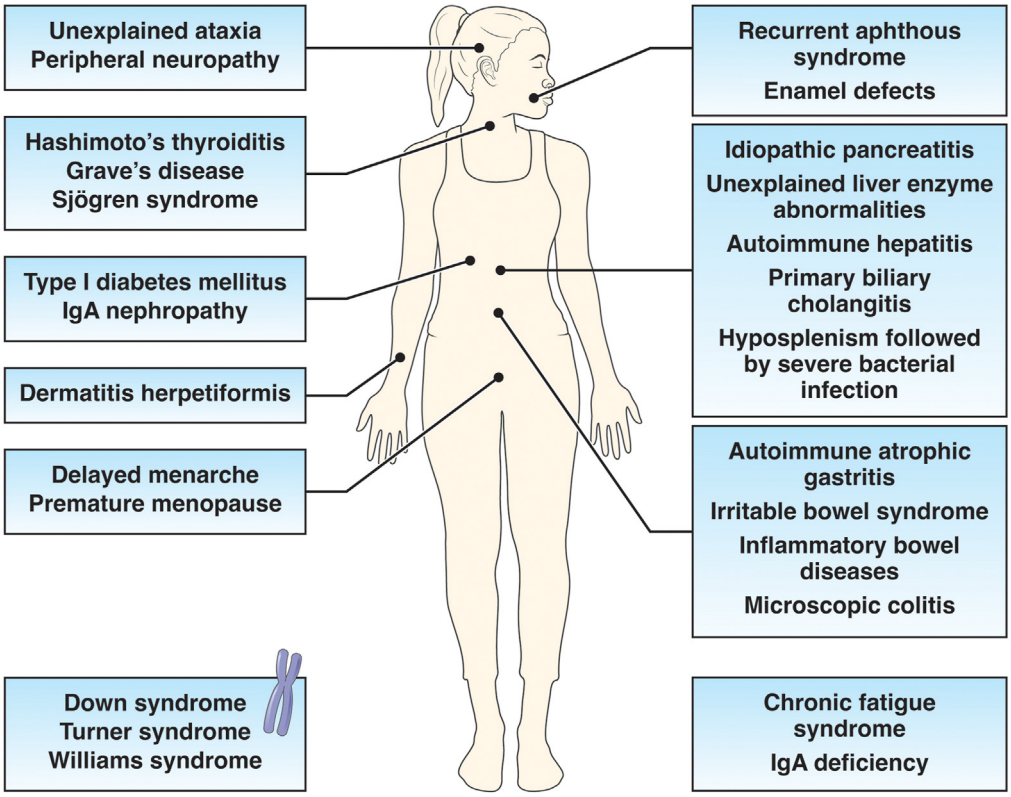

Figure 1. Disorders associated with CeD.

of IBD. An alternative explanation is that CeD may develop later in life, possibly triggered by the inherent inflammation of IBD or a shared trigger. Given the extensive evidence, it seems justifiable that patients with IBD are screened for CeD, especially those who do not respond well to treatment.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a clinicopathological disorder characterized by esophageal dysfunction and eosinophilic inflammation,[64] typically with ≥15 eosinophils/high-power microscopy field.[65] In recent years, there has been a rise in reported cases of EoE.[66] Although the immunologic background of EoE may differ from CeD (Th2 vs Th1), their symptoms may be comparable. In the case of EoE, these may involve dysphagia, feeding difficulties, vomiting, and abdominal discomfort. The usual diagnostic procedure for CeD and EoE requires an upper endoscopy. Such a procedure will increase the likelihood that a patient is diagnosed with CeD, even if symptoms are related to EoE. Diagnostic workup for CeD and EoE will automatically strengthen any disease association. Although several studies have suggested an increased risk of CeD in patients with EoE,[67] few have used control groups. Moreover, the conclusions have frequently relied on a case series comprising fewer than 10 patients with CeD and EoE. Of the only 2 meta-analyses conducted on this issue, the first[68] underlined the limitations of earlier research, and the other,[69] which included a cohort of more than 10,000 children undergoing endoscopy, found no association between CeD and EoE. Hence, patients with EoE should not undergo screening for CeD.[70]

Microscopic Colitis

Microscopic colitis (MC) is a disease of middle old age, with a female predominance.[71] Common symptoms include watery diarrhea,[71] which overlaps with the presentation of CeD in some individuals. Collagenous colitis and CeD share a genetic predisposition.[72] MC has been linked to DQB1_201, which is also seen in CeD.[73] Consequently, it is not possible to assert that the shared genes are exclusive to collagenous colitis or relevant to lymphocytic colitis because of the limited research in the field.

Danish data reported a 10-fold increase in CeD in patients with MC.[74] Still, assuming that most patients with MC underwent CeD testing, the reported prevalence of CeD in this Danish cohort was not higher than expected for the general population (1%).[2] In addition, Bergman et al[75] followed up more than 45,000 individuals with CeD and 224,000 reference individuals to examine the future risk of MC. They found that a higher proportion of patients with MC had a CeD diagnosis compared with the Danish patient population[74] (possibly reflecting differences in CeD patterns between countries). Extrapolating from another MC study[76] obtained from the ESPRESSO (Epidemiology Strengthened by Histopathology Reports in Sweden) cohort,[77] we can assume that roughly 3% of Swedish patients with MC were diagnosed with CeD at some point. Despite that data on the actual

prevalence of CeD in patients with MC are limited, guidelines recommend to screen for CeD at the workup for MC.[78]

Hyposplenism or Functional Asplenia

Hyposplenism has been linked to CeD. The prevalence of this condition increased from 19% in patients with uncomplicated CeD to 59% in those with CeD and other autoimmune diseases and up to 80% in those patients with CeD who had premalignant or malignant complications.[79] A GFD is effective in restoring splenic function, except in patients with an irreversible loss of splenic tissue.[80,81] Hyposplenism and functional asplenia are potential factors contributing to the heightened risk of severe bacterial infections in CeD in children[82,83] and adults,[84–87] particularly those associated with encapsulated bacteria; risks that persist even years after CeD diagnosis. However, the absence of definitive evidence necessitates restricting screening to patients with confirmed hyposplenism and severe bacterial infections.

Unexplained Amylase/Pancreatic Enzyme Abnormalities

Pancreatic dysfunction, including exocrine pancreatic insufficiency (seen in 26.2% of patients with newly diagnosed CeD[88]), chronic asymptomatic pancreatic hyperenzymemia (CAPH), and acute pancreatitis (AP)[89] have been associated with CeD. No association between autoimmune pancreatitis and CeD has been described, however.[90] Reports on CeD have yielded contradictory results for CAPH. Carroccio et al[91] found a CAPH prevalence of approximately 25% in childhood and adult CeD. In contrast, the investigation for CeD in 65 patients with CAPH yielded predominantly negative results.[92]

A prospective study of 169 patients with recurrent abdominal pain suggestive of pancreatic disease found that 12 (7.1%) had histologic evidence consistent with CeD.[93] Two studies from high-quality Swedish national registers showed an almost 3-fold increase in the risk of developing pancreatitis in patients with CeD.[94,95] Concerning the etiology of pancreatitis in CeD, Sadr-Azodi et al[95] showcased an increased risk of non–gallstone AP in patients with CeD after adjusting for alcohol-related disorders. Similarly, Ludvigsson et al[94] showed an increased risk of AP after accounting for high alcohol consumption and gallstone disease. An extensive US population database recently found a higher risk of a new diagnosis of acute and chronic pancreatitis in patients with CeD within 1 month of diagnosis. Idiopathic AP was the most common etiology in patients with CeD.[96] Patients with unexplained pancreatitis should be screened for CeD.[22,23]

Autoimmune Atrophic Gastritis

The prevalence of CeD in autoimmune atrophic gastritis is variable, ranging from 2.1% to 9.1%.[97–100] Although these estimates include newly diagnosed (on screening) cases and already established CeD, the latter should not be an argument for screening. Still, current evidence supports CeD screening in patients with autoimmune atrophic gastritis.[101]

Psoriasis and Other Skin Disorders

Psoriasis is a chronic inflammatory disease affecting approximately 2% of the population and is characterized by well-demarcated, erythematous, scaly plaques.[102]

Recently, a meta-analysis, including 9 studies with 136,536 cases and 5,716,558 controls, found a double risk of earlier CeD in psoriasis (OR, 2.16; 95% CI, 1.74–2.69). However, no association was seen between psoriasis and later CeD.[103] The study also showed that patients with CeD were 1.8-fold more likely to have psoriasis, and the patients with CeD had a 1.7 times higher risk of developing new-onset psoriasis.[103]

A recent population-based cohort study of patients with histologically confirmed CeD evaluated the risk of skin disorders in patients with CeD (n = 43,300) compared with comparators (n = 198,532).[104] In addition to a strong association with dermatitis herpetiformis (hazard ratio [HR], 70.42; 95% CI, 46.62–106.39), the study found a positive association between CeD and all examined skin disorders (ie, eczema, psoriasis, urticaria, vitiligo, acne, and alopecia areata), but with moderate risk estimates (ranging from acne [HR, 1.39] to vitiligo [HR, 1.90]). It should also be noted that part of the association may be coincidental.[105]

Two recent studies have confirmed an association between CeD and atopic dermatitis, although with rather different risk estimates (OR, 1.61[106] and a 4-fold increased risk of later CeD in children with atopic dermatitis[107]). Two other studies have also reported a link with chronic urticaria.[108,109] A meta-analysis by Nieri et al[110] found a higher risk of recurrent aphthous syndrome in patients with CeD (OR, 3.79; 95% CI, 2.67–5.3), confirmed in children and adults. Enamel defects were also observed (OR, 5.69; 95% CI, 3.47–9.33), but only in children.

Although noticeable associations exist between CeD and various skin disorders, these associations tend to be of moderate strength. Based on the current evidence, screening for CeD should be performed in all patients with recurrent aphthous syndrome and enamel defects.[22,23] It is also recommended to perform screenings for other skin disorders (eg, eczema, psoriasis, urticaria, vitiligo, acne, and alopecia areata) exclusively in cases when there is an indication of an increased risk of CeD based on GI symptoms or additional information.

Dermatitis Herpetiformis

Dermatitis herpetiformis is commonly regarded as the cutaneous manifestation of CeD, which is triggered by gluten and improved by a GFD.[111] Therefore, CeD serology is widely recommended.[22,23,112] This rare skin presentation represents the most frequent skin disorder in CeD, as reported by Lebwohl et al.[104] Dermatitis herpetiformis is characterized by intensely pruritic papules and vesicles, primarily on extensor surfaces, such as elbows, knees, buttocks, or the lower back.[113]

Osteopenia, Osteoporosis, and Risk of Bone Fractures

Both osteopenia and osteoporosis have been linked to CeD,[114] and patients with CeD seem to be at increased risk of fractures.[115] However, there is still a lack of consensus regarding the potential risk of CeD in patients with osteopenia or osteoporosis.

Stenson et al[116] reported a higher occurrence of CeD (3.4%) in postmenopausal women compared with women without osteoporosis (0.2%), leading the authors to recommend serologic screening for CeD in all patients with osteoporosis. However, in a comprehensive meta-analysis of more than 3000 patients, the prevalence of CeD (1.6%) was only marginally higher compared with the general population.[117] Recent data from the Netherlands has emphasized the lack of a definitive link between CeD and fractures. In patients with fractures, only 0.38% were found to have biopsy-proven CeD, which aligns with the anticipated prevalence of CeD in Western Europe.[118] This latter study did not recommend screening for CeD in middle-aged patients with fractures.[118] Based on the current evidence, screening for CeD should only be performed in patients with osteoporosis or osteopenia if they exhibit additional signs of CeD.

Chronic Fatigue

Chronic fatigue syndrome is characterized by an overwhelming sense of tiredness, lack of energy, and persistent and prolonged exhaustion, even after rest.[119] This syndrome is associated with systemic immune activation and has been reported frequently in CeD.[120] Previous evidence indicated a prevalence of 2%–3% of CeD in individuals who present with chronic fatigue.[121] Clinical research in this field encounters challenges because of the scarcity of published studies, small sample sizes, diverse study designs, and the use of unspecified instruments for chronic fatigue measurement. In addition, clinical factors, such as depression and anemia, can act as confounders. A recent literature review suggested that the prevalence of chronic fatigue varies significantly at CeD diagnosis and that treatment with a GFD may have a positive impact. However, there are few data to confirm that GFD improves symptoms in patients with CeD.[122] The current guidelines[22,23] suggest CeD screening in patients with chronic fatigue. Nonetheless, additional research is needed.

Chromosomal Syndromes

A high prevalence of CeD has been reported in several chromosomal disorders, warranting the need for CeD screening in at least the following groups: Down syndrome, Turner syndrome, and Williams (Beuren) syndrome.[22,23,101]

Down Syndrome

A meta-analysis of 31 studies encompassing 4383 individuals found a prevalence rate of biopsy-confirmed CeD of 5.8% (95% CI, 4.7%–7.2%) in patients with Down syndrome, particularly in children.[123] In 2020, Liu et al[124] conducted a retrospective study on 1317 children with Down syndrome, finding a 9.8% prevalence of CeD.

Turner Syndrome

A recent systematic review and meta-analysis of 36 eligible studies, including 6291 patients with Turner syndrome, found a crude prevalence of 3.8% in CeD.[125] The risk of CeD in females with Turner syndrome ranged from a 2-fold increase in the first 5 years of life to a more than 5-fold increase in females older than 10 years at CeD diagnosis.[126]

Williams (Beuren) Syndrome

Studies have reported CeD prevalences of 4.1%,[127] 6.9%,[128] and 10.8%.[129]

Neurologic Manifestations

CeD is linked to a variety of neurologic disorders. These conditions may present before the diagnosis of CeD, throughout its progression, and potentially lead to noncompliance with treatment, even in the absence of typical GI symptoms.[130]

Cicarelli et al[131] found that 27.9% of patients with CeD following a GFD exhibited a minimum of 2 of 3 peripheral neurologic symptoms, such as cramps, paresthesia, weakness, reduction of vibratory sense, and hyporeflexia. In a study by Hadjivassiliou et al,[132] it was noted that 67% of patients diagnosed with CeD showed signs of neurologic dysfunction, 24% experienced gait instability, 12% had persistent sensory symptoms, and 42% reported frequent headaches; 21% had at least 2 of these neurologic symptoms.[132]

Gluten ataxia, characterized by a lack of coordination, is associated with antigliadin antibodies. It typically manifests as either pure cerebellar ataxia or, in rare cases, ataxia in combination with myoclonus, palatal tremor, opsoclonus, or chorea.[133] Its onset is commonly insidious, often occurring during adulthood. Of note, few patients with gluten ataxia experience GI symptoms, and roughly one-third will show signs of enteropathy on biopsy.[133] An older study with a small sample size found that 12% of patients with cerebellar ataxia without a confirmed diagnosis had CeD based on serologic and histologic evaluations. However, none of the patients with genetic or Friedreich's ataxia met the criteria for a diagnosis of CeD.[134] Cerebellar atrophy may be observed in up to 60% of patients with gluten ataxia.[133]

The prevalence of epilepsy in CeD has been estimated to range from 1.2% to 5%. Compared with the general population, Italian and Swedish data indicated a 1.4- to 2-fold higher risk of later epilepsy in patients with CeD.[135,136]

Finally, a population-based study found that CeD was associated with a 2-fold increased risk of a later diagnosis of headache.[137] Risk increases were seen for migraine (HR, 1.67) and unclassified headache (HR, 1.67), but not trigeminal neuralgia (HR, 1.35). Routine screening for CeD is recommended in patients with peripheral neuropathy and ataxia.[22,23] Although the connection between CeD and other neurologic disorders is

evident, these associations tend to be of moderate strength, therefore, epilepsy and headache should only prompt screening in patients with concomitant GI symptoms.

Hashimoto's Thyroiditis and Graves' Disease

The prevalence of autoimmune thyroid diseases, namely Hashimoto's thyroiditis and Graves' disease, are approximately 2%–3% and 1%, respectively, in the general population, with a higher incidence in females.[138] For other studies,[139] a Swedish epidemiologic study of 14,021 patients with CeD found a significant association between CeD and hypothyroidism (HR, 4.4; 95% CI, 3.4–5.6), thyroiditis (HR, 3,6; 95% CI, 1.9–6.7), and hyperthyroidism (HR, 2.9; 95% CI, 2.0–4.2).[140] These findings have been confirmed elsewhere (OR, 3.08).[141] A meta-analysis of 27 studies showed a prevalence of biopsy-proven CeD in 6.2% of children and 2.7% of adults with autoimmune thyroid disease.[142] The suggestion to screen for CeD in patients with autoimmune thyroid disease is widely supported.[22,23]

Primary Biliary Cholangitis

PBC is a chronic cholestatic and autoimmune disease affecting women predominantly.[143] These patients have a high prevalence of CeD.[144] A 12-year study in South Wales reported CeD in 4 of 67 (6%) patients with PBC.[145] A Danish study reported a standardized incidence ratio of 27.6 (95% CI, 2.9–133) for PBC in Denmark and 25.1 in Sweden compared with the general population.[146] A more recent large-scale study has confirmed a strong association between CeD and later PBC (HR, 10.16).[147] In contrast, a smaller study from Crete found no increased risk of PBC.[148] A UK longitudinal primary care study on 4732 patients with CeD and 23,620 sex- and age-matched controls reported a 3-fold higher risk of PBC compared with the general population.[149] A literature review found that the prevalence of PBC in CeD ranged between 0% and 11%.[150] In conclusion, the evidence suggests the need to screen patients with PBC for CeD.[101]

Sjögren's Syndrome

Sjögren's syndrome (SjS) is an autoimmune disease characterized by the destruction of exocrine glands, leading to ocular and oral sicca. The diagnosis is based on antibodies and biopsies of salivary gland tissue.[151] Celiac seroprevalence (anti-transglutaminase IgA) appears to be more frequent in SjS than in other rheumatic diseases (eg, systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis).[152] A large multicenter study in Italy found that patients with SjS (n = 354) had a higher prevalence of CeD than controls (n = 14,298) (6.78% vs 0.64%; $P < .0001$).[153] In a study of 111 Hungarian patients with SjS, a CeD prevalence rate of 4.5% was found.[154] In another study involving 34 Finnish patients diagnosed with SjS, 5 cases of histology-proven CeD were observed (14.7%).[155] Current evidence supports CeD screening in all patients with SjS.[101]

IgA Nephropathy

IgA nephropathy is one of the most common kidney diseases worldwide.[156] This disease is chronic and lifelong and induced by IgA deposits in the renal glomeruli, leading to complement activation and injury.[157] Research on CeD and IgA nephropathy has found a 3-fold higher risk of IgA nephropathy in patients with CeD.[158,159] Another study that comprised 223 patients with IgA nephropathy showed a CeD prevalence of 3.6%.[160] Patients with unexplained IgA nephropathy should undergo screening for CeD.[22]

IgA Deficiency

Selective IgA deficiency (IgAD), an isolated IgAD with normal IgM and IgG levels, is the most common primary immune defect.[161] More than 1 in 4 patients with IgAD have a concomitant autoimmune disease.[161] The prevalence of IgAD in patients with CeD is approximately 2%.[162–164] A study of 65 children with IgAD revealed a prevalence rate for CeD of 7.7%.[165] A Swedish study detected 54 biopsy-proven cases of CeD in sera from 356 patients with IgAD (15.2%).[166] Testing only IgA anti-tissue transglutaminase may result in false-negative CeD serology in individuals with IgAD.[166] Hence, it is important to confirm the CeD diagnosis in these patients through IgG serology (tissue transglutaminase IgG or deamidated gliadin peptide IgG) and, if positive, duodenal biopsy.[22,23] Screening for CeD is advisable for patients with IgAD.

Infertility and Recurrent Spontaneous Abortion

As per the World Health Organization (WHO), *infertility* is defined as failure to conceive after engaging in regular unprotected sexual intercourse for a period of 12 months. Recurrent spontaneous abortion (RSA), occurring in 1%–2% of all women, is determined by the presence of 2 or more consecutive abortions of unknown origin.[167] Data on infertility and RSA in CeD are conflicting.[168,169] Three population-based cohort studies found comparable fertility rates in women with CeD adhering to a GFD and those without CeD.[170–172] However, the data from these studies may suggest a potential decrease in fertility for women between the ages of 25 and 29 years who are diagnosed with CeD. This decrease is observed both before and after the diagnosis, which could be due to individuals choosing to delay their pregnancies (either voluntarily or involuntarily) out of concern for symptoms or because they are undergoing medical investigations, including endoscopy, or postponing pregnancy because of nutritional concerns (from a recently diagnosed CeD). Data from meta-analysis do not suggest an increased CeD seroprevalence in women with unexplained infertility.[173] Also, a subsequent meta-analysis conducted in 2021 applied more stringent inclusion criteria (11 studies, 1617 women) and found no association between infertility and CeD.[174] Evidence showed that CeD can manifest clinically for the first time during pregnancy or in the puerperium.[175] In conclusion, based on current evidence, women who experience repeated adverse pregnancy

outcomes should be screened for CeD; however, screening for CeD should not rely exclusively on infertility.

Delayed Menarche and Premature Menopause

Data on age at menarche and menopause in CeD are limited and conflicting. In line with 2 other studies,[176,177] a 2-center cross-sectional study with 228 children with CeD demonstrated an older mean age at menarche compared with healthy individuals (13.13 vs 12.15 years).[178] Some other studies found no difference in mean age at menarche.[179,180] In a few studies, later menarche and earlier menopause have been observed in untreated CeD compared with GFD-treated CeD.[175,181] Based on recent guidelines, CeD is recommended for young women with amenorrhea or delayed menarche.[22,23]

First-Degree Relatives

The heritability of CeD is high, as reported by Fasano et al[182] in 2003, who found an increased prevalence of CeD in first- and second-degree relatives. In 2015, Singh et al[183] evaluated 54 studies and documented a pooled prevalence of CeD of 7.5% in first-degree relatives. The current guidelines suggest screening for CeD in first-degree relatives of patients with CeD.[22,23] Regarding the risk of CeD in second-degree relatives, Singh et al reported a prevalence of 2.3% in CeD. However, further research is necessary before recommending screening for second-degree relatives.

Discussion

This article aims to provide an overview of the screening process for CeD in high-risk groups. Screening is recommended in diseases mimicking CeD (eg, IBD and MC), as well as in high-risk groups, such as first-degree relatives and patients with autoimmune diseases. In addition, patients displaying symptoms and signs suggestive of CeD should undergo CeD investigation, although this falls outside the realm of traditional screening. We believe that more cost-effectiveness research on cutoffs for CeD screening is needed. Applying a cutoff level for undiagnosed CeD implies that screening recommendations could change. With an increase in the incidence and prevalence of CeD in many countries,[184] efforts should be made to increase case finding for CeD. The WHO mandates the fulfillment of several criteria for mandatory general screening. Although we do not advocate for CeD screening of the general population, WHO criteria can help readers determine which high-risk groups should undergo screening. CeD is well-defined (criterion I). We emphasize the importance of confirming asymptomatic CeD through a small intestinal biopsy. This is because the costs of a false-positive CeD diagnosis are high in a patient who may not have sought the diagnosis (testing of patients with GI symptoms constitutes case finding and not screening). Moreover, the establishment of a diagnosis of CeD would require lifetime dedication to a GFD. There is growing research on the quality of life and the benefits of a GFD in patients with screen-detected CeD.[185–189]

Screening tests for CeD are also simple, safe, and accurate (criterion II). However, one must consider that as the expected prevalence of CeD decreases in a screened patient group, the positive predictive value (the probability that positive serology indicates true CeD) also decreases. This is because of the significant risk of false-positive cases, even with a specificity of 99% in screening populations with a CeD prevalence of 1%–2%. Screening for CeD seems culturally acceptable worldwide (criterion III). Treatment is readily available (ie, the GFD) (criterion IV). However, treatment does not prohibit all consequences of CeD. Although adhering to a strict GFD is expected to reduce symptoms, dietary treatment has fewer benefits in an asymptomatic individual. A GFD can also induce mucosal healing, either partially or completely.

Finally, the WHO suggests that screening should only be performed in diseases for which clinical detection is difficult (criterion V). Although that condition is met, it is unclear whether detecting undiagnosed CeD will prevent complications (criterion VI) or whether testing and treatment is cost-effective (criterion VII) in patients with asymptomatic CeD.

Many questions remain regarding CeD screening (some are discussed in more detail in our earlier study[190]). It has been suggested that a strict GFD may prevent the development of other autoimmune disorders. This could be used as a rationale for implementing early screening.[191]

As mentioned, the comorbidities discussed in this review may be linked to various mechanisms. Mucosal damage can lead to malnutrition, resulting in nutritional deficiencies that underlie conditions, such as osteopenia and fatigue. A shared genetic background has been well established for T1DM, with similar assumptions for other conditions, including Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, and asthma. Inflammation can serve as a trigger for additional comorbidities, such as IBD. Finally, shared symptoms can serve as a catalyst for investigations into CeD, as evidenced in cases of IBS.

This review focused on screening of high-risk groups with comorbidities. Not all of these patients require screening unless they are symptomatic. However, there is 1 group of individuals for whom we believe the evidence for screening is strong: first-degree relatives.[183] In the largest meta-analysis, the pooled prevalence of CeD was 7.5% in first-degree relatives, with siblings showing the highest rates. Testing family members for gluten sensitivity presents unique challenges because of potential lower gluten consumption, increasing the risk of false-negative screening results.

The recommendation for repeated screening for CeD applies only to patients with T1DM, justified by 2 factors. First, T1DM often occurs at a young age, so individuals are still at a high risk of developing CeD later in life. Second, the prevalence of undiagnosed CeD may be higher in T1DM than in most other diseases analyzed in our review.[43]

Most current guidelines recommend conducting CeD screening for numerous conditions. We concur that indications for screening should be broad, with emphasis on identifying aggressive cases and symptomatic patients with CeD. In these specific patients, a diagnosis can provide relief

from celiac symptoms, although the impact of diagnosing CeD on life expectancy and quality of life remains uncertain. There is still a need for data on the cost-effectiveness of CeD. Several articles have recently investigated the economic burden of CeD, both pre and post diagnosis,[192–194] particularly in terms of health care costs, productivity loss among patients in the workforce and school, drug costs, as well as the prognosis of undiagnosed and asymptomatic CeD. As yet, there is no evidence supporting mass screening.[190]

Our review has some limitations. Space and the scope to discuss individual disorders and CeD screening were limited. Many of the studies included in this review were performed in Europe or North America. However, further research from other regions is necessary, as screening recommendations may vary based on the prevalence of CeD in the general population. Although health economy research on CeD is growing,[192–194] there is a lack of specific data on the cost–benefit analysis of screening. There is also a need for more data on screen-detected CeD and quality of life.

In conclusion, screening for CeD should be considered for a broad spectrum of disorders. Screening tests are safe and valid; however, they should be performed according to strict principles prioritizing the transparency of benefits to patients and society.

References

1. Pinto-Sanchez MI, Silvester JA, Lebwohl B, et al. Society for the Study of Celiac Disease position statement on gaps and opportunities in coeliac disease. Nat Rev Gastroenterol Hepatol 2021;18:875–884.
2. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:823–836.e2.
3. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013; 62:43–52.
4. Ciacci C, Bilancio G, Russo I, et al. 25-Hydroxyvitamin D, 1,25-dihydroxyvitamin D, and peripheral bone densitometry in adults with celiac disease. Nutrients 2020; 12:929.
5. Corazza GR, Di Sario A, Cecchetti L, et al. Bone mass and metabolism in patients with celiac disease. Gastroenterology 1995;109:122–128.
6. Lebwohl B, Michaëlsson K, Green PH, et al. Persistent mucosal damage and risk of fracture in celiac disease. J Clin Endocrinol Metab 2014;99:609–616.
7. Kuja-Halkola R, Lebwohl B, Halfvarson J, et al. Heritability of non-HLA genetics in coeliac disease: a population-based study in 107 000 twins. Gut 2016;65:1793–1798.
8. Liu E, Lee HS, Agardh D. Risk of celiac disease according to HLA haplotype and country. N Engl J Med 2014; 371:1074.
9. Medrano LM, Dema B, López-Larios A, et al. HLA and celiac disease susceptibility: new genetic factors bring open questions about the HLA influence and gene-dosage effects. PLoS One 2012;7:e48403.
10. Megiorni F, Pizzuti A. HLA-DQA1 and HLA-DQB1 in celiac disease predisposition: practical implications of the HLA molecular typing. J Biomed Sci 2012;19:88.
11. Li T, Feng Y, Wang C, et al. Causal relationships between autoimmune diseases and celiac disease: a Mendelian randomization analysis. Biotechnol Genet Eng Rev 2023:1–16.
12. Verdu EF, Danska JS. Common ground: shared risk factors for type 1 diabetes and celiac disease. Nat Immunol 2018;19:685–695.
13. Steck AK, Rewers MJ. Genetics of type 1 diabetes. Clin Chem 2011;57:176–185.
14. Lebwohl B, Granath F, Ekbom A, et al. Mucosal healing and mortality in coeliac disease. Aliment Pharmacol Ther 2013;37:332–339.
15. Lebwohl B, Green PHR, Emilsson L, et al. Cancer risk in 47,241 individuals with celiac disease: a nationwide cohort study. Clin Gastroenterol Hepatol 2022;20:e111–e131.
16. Lebwohl B, Green PHR, Söderling J, et al. Association between celiac disease and mortality risk in a Swedish population. JAMA 2020;323:1277–1285.
17. Marafini I, Monteleone G, Stolfi C. Association between celiac disease and cancer. Int J Mol Sci 2020;21:4155.
18. Pelizzaro F, Marsilio I, Fassan M, et al. The Risk of malignancies in celiac disease-a literature review. Cancers (Basel) 2021;13:5288.
19. Vanoli A, Parente P, Fassan M, et al. Gut inflammation and tumorigenesis: every site has a different tale to tell. Intern Emerg Med 2023;18:2169–2179.
20. Dieterich W, Laag E, Schöpper H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. Gastroenterology 1998;115:1317–1321.
21. Sulkanen S, Halttunen T, Laurila K, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology 1998;115:1322–1328.
22. Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J 2019; 7:583–613.
23. Rubio-Tapia A, Hill ID, Semrad C, et al. American College of Gastroenterology guidelines update: diagnosis and management of celiac disease. Am J Gastroenterol 2023;118:59–76.
24. Bai JC, Verdú EF. Evolving paradigms in the diagnosis of adult patients with celiac disease. Am J Gastroenterol 2019;114:854–857.
25. Ciacci C, Bai JC, Holmes G, et al. Serum anti-tissue transglutaminase IgA and prediction of duodenal villous atrophy in adults with suspected coeliac disease without IgA deficiency (Bi.A.CeD): a multicentre, prospective cohort study. Lancet Gastroenterol Hepatol 2023;8:1005–1014.
26. Vosughimotlagh A, Rasouli SE, Rafiemanesh H, et al. Clinical manifestation for immunoglobulin A deficiency: a systematic review and meta-analysis. Allergy Asthma Clin Immunol 2023;19:75.
27. Schiepatti A, Sanders DS, Biagi F. Seronegative coeliac disease: clearing the diagnostic dilemma. Curr Opin Gastroenterol 2018;34:154–158.
28. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional

gastrointestinal disorders, results of Rome Foundation Global Study. Gastroenterology 2021;160:99–114.e3.
29. Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with celiac, disease: a meta-analysis. Clin Gastroenterol Hepatol 2013;11:359–365.e1.
30. Savarino E, Zingone F, Barberio B, et al. Functional bowel disorders with diarrhoea: clinical guidelines of the United European Gastroenterology and European Society for Neurogastroenterology and Motility. United European Gastroenterol J 2022;10:556–584.
31. Ford AC, Sperber AD, Corsetti M, et al. Irritable bowel syndrome. Lancet 2020;396:1675–1688.
32. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol 2017; 112:65–76.
33. Hill ID, Fasano A, Guandalini S, et al. NASPGHAN clinical report on the diagnosis and treatment of gluten-related disorders. J Pediatr Gastroenterol Nutr 2016; 63:156–165.
34. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr 2020;70:141–156.
35. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013;108:656–676.
36. Bergman D, King J, Lebwohl B, et al. Two waves of coeliac disease incidence in Sweden: a nationwide population-based cohort study from 1990 to 2015. Gut 2022;71:1088–1094.
37. Gregory GA, Robinson TIG, Linklater SE, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 2022;10:741–760.
38. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. Lancet 2016;387:2331–2339.
39. Thomas NJ, Walkey HC, Kaur A, et al. The relationship between islet autoantibody status and the genetic risk of type 1 diabetes in adult-onset type 1 diabetes. Diabetologia 2023;66:310–320.
40. Mäkimattila S, Harjutsalo V, Forsblom C, et al. Every fifth individual with type 1 diabetes suffers from an additional autoimmune disease: a Finnish nationwide study. Diabetes Care 2020;43:1041–1047.
41. Pham-Short A, Donaghue KC, Ambler G, et al. Screening for celiac disease in type 1 diabetes: a systematic review. Pediatrics 2015;136:e170–e176.
42. Albatineh A, Dehvan F, Shariari H, et al. Prevalence of celiac disease in patients with type 1 diabetes: a systematic review and meta-analysis. Clin Diabetol 2021; 10:447–461.
43. Elfstrom P, Sundstrom J, Ludvigsson JF. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. Aliment Pharmacol Ther 2014;40:1123–1132.
44. Mollazadegan K, Fored M, Lundberg S, et al. Risk of renal disease in patients with both type 1 diabetes and coeliac disease. Diabetologia 2014;57:1339–1345.
45. Mollazadegan K, Kugelberg M, Montgomery SM, et al. A population-based study of the risk of diabetic retinopathy in patients with type 1 diabetes and celiac disease. Diabetes Care 2013;36:316–321.
46. Mollazadegan K, Sanders DS, Ludvigsson J, et al. Long-term coeliac disease influences risk of death in patients with type 1 diabetes. J Intern Med 2013;274:273–280.
47. Mahmud FH, Clarke ABM, Joachim KC, et al. Screening and treatment outcomes in adults and children with type 1 diabetes and asymptomatic celiac disease: the CD-DIET study. Diabetes Care 2020;43:1553–1556.
48. Mozzillo E, Franceschi R, Di Candia F, et al. The impact of gluten-free diet on growth, metabolic control and quality of life in youth with type 1 diabetes and celiac disease: a systematic review. Diabetes Res Clin Pract 2022;191: 110032.
49. American Diabetes Association Professional Practice Committee. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43(Suppl 1):S37–S47.
50. Mack CL, Adams D, Assis DN, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020;72:671–722.
51. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63:971–1004.
52. Teufel A, Weinmann A, Kahaly GJ, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. J Clin Gastroenterol 2010;44:208–213.
53. Mirzaagha F, Azali SH, Islami F, et al. Coeliac disease in autoimmune liver disease: a cross-sectional study and a systematic review. Dig Liver Dis 2010;42:620–623.
54. Sima H, Hekmatdoost A, Ghaziani T, et al. The prevalence of celiac autoantibodies in hepatitis patients. Iran J Allergy Asthma Immunol 2010;9:157–162.
55. Nastasio S, Sciveres M, Riva S, et al. Celiac disease-associated autoimmune hepatitis in childhood: long-term response to treatment. J Pediatr Gastroenterol Nutr 2013;56:671–674.
56. Haggård L, Glimberg I, Lebwohl B, et al. High prevalence of celiac disease in autoimmune hepatitis: systematic review and meta-analysis. Liver Int 2021;41:2693–2702.
57. Yoosuf S, Singh P, Khaitan A, et al. Prevalence of celiac disease in patients with liver diseases: a systematic review and meta-analyses. Am J Gastroenterol 2023; 118:820–832.
58. Geng X, Biancone L, Dai HH, et al. Tropomyosin isoforms in intestinal mucosa: production of autoantibodies to tropomyosin isoforms in ulcerative colitis. Gastroenterology 1998;114:912–922.
59. Mirkov MU, Verstockt B, Cleynen I. Genetics of inflammatory bowel disease: beyond NOD2. Lancet Gastroenterol Hepatol 2017;2:224–234.
60. Pinto-Sanchez MI, Seiler CL, Santesso N, et al. Association between inflammatory bowel diseases and celiac disease: a systematic review and meta-analysis. Gastroenterology 2020;159:884–903.e31.

61. Mårild K, Söderling J, Lebwohl B, et al. Association of celiac disease and inflammatory bowel disease: a nationwide register-based cohort study. Am J Gastroenterol 2022;117:1471–1481.
62. Kori M, Zamir Y, Yermiyahu SO, et al. The association of inflammatory bowel disease with coeliac disease and coeliac autoimmunity in children and adults: a nationwide study from the epi-IIRN. J Crohns Colitis 2023; 17:700–705.
63. Sonnenberg A, Genta RM. Case-control study of the concurrence of coeliac disease with inflammatory bowel disease. Aliment Pharmacol Ther 2023;57:988–992.
64. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014;12:589–596.e1.
65. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015;373:1640–1648.
66. Garber JJ, Lochhead PJ, Uchida AM, et al. Increasing incidence of eosinophilic esophagitis in Sweden: a nationwide population study. Esophagus 2022;19:535–541.
67. Stewart MJ, Shaffer E, Urbanski SJ, et al. The association between celiac disease and eosinophilic esophagitis in children and adults. BMC Gastroenterol 2013;13:96.
68. Lucendo AJ, Arias Á, Tenias JM. Systematic review: the association between eosinophilic oesophagitis and coeliac disease. Aliment Pharmacol Ther 2014; 40:422–434.
69. Hommeida S, Alsawas M, Murad MH, et al. The association between celiac disease and eosinophilic esophagitis: Mayo experience and meta-analysis of the literature. J Pediatr Gastroenterol Nutr 2017;65:58–63.
70. Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5:335–358.
71. Burke KE, D'Amato M, Ng SC, et al. Microscopic colitis. Nat Rev Dis Primers 2021;7:39.
72. Stahl E, Roda G, Dobbyn A, et al. Collagenous colitis is associated with HLA signature and shares genetic risks with other immune-mediated diseases. Gastroenterology 2020;159:549–561.e8.
73. Green HD, Beaumont RN, Thomas A, et al. Genome-wide association study of microscopic colitis in the UK Biobank confirms immune-related pathogenesis. J Crohns Colitis 2019;13:1578–1582.
74. Wildt S, Munck LK, Winther-Jensen M, et al. Autoimmune diseases in microscopic colitis: a Danish nationwide case-control study. Aliment Pharmacol Ther 2021; 54:1454–1462.
75. Bergman D, Khalili H, Lebwohl B, et al. Celiac disease and risk of microscopic colitis: A nationwide population-based matched cohort study. United European Gastroenterol J 2023;11:189–201.
76. Khalili H, Bergman D, Roelstraete B, et al. Mortality of patients with microscopic colitis in Sweden. Clin Gastroenterol Hepatol 2020;18:2491–2499.e3.
77. Ludvigsson JF, Lashkariani M. Cohort profile: ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden). Clin Epidemiol 2019;11:101–114.
78. Miehlke S, Guagnozzi D, Zabana Y, et al. European guidelines on microscopic colitis: United European Gastroenterology and European Microscopic Colitis Group statements and recommendations. United European Gastroenterol J 2021;9:13–37.
79. Di Sabatino A, Rosado MM, Cazzola P, et al. Splenic hypofunction and the spectrum of autoimmune and malignant complications in celiac disease. Clin Gastroenterol Hepatol 2006;4:179–186.
80. Corazza G, Frisoni M, Vaira D, et al. Effect of gluten-free diet on splenic hypofunction of adult coeliac disease. Gut 1983;24:228–230.
81. Di Sabatino A, Brunetti L, Maffè GC, et al. Is it worth investigating splenic function in patients with celiac disease? World J Gastroenterol 2013;19:2313–2315.
82. Ludvigsson JF, Olén O, Bell M, et al. Coeliac disease and risk of sepsis. Gut 2008;57:1074–1080.
83. Canova C, Ludvigsson J, Baldo V, et al. Risk of bacterial pneumonia and pneumococcal infection in youths with celiac disease - a population-based study. Dig Liver Dis 2019;51:1101–1105.
84. Thomas HJ, Wotton CJ, Yeates D, et al. Pneumococcal infection in patients with coeliac disease. Eur J Gastroenterol Hepatol 2008;20:624–628.
85. Rockert Tjernberg A, Bonnedahl J, Inghammar M, et al. Coeliac disease and invasive pneumococcal disease: a population-based cohort study. Epidemiol Infect 2017; 145:1203–1209.
86. Röckert Tjernberg A, Mårild K, Söderling J, et al. Celiac disease and serious infections: a nationwide cohort study from 2002 to 2017. Am J Gastroenterol 2022; 117:1675–1683.
87. Zingone F, Abdul Sultan A, Crooks CJ, et al. The risk of community-acquired pneumonia among 9803 patients with coeliac disease compared to the general population: a cohort study. Aliment Pharmacol Ther 2016; 44:57–67.
88. Jiang C, Barkin JA, Barkin JS. Exocrine pancreatic insufficiency is common in celiac disease: a systematic review and meta-analysis. Dig Dis Sci 2023; 68:3421–3427.
89. Conti Bellocchi MC, Crinò SF, De Marchi G, et al. A clinical and pathophysiological overview of intestinal and systemic diseases associated with pancreatic disorders: causality or casualty? Biomedicines 2023;11:1393.
90. De Marchi G, Zanoni G, Conti Bellocchi MC, et al. There is no association between coeliac disease and autoimmune pancreatitis. Nutrients 2018;10:1157.
91. Carroccio A, Di Prima L, Scalici C, et al. Unexplained elevated serum pancreatic enzymes: a reason to suspect celiac disease. Clin Gastroenterol Hepatol 2006;4:455–459.
92. Migliori M, Galassi E, Gullo L. Search for celiac disease in subjects with asymptomatic pancreatic hyperenzymemia. Pancreas 2011;40:979–981.
93. Patel RS, Johlin FC Jr, Murray JA. Celiac disease and recurrent pancreatitis. Gastrointest Endosc 1999; 50:823–827.
94. Ludvigsson JF, Montgomery SM, Ekbom A. Risk of pancreatitis in 14,000 individuals with celiac disease. Clin Gastroenterol Hepatol 2007;5:1347–1353.

95. Sadr-Azodi O, Sanders DS, Murray JA, et al. Patients with celiac disease have an increased risk for pancreatitis. Clin Gastroenterol Hepatol 2012;10:1136–1142.e3.
96. Alkhayyat M, Saleh MA, Abureesh M, et al. The risk of acute and chronic pancreatitis in celiac disease. Dig Dis Sci 2021;66:2691–2699.
97. Conti L, Galli G, Ligato C, et al. Autoimmune atrophic gastritis and coeliac disease: a case-control study. Dig Liver Dis 2023;55:69–74.
98. Kalkan Ç, Soykan I. Polyautoimmunity in autoimmune gastritis. Eur J Intern Med 2016;31:79–83.
99. Zingone F, Marsilio I, Fassan M, et al. Duodenal histological findings and risk of coeliac disease in subjects with autoimmune atrophic gastritis: a retrospective evaluation. Digestion 2021;102:615–621.
100. Miceli E, Lenti MV, Padula D, et al. Common features of patients with autoimmune atrophic gastritis. Clin Gastroenterol Hepatol 2012;10:812–824.
101. Zingone F, Maimaris S, Auricchio R, et al. Guidelines of the Italian societies of gastroenterology on the diagnosis and management of coeliac disease and dermatitis herpetiformis. Dig Liver Dis 2022;54:1304–1319.
102. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol 2017;31:205–212.
103. Acharya P, Mathur M. Association between psoriasis and celiac disease: a systematic review and meta-analysis. J Am Acad Dermatol 2020;82:1376–1385.
104. Lebwohl B, Söderling J, Roelstraete B, et al. Risk of skin disorders in patients with celiac disease: a population-based cohort study. J Am Acad Dermatol 2021;85:1456–1464.
105. Verdelli A, Corrà A, Mariotti EB, et al. Skin gluten-related disorders: new and old cutaneous manifestations to be considered. Front Med (Lausanne) 2023;10:1155288.
106. Shalom G, Kridin K, Raviv KO, et al. Atopic dermatitis and celiac disease: a cross-sectional study of 116,816 patients. Am J Clin Dermatol 2020;21:133–138.
107. Ress K, Annus T, Putnik U, et al. Celiac disease in children with atopic dermatitis. Pediatr Dermatol 2014;31:483–488.
108. Ludvigsson JF, Lindelöf B, Rashtak S, et al. Does urticaria risk increase in patients with celiac disease? A large population-based cohort study. Eur J Dermatol 2013;23:681–687.
109. Kolkhir P, Borzova E, Grattan C, et al. Autoimmune comorbidity in chronic spontaneous urticaria: a systematic review. Autoimmun Rev 2017;16:1196–1208.
110. Nieri M, Tofani E, Defraia E, et al. Enamel defects and aphthous stomatitis in celiac and healthy subjects: systematic review and meta-analysis of controlled studies. J Dent 2017;65:1–10.
111. Caproni M, Antiga E, Melani L, et al. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. J Eur Acad Dermatol Venereol 2009;23:633–638.
112. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part II. Diagnosis, management, and prognosis. J Am Acad Dermatol 2011;64:1027–1033; quiz 1033–1034.
113. Leffler DA, Green PH, Fasano A. Extraintestinal manifestations of coeliac disease. Nat Rev Gastroenterol Hepatol 2015;12:561–571.
114. Zanchetta MB, Longobardi V, Bai JC. Bone and celiac disease. Curr Osteoporos Rep 2016;14:43–48.
115. Heikkilä K, Pearce J, Mäki M, et al. Celiac disease and bone fractures: a systematic review and meta-analysis. J Clin Endocrinol Metab 2016;2:16047.
116. Stenson WF, Newberry R, Lorenz R, et al. Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. Arch Intern Med 2005;165:393–399.
117. Laszkowska M, Mahadev S, Sundström J, et al. Systematic review with meta-analysis: the prevalence of coeliac disease in patients with osteoporosis. Aliment Pharmacol Ther 2018;48:590–597.
118. de Bruin IJA, Vranken L, Wyers CE, et al. The prevalence of celiac disease in a fracture liaison service population. Calcif Tissue Int 2020;107:327–334.
119. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol 1996;9:456–460.
120. Zingone F, Swift GL, Card TR, et al. Psychological morbidity of celiac disease: a review of the literature. United European Gastroenterol J 2015;3:136–145.
121. Skowera A, Peakman M, Cleare A, et al. High prevalence of serum markers of coeliac disease in patients with chronic fatigue syndrome. J Clin Pathol 2001;54:335–336.
122. Skjellerudsveen BM, Omdal R, Grimstad T. Fatigue in celiac disease: a review of the literature. JGH Open 2019;3:242–248.
123. Du Y, Shan LF, Cao ZZ, et al. Prevalence of celiac disease in patients with Down syndrome: a meta-analysis. Oncotarget 2018;9:5387–5396.
124. Liu E, Wolter-Warmerdam K, Marmolejo J, et al. Routine screening for celiac disease in children with down syndrome improves case finding. J Pediatr Gastroenterol Nutr 2020;71:252–256.
125. Al-Bluwi GSM, AlNababteh AH, Östlundh L, et al. Prevalence of celiac disease in patients with turner syndrome: systematic review and meta-analysis. Front Med (Lausanne) 2021;8:674896.
126. Mårild K, Størdal K, Hagman A, et al. Turner syndrome and celiac disease: a case-control study. Pediatrics 2016;137:e20152232.
127. Mıhçı E, Nur BG, Berker-Karaüzüm S, et al. Celiac disease in patients with Williams-Beuren syndrome. Turk J Pediatr 2015;57:599–604.
128. Pangallo E, Parma B, Mariani M, et al. Williams-Beuren syndrome and celiac disease: a real association? Eur J Med Genet 2020;63:103999.
129. Ghisleni C, Parma B, Cianci P, et al. Celiac disease prevalence and predisposing-HLA in a cohort of 93 Williams-Beuren syndrome patients. Am J Med Genet A 2023;191:84–89.
130. Bushara KO. Neurologic presentation of celiac disease. Gastroenterology 2005;128(Suppl 1):S92–S97.
131. Cicarelli G, Della Rocca G, Amboni M, et al. Clinical and neurological abnormalities in adult celiac disease. Neurol Sci 2003;24:311–317.

132. Hadjivassiliou M, Croall ID, Zis P, et al. Neurologic deficits in patients with newly diagnosed celiac disease are frequent and linked with autoimmunity to transglutaminase 6. Clin Gastroenterol Hepatol 2019; 17:2678–2686.e2.
133. Hadjivassiliou M, Sanders DD, Aeschlimann DP. Gluten-related disorders: gluten ataxia. Dig Dis 2015; 33:264–268.
134. Pellecchia MT, Scala R, Filla A, et al. Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features. J Neurol Neurosurg Psychiatry 1999;66:32–35.
135. Ludvigsson J, Zingone F, Tomson T, et al. Increased risk of epilepsy in biopsy-verified celiac disease: a population-based cohort study. Neurology 2012; 78:1401–1407.
136. Canova C, Ludvigsson J, Barbiellini Amidei C, et al. The risk of epilepsy in children with celiac disease: a population-based cohort study. Eur J Neurol 2020; 27:1089–1095.
137. Lebwohl B, Roy A, Alaedini A, et al. Risk of Headache-related healthcare visits in patients with celiac disease: a population-based observational study. Headache 2016;56:849–858.
138. Antonelli A, Ferrari SM, Corrado A, et al. Autoimmune thyroid disorders. Autoimmun Rev 2015;14:174–180.
139. Dore MP, Fanciulli G, Rouatbi M, et al. Autoimmune thyroid disorders are more prevalent in patients with celiac disease: a retrospective case-control study. J Clin Med 2022;11:6027.
140. Elfström P, Montgomery SM, Kämpe O, et al. Risk of thyroid disease in individuals with celiac disease. J Clin Endocrinol Metab 2008;93:3915–3921.
141. Sun X, Lu L, Yang R, et al. Increased incidence of thyroid disease in patients with celiac disease: a systematic review and meta-analysis. PLoS One 2016;11:e0168708.
142. Roy A, Laszkowska M, Sundström J, et al. Prevalence of Celiac disease in patients with autoimmune thyroid disease: a meta-analysis. Thyroid 2016;26:880–890.
143. Gulamhusein AF, Hirschfield GM. Primary biliary cholangitis: pathogenesis and therapeutic opportunities. Nat Rev Gastroenterol Hepatol 2020;17:93–110.
144. Callichurn K, Cvetkovic L, Therrien A, et al. Prevalence of celiac disease in patients with primary biliary cholangitis. J Can Assoc Gastroenterol 2021;4:44–47.
145. Kingham JG, Parker DR. The association between primary biliary cirrhosis and coeliac disease: a study of relative prevalences. Gut 1998;42:120–122.
146. Sorensen HT, Thulstrup AM, Blomqvist P, et al. Risk of primary biliary liver cirrhosis in patients with coeliac disease: Danish and Swedish cohort data. Gut 1999;44:736–738.
147. Ludvigsson JF, Elfström P, Broomé U, et al. Celiac disease and risk of liver disease: a general population-based study. Clin Gastroenterol Hepatol 2007;5:63–69.e1.
148. Chatzicostas C, Roussomoustakaki M, Drygiannakis D, et al. Primary biliary cirrhosis and autoimmune cholangitis are not associated with coeliac disease in Crete. BMC Gastroenterol 2002;2:5.
149. Lawson A, West J, Aithal GP, et al. Autoimmune cholestatic liver disease in people with coeliac disease: a population-based study of their association. Aliment Pharmacol Ther 2005;21:401–405.
150. Rubio-Tapia A, Murray JA. The liver in celiac disease. Hepatology 2007;46:1650–1658.
151. Brito-Zerón P, Baldini C, Bootsma H, et al. Sjögren syndrome. Nat Rev Dis Primers 2016;2:16047.
152. Luft LM, Barr SG, Martin LO, et al. Autoantibodies to tissue transglutaminase in Sjögren's syndrome and related rheumatic diseases. J Rheumatol 2003; 30:2613–2619.
153. Bartoloni E, Bistoni O, Alunno A, et al. Celiac disease prevalence is increased in primary Sjögren's syndrome and diffuse systemic sclerosis: lessons from a large multi-center study. J Clin Med 2019;8:540.
154. Szodoray P, Barta Z, Lakos G, et al. Coeliac disease in Sjögren's syndrome—a study of 111 Hungarian patients. Rheumatol Int 2004;24:278–282.
155. Iltanen S, Collin P, Korpela M, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjögren's syndrome. Am J Gastroenterol 1999; 94:1042–1046.
156. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant 2011; 26:414–430.
157. Galla JH. IgA nephropathy. Kidney Int 1995;47:377–387.
158. Slavin SF. IgA Nephropathy as the initial presentation of celiac disease in an adolescent. Pediatrics 2021;148: e2021051332.
159. Welander A, Sundelin B, Fored M, et al. Increased risk of IgA nephropathy among individuals with celiac disease. J Clin Gastroenterol 2013;47:678–683.
160. Collin P, Syrjänen J, Partanen J, et al. Celiac disease and HLA DQ in patients with IgA nephropathy. Am J Gastroenterol 2002;97:2572–2576.
161. Odineal DD, Gershwin ME. The epidemiology and clinical manifestations of autoimmunity in selective IgA dDeficiency. Clin Rev Allergy Immunol 2020;58:107–133.
162. Chow MA, Lebwohl B, Reilly NR, et al. Immunoglobulin A deficiency in celiac disease. J Clin Gastroenterol 2012; 46:850–854.
163. Cataldo F, Marino V, Ventura A, et al. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and "Club del Tenue" Working Groups on Coeliac Disease. Gut 1998;42:362–265.
164. Pallav K, Xu H, Leffler DA, et al. Immunoglobulin A deficiency in celiac disease in the United States. J Gastroenterol Hepatol 2016;31:133–137.
165. Meini A, Pillan NM, Villanacci V, et al. Prevalence and diagnosis of celiac disease in IgA-deficient children. Ann Allergy Asthma Immunol 1996;77:333–336.
166. Wang N, Truedsson L, Elvin K, et al. Serological assessment for celiac disease in IgA deficient adults. PLoS One 2014;9:e93180.
167. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: early pregnancy loss. Obstet Gynecol 2018;132:e197–e207.

168. Pogačar M, Vlaisavljević V, Turk E, et al. Reproductive complications in celiac disease patients in Slovenia. Eur J Obstet Gynecol Reprod Biol 2019;238:90–94.
169. Celdir MG, Choung RS, Rostamkolaei SK, et al. Reproductive characteristics and pregnancy outcomes in hidden celiac disease autoimmunity. Am J Gastroenterol 2021;116:593–599.
170. Tata LJ, Card TR, Logan RF, et al. Fertility and pregnancy-related events in women with celiac disease: a population-based cohort study. Gastroenterology 2005;128:849–855.
171. Zugna D, Richiardi L, Akre O, et al. A nationwide population-based study to determine whether coeliac disease is associated with infertility. Gut 2010;59:1471–1475.
172. Dhalwani NN, West J, Sultan AA, et al. Women with celiac disease present with fertility problems no more often than women in the general population. Gastroenterology 2014;147:1267–1274.e1; quiz e13–e14.
173. Castaño M, Gómez-Gordo R, Cuevas D, et al. Systematic review and meta-analysis of prevalence of coeliac disease in women with infertility. Nutrients 2019;11:1950.
174. Glimberg I, Haggård L, Lebwohl B, et al. The prevalence of celiac disease in women with infertility-a systematic review with meta-analysis. Reprod Med Biol 2021;20:224–233.
175. Smecuol E, Mauriño E, Vazquez H, et al. Gynaecological and obstetric disorders in coeliac disease: frequent clinical onset during pregnancy or the puerperium. Eur J Gastroenterol Hepatol 1996;8:63–89.
176. Kotze L, Mallmann A, Miecznikowski RC, et al. Reproductive aspects in brazilian celiac women. Arq Gastroenterol 2020;57:107–109.
177. Moleski SM, Lindenmeyer CC, Veloski JJ, et al. Increased rates of pregnancy complications in women with celiac disease. Ann Gastroenterol 2015;28:236–240.
178. Bayrak NA, Volkan B, Haliloglu B, et al. The effect of celiac disease and gluten-free diet on pubertal development: a two-center study. J Pediatr Endocrinol Metab 2020;33:409–415.
179. Mičetić-Turk D, Vlaisavljević V, Turk E, et al. Onset of menarche is not delayed in Slovenian patients with celiac disease. J Int Med Res 2019;47:815–822.
180. Sferlazzas C, Arrigo T, Salzano G, et al. Menarcheal age in celiac disease may not be delayed and may be irrespective of age at diagnosis and dietary management. J Endocrinol Invest 2008;31:432–435.
181. Ferguson R, Holmes GK, Cooke WT. Coeliac disease, fertility, and pregnancy. Scand J Gastroenterol 1982; 17:65–68.
182. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003; 163:286–292.
183. Singh P, Arora S, Lal S, et al. Risk of celiac disease in the first- and second-degree relatives of patients with celiac disease: a systematic review and meta-analysis. Am J Gastroenterol 2015;110:1539–1548.
184. King JA, Bakal JA, Li B, et al. Variation in testing for and incidence of celiac autoimmunity in Canada: a population-based study. Gastroenterology 2023; 164:567–578.e7.
185. Johnston SD, Rodgers C, Watson RGP. Quality of life in screen-detected and typical coeliac disease and the effect of excluding dietary gluten. Eur J Gastroenterol Hepatol 2004;16:1281–1286.
186. Vilppula A, Kaukinen K, Luostarinen L, et al. Clinical benefit of gluten-free diet in screen-detected older celiac disease patients. BMC Gastroenterol 2011;11:136.
187. Ukkola A, Mäki M, Kurppa K, et al. Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease. Clin Gastroenterol Hepatol 2011;9:118–123.e1.
188. Kurppa K, Paavola A, Collin P, et al. Benefits of a gluten-free diet for asymptomatic patients with serologic markers of celiac disease. Gastroenterology 2014;147:610–617.e1.
189. Mustalahti K, Lohiniemi S, Collin P, et al. Gluten-free diet and quality of life in patients with screen-detected celiac disease. Eff Clin Pract 2002;5:105–113.
190. Ludvigsson JF, Card TR, Kaukinen K, et al. Screening for celiac disease in the general population and in high-risk groups. United European Gastroenterol J 2015;3:106–120.
191. Cosnes J, Cellier C, Viola S, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. Clin Gastroenterol Hepatol 2008; 6:753–758.
192. Mearns ES, Taylor A, Boulanger T, et al. Systematic literature review of the economic burden of celiac disease. Pharmacoeconomics 2019;37:45–61.
193. Mårild K, Söderling J, Bozorg SR, et al. Costs and use of health care in patients with celiac disease: a population-based longitudinal study. Am J Gastroenterol 2020; 115:1253–1263.
194. Bozorg SR, Söderling J, Everhov ÅH, et al. Work loss in patients with celiac disease: a population-based longitudinal study. Clin Gastroenterol Hepatol 2022; 20:1068–1076.e6.

Received November 10, 2023. Accepted February 15, 2024.

Correspondence
Address correspondence to: Fabiana Zingone, MD, Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Via Giustiniani 2, Padua 35128 Italy. e-mail: fabiana.zingone@unipd.it.

CrediT Authorship Contributions
Fabiana Zingone, MD (Conceptualization: Equal; Methodology: Equal; Validation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Julio C. Bai, MD (Validation: Equal; Writing – review & editing: Equal)
Christophe Cellier, MD (Validation: Equal; Writing – review & editing: Equal)
Jonas F. Ludvigsson, MD (Conceptualization: Equal; Methodology: Equal; Validation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Conflicts of interest
These authors disclose the following: Jonas F. Ludvigsson has an ongoing research collaboration on celiac disease with Takeda. Fabiana Zingone served as a speaker for Werfen and as a consultant for Takeda. Christophe Cellier was engaged as a speaker for Dr Shar and a consultant for Takeda. The remaining author discloses no conflicts.