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Celiac Disease: Extraintestinal Manifestations and Associated Conditions

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Abstract

Celiac disease (CeD) is a common form of enteropathy with frequent extraintestinal manifestations (EIM). Misrecognition of these presentations may lead to significant delays in diagnosis. Any organ may be involved, either through an immune / inflammatory phenomenon, or nutritional deficiencies. Some EIM, such as gluten ataxia, may be irreversible if left untreated, but most will improve with gluten-free diet (GFD). Knowledge of the various EIM as well as the associated conditions which do not improve on a GFD will avoid delays in the diagnosis and management of CeD and associated manifestations.

Keywords

Celiac disease; extraintestinal manifestations; gluten-free diet

Celiac disease (CeD) is common with an estimated global prevalence of 0.7 to 1.4%¹. It is a T-cell enteropathy induced by gluten exposure among genetically predisposed individuals. Classically, CeD was diagnosed among children presenting with gastrointestinal manifestations and failure to thrive. The discovery of tissue transglutaminase as an immunological target offered a convenient first line diagnostic test², and liberalization of screening led to recognition of many other presentations of CeD that are unrelated to the digestive tract³. A recent retrospective cohort study showed that 62% of adults had extraintestinal manifestations (EIM) of CeD at diagnosis, which were unaccompanied by

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intestinal manifestations in 9% of cases⁴. Antigenic mimicry, circulating auto-antibodies, inflammatory cytokines, and nutritional deficiencies are all factors contributing to EIM. Lack of knowledge of the various atypical manifestations of CeD may lead to delays in diagnosis. In an adult cohort study, the mean time to diagnosis was 2.3 months for those with GI symptoms, compared to 42 months for those without GI symptoms⁵. Children presenting with primarily EIM had more severe small intestinal histologic injury at the time of diagnosis⁶. This review will first summarize common vitamin and mineral deficiencies associated with CeD and their clinical manifestations, then provide a system-oriented overview of the various EIM of CeD. The latter will detail extra-intestinal manifestations responding to GFD, as well as complications from long term untreated disease, including those that are generally associated with systemic inflammation (Figure 1). Finally, associated diseases without a causative link with CeD will be mentioned.

Overview of GI symptoms and associated vitamin deficiencies

Classic presentation of CeD includes diarrhea, steatorrhea, abdominal pain, bloating and weight loss, a symptomatology mainly attributed to the maldigestion and malabsorption associated with intestinal villous atrophy. However, some individuals present with constipation, recurrent vomiting or heartburn, which may be mistaken for a functional disorder or irritable bowel syndrome⁷.

Due to insufficient nutritional intake, malabsorption and maldigestion, deficiencies in electrolytes, vitamins and minerals are very frequent among untreated CeD. Indeed, a recent prospective found deficiencies in almost 90%, notably zinc deficiency in 66.7%⁸. These deficiencies may have some systemic consequences (Table 1). Although rare nowadays, untreated CeD may result in severe malabsorption and malnutrition.

As mentioned in Table 1, vitamin D deficiency has several consequences, notably secondary hyperparathyroidism which is found in 19 to 28% of individuals with CeD^{12, 13} and may progress to primary hyperparathyroidism if untreated¹⁵; some with initial normocalcemic hyperparathyroidism subsequently develop hypercalcemic hyperparathyroidism despite vitamin D repletion and gluten avoidance¹⁶.

In addition to oligosaccharides and oligopeptides maldigestion due to loss of brush border enzymes, fat maldigestion and malabsorption may also occur and is a well known cause of hyperoxaluria and oxalate kidney stones¹⁷. Some have proposed that urinary stones may be the first manifestations of subclinical CeD, which could account for 1–1.5% of all cases of urinary stone disease¹⁸. Studies have shown an increased risk of urinary stones among untreated CeD^{18, 19} but that risk was comparable to the general population among treated CeD¹⁸. Hyperoxaluria was not associated with overt fat malabsorption in the presence of CeD¹⁸.

Refractory celiac disease (RCD) is defined as persistent immune activation, villous atrophy and signs and symptoms of malabsorption despite adhering strictly to a GFD for at least one year²⁰. There are two types of RCD; type 1 is indistinguishable from active CeD, whereas type 2 is characterized by the presence of aberrant T cells and clonal T-cell receptor gene

rearrangement²¹. Individuals with RCD are at high risk of malnutrition and related complications, and those with RCD type 2 may suffer from gastrointestinal bleeds, obstruction or perforation as a result of ulcerative jejunitis. RCD is defined clinically based on intestinal symptoms (diarrhea, weight loss, abdominal pain, bloating) and EIM have not been well described. A recent series of RCD cases treated with oral budesonide reported that 72% had a *classical* presentation (i.e diarrhea) and 18% had dermatitis herpetiformis²². Only 21% reported fatigue²². In a similar retrospective cohort including 21 well-defined RCD type 1 cases from two US Celiac Centers, 29% reported fatigue and 19% had other EIM, including brain fog, joint pain, headaches, dermatitis herpetiformis and neuropathy (Therrien et al., submitted manuscript).

Extraintestinal manifestations and complications of CeD

Neurological manifestations

The prevalence of neurological symptoms among individuals with CeD is estimated to be between 6 and 10%²³, but may be as high as 42% in untreated CeD²⁴. Many mechanisms have been implicated, notably cross-reacting antibodies, immune-complex deposition, direct neurotoxicity and vitamin or nutrient deficiencies^{24, 25}.

Headaches and migraine—Headaches, especially migraines, may be the first manifestation of CeD and may be of higher intensity compared to the general population, leading those affected to seek medical care more frequently^{26, 27, 28}. A pooled estimated prevalence of headache in adults with CeD is 26%, slightly higher than a pooled prevalence of 18.3% in children^{28, 29}. Idiopathic headache, migraine and tension headache are more frequent among individuals with CeD, while there is no association with cluster headache, hemicrania continua or trigeminal neuralgia^{26, 27, 28}. Furthermore, an increased rate of medical visits for headaches and migraines in the setting of potential CeD has been reported²⁶, and these symptoms may also occur with gluten exposure in treated CeD³⁰. Fortunately, both frequency and intensity of headaches decrease with the GFD, especially in children^{4, 24, 27, 28}.

Peripheral neuropathy—There is a 2.5 to 3.4 -fold increased risk of peripheral neuropathy in the CeD population compared to the general population^{31, 32}. However, an even more common entity, called “gluten-induced neuropathy”, is a peripheral idiopathic neuropathy associated with positive celiac serology but without enteropathy³³. When associated with CeD, peripheral neuropathy may present either before or after the diagnosis or may be the only manifestation of the disease^{32, 34}. A population-based study recently showed an association between polyneuropathy and being subsequently diagnosed with CeD (OR 5.4 95% CI 3.6–8.2)³¹. Various type of neuropathies have been described; small fiber sensory neuropathy, symmetric predominantly sensory neuropathy, mononeuritis multiplex and multifocal motor or sensorimotor polyneuropathy³⁴. According to the type of neuropathy, clinical signs and symptoms may include painful paresthesia (may be facial or oral), mild gait instability, mild lower limbs or focal weakness³⁴. It is associated with a significant reduction of quality of life³³.

Molecular mimicry between ganglioside molecules of peripheral nerves and gluten is a proposed mechanism³⁴ and antiganglioside antibodies were present in serum of 65% of a small cohort of CeD patients with neuropathy³⁵. Improvement on GFD is variable, and may depend on dietary compliance, the duration of the inflammatory process, and the etiology of the neuropathy; the presence of anti-neuronal antibodies is an indicator of non response to GFD^{25, 36}.

Gluten Ataxia—Although gluten ataxia is the most extensively studied neurological manifestation in CeD, most of the available literature is from a single group from the United Kingdom. Gluten ataxia is also considered as a “gluten related disorder”, implying that it can be triggered by gluten in the absence of CeD. Gluten ataxia typically develops among middle-age adults³⁷ and is characterized by gait ataxia and mostly lower limb ataxia, dysarthria, nystagmus and other oculomotor disorders^{25, 37}. Less than 10% have GI symptoms but about 40% have duodenal histology compatible with CeD^{37, 38}. Elevated celiac serology and HLA-DQ2/DQ8 may help discriminate between CeD and gluten ataxia in the absence of enteropathy. Although anti-gliadin antibodies may be found in gluten ataxia without CeD, tTG antibodies are rarely elevated^{38, 39}.

Gluten ataxia is believed to be related to antibody cross-reactivity between Purkinje and other cerebellar cells and gluten peptides, and IgA tissue transglutaminase 6 (TTG6) deposits can be observed in the cerebellum³⁷. These antibodies were found in circulation in 73% of individuals with gluten ataxia (of which 51% had an enteropathy), and the titers significantly decreased with a GFD⁴⁰.

A GFD seems to be an effective treatment for gluten ataxia, but it may depend on the duration of symptoms prior to the diagnosis, since there may be irreversible loss of Purkinje cells in the cerebellum^{37, 41}. Nevertheless, improvement after one year of GFD was independent of the presence of enteropathy⁴¹. Screening for CeD with anti-tTG-2 IgA and IgG deamidated gliadin peptide as well as other antibodies associated with gluten ataxia (native anti-gliadin antibodies and, if available, anti-tTG-6), and subsequent initiation of GFD should be performed promptly in this population. MR spectroscopy of the cerebellum may be a useful tool for follow-up³⁹.

Interestingly, a recent prospective cohort of 100 consecutive newly diagnosed CeD patients reported gait instability in 24%, gait ataxia in 29%, nystagmus in 11% and the presence of circulating tTG6 among 40%²⁴. Moreover, 47% had abnormal MR spectroscopy of the cerebellum and 25% had white matter lesions on brain MRI. There was an overall improvement after one year of GFD. Although a referral bias cannot be excluded, and some manifestations may be attributed to vitamin deficiencies, these data provide compelling evidence about a potentially frequent neurological immune related manifestation of CeD and how GFD may prevent progression to the more severe condition that is gluten ataxia²⁴.

Gluten-induced cognitive impairment (Brain fog)—Although “brain fog” is not a medically or psychologically recognized condition, this term is often used colloquially by patients to refer to difficulty concentrating, lack of attentiveness, short-term memory

deficits, word-finding difficulties, reduced creativity, confusion and disorientation after gluten exposure^{42, 43}.

Interestingly, this type of cognitive impairment is not specific to gluten ingestion; this phenomenon has also been observed in many other conditions, notably multiple sclerosis, fibromyalgia, and those undergoing chemotherapy⁴². Few studies are available on gluten-induced cognitive impairment in CeD, but a small cohort study showed objective minor deficits to the short-term memory, processing speed and visual-spatial memory at diagnosis that improved after one year on a GFD⁴³. Cognitive improvement also significantly correlated with the extent of mucosal healing⁴³. Proposed mechanisms for gluten-induced cognitive impairment involve circulating pro-inflammatory cytokines that may act directly upon neurons⁴³ or affect blood-brain barrier permeability enhancing inflammation by increasing leukocytes migration⁴². Other hypotheses include reduced brain tryptophan concentration leading to a deficit in serotonin, effects of exorphins (which are opioid peptides derived from partially digested gluten) and microbiome changes⁴³. Individuals who experience gluten-induced cognitive impairment upon accidental gluten exposure often report that this symptom may be more prolonged (one to four weeks) than gastrointestinal symptoms⁴⁴.

Epilepsy—The risk of epilepsy is increased among individuals with CeD⁴⁵, with complex partial seizures being the most frequent type²³. There is a well-known triad of CeD, bilateral parieto-occipital calcifications, and seizures^{46, 47}. Interestingly, in this presentation, the seizures do not arise specifically from the sites of the calcifications^{46, 47}, which may also be associated with headaches rather than epilepsy³⁹. Many hypotheses have been proposed for these lesions, notably folic acid deficiency or an autoimmune phenomenon, being often associated with white matter abnormalities^{23, 46, 47}. Interestingly, this syndrome appears to be restricted to HLA-DQ2⁴⁷. Although incidence and seizure activity may be reduced by strict adherence to GFD^{48, 49}, cerebral calcifications are possibly irreversible⁴⁸.

Other rare presentations—Many other neurological presentations of CeD have been described, notably acute generalized chorea⁵⁰, pseudotumor cerebri⁵¹ and cerebral vasculitis⁵², all of which appear responsive to GFD.

Psychiatric conditions

Although anxiety, depression, attention-deficit/hyperactivity and eating disorders have been associated with CeD⁵³, distinguishing between specific manifestations of CeD, and the consequences of suffering from a chronic GI disorder and following a strict diet is challenging⁵³. For instance, a recent study showed an association between the development of anxiety after a CeD diagnosis and achieving mucosal recovery, illustrating the impact of strict adherence to the GFD on psychological well-being⁵⁴. Nevertheless, psychiatric disorders were found among 24% of adults at diagnosis and tended to improve after 24 months of GFD⁴. More specifically, some studies still showed improvement in anxiety symptoms on a GFD, but there is controversy whether depressive symptoms improve^{55, 56}. One possible explanation is that treating CeD may increase circulating L-tryptophan levels and production of serotonin and dopamine⁵⁷.

Although there is scant literature on the subject, it is the authors experience that intermittent gluten exposure may trigger feelings of depression, anxiety and personality changes in some individuals with CeD ³⁰.

Fatigue—Fatigue is common in CeD, with an incidence as high as 37% at diagnosis ⁴. There is no standard definition for fatigue and studies have used different instruments to measure it ⁵⁸. Chronic fatigue may be an indication to screen for CeD, since it was found more often among undiagnosed cases of CeD ⁵⁹. Acute fatigue may also be a sign of gluten exposure ³⁰. There is controversy about the effects of the GFD on fatigue, as only 50% of adults may improve after two years on a GFD ^{4, 60}. The etiology of fatigue in the non-responders is multifactorial, and screening for depression, sleep disorders, and thyroid disease is advisable, particularly in the absence of anemia, ^{60, 61}.

Ocular manifestations

There are few ocular complications of untreated CeD. In addition to retinopathy related to vitamin A deficiency, cataracts (HR 1.28 95CI 1.19–1.36)⁶² and uveitis (HR 1.32 95CI 1.10 – 1.58)⁶³ have been reported, with subsequent resolution of the uveitis on a GFD ⁶⁴. Oxidative stress, vitamin deficiencies and hypocalcemia have been hypothesized as an explanation for the association between cataract formation and CeD⁶⁵. The risk was the highest among individuals diagnosed with CeD at 40–49 years (HR 1.40 95CI 1.11–1.77) and 50–59 years (HR 1.23 95CI 1.04–1.43)⁶². Interestingly, individuals with previous cataract were also at increased risk to be later diagnosed with CeD (OR 1.14 95CI 1.02–1.30) ⁶².

Dermatologic manifestations

Many skin conditions occur more frequently among individuals with CeD, such as eczema, psoriasis, atopic dermatitis and urticaria (Table 2). Non-specific rashes have also been associated with gluten exposure ³⁰. The following section will focus on specific skin and hair conditions which typically improve on a GFD; however, only dermatitis herpetiformis has been demonstrated to have a clear gluten-related immune mechanism.

Dermatitis herpetiformis—Dermatitis herpetiformis (DH) is the most frequent dermatologic manifestation of CeD. The rash is characterized by extremely pruritic small vesicles and papules on the elbows, knees and buttocks that may be obscured by excoriations. Oral involvement is very rare ⁶⁶. In contrast to CeD, the incidence of DH seems to be decreasing over time, probably since it is mostly diagnosed among untreated CeD and the disease's global awareness is increasing ^{68, 69}. Indeed, compared to previous cohort studies showing a 17–20% prevalence of DH among untreated CeD^{14, 70}, the rate in a more recent ten-year cohort in Finland was only 4%⁷¹. Diagnosis before 16 years of age is rare and the highest incidence is among men between 60 and 69 years old and women between 50 and 59 years old ⁶⁸. Although most with DH have enteropathy, they rarely report gastrointestinal symptoms ^{72, 73}. DH is characterized by deposits in the superficial papillary dermis of anti-tissue transglutaminase 3, an epidermal transglutaminase ⁷⁴. Thus, in addition to the clinical characteristics, DH diagnosis is confirmed by a skin biopsy showing pathognomonic granular IgA deposits on the papillary dermis by immunofluorescence ⁷⁵.

Typically, DH lesions respond to GFD⁷⁶, therefore, when DH develops or persists in a patient with treated CeD, ongoing gluten exposure must be suspected and adherence to the GFD reassessed. Fortunately, the rash tends to heal without scarring, but remission may take months or years to achieve⁷⁷. Dapsone is often used initially because the GFD prevents further inflammation, but does not affect the ongoing skin process⁷⁷.

Psoriasis—Psoriasis can be associated with CeD, with a risk 1.44 to 3.09 times greater than the general population^{78, 79}. Some studies have reported that the GFD improves psoriasis in CeD⁸⁰. It may be due to a better absorption of vitamin D, or improved intestinal barrier function⁷⁷. Some authors have suggested that psoriasis may be the only clinical manifestation of CeD⁷⁷.

Chronic urticaria—Chronic urticaria (hives lasting more than six weeks) is associated with HLA-DQ8 and is more common among individuals with CeD (HR 1.92, 95%CI 1.48 – 2.48)^{77, 81}. A GFD may lead to complete remission of urticaria, allowing some to conclude that urticaria may be a manifestation of CeD⁸².

Leucocytoclastic vasculitis—Leucocytoclastic vasculitis is a small vessel vasculitis presenting with palpable purpura, hemorrhagic vesicles and livedo reticularis⁷³. There are few reports of cutaneous vasculitis associated with CeD, including most interestingly, a 38 year-old woman with untreated CeD and leucocytoclastic vasculitis who had complete resolution of her skin lesions after adoption of a strict GFD⁸³.

Alopecia areata—Alopecia areata is an autoimmune disease presenting with well circumscribed patches of hair loss without scarring⁷³. The prevalence of CeD in alopecia areata is the same as general population⁷³; however, some cases, especially children, may improve with a GFD⁸⁴.

Oral manifestations

There is no pathognomonic oral manifestation of CeD. As mentioned in Table 1, many vitamin deficiencies may induce glossitis or stomatitis. In addition, recurrent aphthous stomatitis (RAS) and dental enamel defects have been observed more frequently among those with CeD and may be partly immune-mediated and gluten responsive.

Recurrent aphthous stomatitis—RAS is characterized by painful small well circumscribed ulcers in the oral cavity⁷³. It is more frequent among individuals with CeD than the general population (OR 3.79 95%CI 2.67 – 5.39)⁸⁵. It is unclear whether this condition is related to direct immune effects from gluten exposure or nutritional deficiencies, such as iron, folic acid and vitamin B12^{73, 86}. In addition to nutritional deficiencies, some drugs such as NSAIDs, captopril, and phenobarbital have been associated with RAS⁸⁷. Differential diagnoses include Behcet's syndrome, inflammatory bowel disease, Sweet syndrome, cyclic neutropenia and HIV infection⁸⁸. Nevertheless, in favor of its being gluten-related, GFD may lead to complete remission of the stomatitis, and gluten exposure induces recurrence^{30, 89}.

Dental enamel defects—Dental enamel defects include defects in color, pitting, grooving and complete loss of enamel and are most commonly described involving the secondary incisors in children ^{67, 86}. Severity seems to be correlated with the duration of gluten exposure ⁹⁰. Disease pathways may be either immune-mediated or nutrition-related ⁸⁶. Interestingly, dental enamel defects have also been found among healthy first-degree relatives of CeD patients carrying HLA DQ2 with normal duodenal histology⁹¹.

Musculoskeletal manifestations

Osteoporosis—Reduced bone density at diagnosis in CeD is found at a variable rate ranging from 26 to 72%, and may be independent of the presence of GI symptoms^{92, 93}. Although many meta-analyses found an increased risk of osteoporosis in CeD ⁹⁴, the inverse has not been shown as CeD is not more prevalent among those with osteoporosis ⁹⁵. A recent meta-analysis of prospective studies showed that CeD was associated with a 30% increased risk of any fracture and a 69% increased risk of hip fracture⁹⁶. Factors associated with osteoporosis at the time of CeD diagnosis, justifying an earlier DEXA scan, include male sex, age >45 years old, being underweight and severe histological damage (Marsh 3c) ⁹⁷. Many mechanisms link decrease in bone density and CeD. Calcium and vitamin D malabsorption may lead to hyperparathyroidism, and overall malnutrition leads to low body mass index and hypogonadism ⁹⁸. Furthermore, circulating cytokines and autoantibodies against osteoprotegerin may affect bone turnover^{99, 100}. Some studies showed improvement or stabilization of bone density on a GFD, but persistence of fracture risk ^{101, 102}, while a systematic review concluded that bone density improves after one year on a GFD and may even return to normal after five or more years on a GFD¹⁰³. Persistent villous atrophy may be an important risk modifier ^{104, 105}. A DEXA scan is recommended, either at diagnosis or one year after the initiation of GFD ^{20, 101}.

Osteomalacia—Osteomalacia is a decreased bone mineralization at sites of bone turnover caused by vitamin D deficiency. A recent meta-analysis showed a mean incidence of osteomalacia of 18.3% (4.7–38.1%) in CeD ⁹⁴. Osteomalacia may be asymptomatic, or cause bone pain, muscle spasm or tenderness, and fractures ¹⁰⁶. Common laboratory findings include elevated alkaline phosphatase, reduced serum calcium and phosphorus, reduced urinary calcium, markedly reduced ergocalciferol and elevated PTH ¹⁰⁶. GFD and vitamin D supplementation are the current treatments for osteomalacia in CeD.

Myalgia—Myalgia are common initial symptoms of CeD ⁴ which may be related to either nutritional deficiencies or systemic inflammation. In contrast to children, only half of adults with CeD had decreased muscle pain after 24 months of GFD ⁴. However, other causes of muscle pain, such as idiopathic inflammatory myopathies and fibromyalgia, are also frequently associated with CeD and may not respond to the GFD⁹⁸.

Arthralgia and arthritis—Another frequent musculoskeletal manifestation is joint pain, occurring in 20–30% at CeD diagnosis⁹⁴. Some have described a presentation similar to seronegative spondyloarthropathies with non-erosive, non-deforming oligoarthritis and axial or sacroiliac involvement ¹⁰⁷. However, a recent meta-analysis did not show an increased risk of arthritis in CeD ⁹⁴. Studies are contradictory regarding whether joint pain improves

on a GFD^{4, 108}, and response to GFD may help distinguish whether joint pain is directly related to CeD and gluten exposure, as opposed to synovial effusion, sacroiliitis and joint stiffness, which may be signs of associated autoimmune rheumatologic disease and do not improve on a GFD^{109, 110, 111}. Although the evidence is limited, some individuals on a longstanding GFD may experience joint pain upon accidental gluten exposure⁴⁴. Finally, a higher prevalence of lower limb enthesopathy has been found among untreated CeD^{107, 112}.

Cardiovascular system

Pericardial effusion, myocarditis and cardiomyopathy—CeD may present with asymptomatic pericardial effusion, which resolves on a GFD^{113, 114}. Untreated silent CeD is frequent among individuals with auto-immune myocarditis, with an incidence of biopsy-confirmed CeD of 4.4%¹¹⁵. The myocarditis is mostly lymphocytic infiltrate and is usually not associated with any chronic GI symptoms¹¹⁵. While some studies showed an increased prevalence of untreated CeD among individuals with dilated or idiopathic cardiomyopathies¹¹⁶, other population studies showed that cases with CeD are not at increased risk for these conditions^{117, 118}. Although the precise immune mechanism has not been elucidated yet, idiopathic dilated cardiomyopathy with coexisting CeD improves on a GFD, compared to nonadherent individuals^{119, 120}.

Pulmonary manifestations

Lungs are rarely involved in CeD. An increased risk of developing chronic obstructive lung disease before and after CeD diagnosis has been reported, although no strong causative relationship was established¹²¹ (Table 2). To our knowledge, the only proven lung involvement of CeD is pulmonary hemosiderosis.

Pulmonary hemosiderosis—Pulmonary hemosiderosis is characterized by recurrent alveolar hemorrhages. Lane-Hamilton syndrome is the association of CeD and pulmonary hemosiderosis caused by an increased permeability of alveolar capillaries due to deposition of immune complexes¹²². This syndrome may occur in both children and adults, and is not always associated with GI symptoms^{123, 124}. GFD allows some improvement, possibly in part because of a better absorption of the immunosuppressive treatment¹²⁴. Some recommend that pulmonary hemosiderosis is an indication to screen for CeD¹²².

Renal disease

The prevalence of CeD is increased among individuals with chronic kidney diseases¹²⁵, and although controversial, an increased risk of end-stage renal disease has been reported in CeD¹²⁶. The strongest associations remain IgA nephropathy and diabetic nephropathy¹²⁷; interestingly, CeD may be a specific risk factor for the development of diabetic nephropathy in type I diabetes¹²⁸. In addition, it has been hypothesized that nutritional deficiencies may exacerbate renal insults¹⁷.

IgA Nephropathy—IgA nephropathy (*Maladie de Berger*) is an immune-complex mediated glomerulonephritis caused by glomerular IgA deposits and is characterized by macroscopic hematuria and impaired renal function. Although the overall prevalence is low (0.026%)¹²⁹, a metaanalysis showed an increased risk among in CeD, especially among

males¹²⁷. Recently, shared disease pathways between these two disorders were elucidated, including overexpression of the IgA1 mesangial receptor (TfR1)^{130, 131}. Antigliadin IgA complexes trigger the activity of transglutaminase 2 present in the kidney and upregulate the expression of TfR1 and enhance glomerular injury¹³². Some individuals without CeD experienced clinical and histological improvement of the IgA nephropathy with GFD, but the diet did not prevent renal failure^{133, 134}.

Other nephropathies—A few case series described other glomerulopathies in the context of CeD, such as membranous nephropathy and membranoproliferative nephropathy, the later being improved with GFD in four case reports¹⁷.

Endocrine disorders

Autoimmune endocrine disorders (thyroid diseases, Addison disease, type 1 diabetes) are conditions associated with CeD, because of common genetic predisposition and shared T_H1 immunity pathways (Table 2); they are not manifestations of CeD per se^{135, 136}. Nevertheless, an elegant study showed anti-tissue transglutaminase 2 deposits in primate thyroid tissue as well as a correlation between tTG IgA and TPO antibodies titers in individuals with CeD, suggesting that tTG may play a role in auto-immune thyroiditis among CeD patients¹³⁷.

Reproductive system

CeD is associated with unexplained infertility and increases the risk of several obstetrical complications¹³⁸. Initial presentation of CeD has been described during the third trimester of pregnancy or the postpartum period¹³⁹.

Amenorrhea, delayed menarche and early menopause—CeD has been associated with delayed menarche of two years or more among untreated girls¹⁴⁰. Amenorrhea is a frequent complication of untreated CeD^{140, 141}. Menopause may also start earlier among untreated CeD women^{140, 142}. Interestingly, although functional hypopituitarism associated with malnutrition may reduce gonadotrophins and sexual hormones, it has been proposed that circulating gluten peptides may also have direct immunologic effect on the hypothalamo-pituitary-gonadal axis¹³⁸. GFD may correct these effects; those with treated CeD have menarche and menopause at typical ages¹⁴¹.

Infertility—There is a well-known association between unexplained infertility and CeD¹⁴³. Initial studies suggested that the prevalence of asymptomatic CeD among unexplained infertility may be from 4 to 10.3%^{67, 144, 145, 146}. More recently, this concept has been challenged by two studies from fertility centers^{147, 148}. However, these recent studies included women who had been referred for fertility treatment in countries where screening for CeD may be more intensive. Infertility affects mostly untreated women. In men, studies more than 30 years ago described hormonal imbalances and alterations in spermatozoid morphology and motility, but recent epidemiologic studies have failed to show this association.^{149, 150, 151} In addition to hormonal imbalances, nutritional deficiencies, such as iron, folate, zinc and selenium deficiencies may be linked to infertility¹⁵², which may resolve with a GFD^{138, 153}. However, infertility is also frequent among women without any

severe malabsorption or trace elements deficiency, suggesting that immune mechanisms may also prevent trophoblast implantation^{154, 155}.

Obstetrical complications—Untreated CeD is associated with recurrent miscarriage and intra-uterine growth restriction^{154, 156}. The mechanisms may be similar to infertility; malnutrition, zinc and selenium deficiencies having a deleterious effect on gonadotropin secretion leading to spontaneous abortion¹⁵². Furthermore, because tissue transglutaminases are active in the placenta and endometrium tissues, anti-tissue transglutaminase 2 antibodies can impair placental implantation and development, leading to intrauterine growth restriction¹⁵⁴. Finally, CeD is more frequently found among women with a history of pre-term deliveries and low birth weight infants, who may be otherwise asymptomatic from their CeD^{156, 157}. Fortunately, GFD appears to reduce these risks to the same as general population¹⁵⁷.

Hematologic manifestations

Anemia—Anemia is the most frequent EIM of CeD⁴. Although iron deficiency is the most common cause, B12, folate deficiency and systemic inflammation account for more than 15% of anemia in CeD¹⁵⁸. In a recent systematic review and meta-analysis, CeD was present in 3.2–5.5% of individuals with iron deficiency anemia¹⁵⁹. Furthermore, in a large cohort from Italy of subclinical CeD, iron deficiency anemia was the most frequent manifestation in both adults (46.3%) and children (34.8%)¹⁴. Iron deficiency anemia improves with iron supplementation on a GFD⁴; lack of improvement requires further investigation.

Hyposplenism—The spleen plays a key role in mounting the immune response to encapsulated micro-organisms¹⁶⁰. The extent of the association between these two conditions is not well known, since the reported incidence of hyposplenism in CeD is highly variable according to studies and diagnostic modalities^{162, 163}. It does not appear to occur among children¹⁶⁴ and may be associated with other auto-immune comorbidities^{161, 165}. Clinical clues of hyposplenism include thrombocytosis and Howell-Jolly bodies on the blood smear. Other diagnostic modalities are scintigraphy and detection of pitted red cells by phase-interference microscopy¹⁶⁰. An association between splenic atrophy and mesenteric lymph node cavitation has been described in over 30 cases¹⁶⁶. Hyposplenism causes a susceptibility to infections, and studies conducted over the past fifty years showed that those with CeD were at increased risk for pneumococcal infections¹⁶⁷. Some societies now recommend pneumococcal vaccination for those with a diagnosis of CeD^{101, 168}. The World Gastroenterology Organization also recommends vaccination against *Haemophilus influenzae* and meningococci¹⁶⁸. Hyposplenism may be reversible with the GFD, but that remains controversial^{169, 170}.

Response to hepatitis B virus vaccine—An attenuated response to the hepatitis B virus (HBV) vaccine has been observed among individuals with CeD^{171, 172}. A predisposition to poor immune response to the vaccine may be due to the specific haplotypes, especially DQ2, which may fail to induce a Th2 response to the HBV surface antigen^{171, 173}. However, this non-response is mostly seen in the context of ongoing gluten ingestion, and may be reversible with a GFD¹⁷⁴. Some have proposed to screen for CeD

among non-responders to the HBV vaccine, and to revaccinate once adherence to the GFD is optimal^{172, 174}. Confirming HBV vaccine response among individuals with CeD is advisable.

Liver

Autoimmune liver diseases have been associated with CeD (Table 2). Active intestinal inflammation and immune reaction towards gluten and tissue transglutaminase may also have direct effects on the liver.

Celiac hepatitis—Mild elevation of liver enzymes is frequent at the time of CeD diagnosis^{175, 176}. As such, CeD may be the etiology of unexplained transaminitis in 2–12%^{176, 177}. Celiac hepatitis is characterized by an asymptomatic elevation of less than five times the upper limit of normal and AST/ALT <1, in the setting of a normal physical exam and liver ultrasound¹⁷⁸. Histologic features of celiac hepatitis include mild reactive hepatitis, focal microvesicular fatty changes and chronic hepatitis, without features suggestive of autoimmune hepatitis¹⁷⁷. Serum transaminase levels usually normalize after 6–12 months of GFD¹⁷⁵, so persistent elevation justifies additional investigations¹⁷⁸. Rarely, CeD presents with acute liver failure, chronic hepatitis or cryptogenic cirrhosis, with some improvement on the GFD^{179, 180}.

Steatosis—Liver steatosis is common in CeD, with the prevalence being higher in the first five years after the diagnosis¹⁸¹. Liver steatosis in the absence of metabolic syndrome may justify testing for CeD^{178, 182}. Altered intestinal permeability leading to increased LPS, bacterial antigens and cytokines in the portal circulation is a putative mechanism¹⁸³. Interestingly, a recent animal model study showed that inactivation of tissue transglutaminase in the liver lead to worsening of fatty liver disease¹⁸⁴; alteration of the liver tissue transglutaminase by CeD antibodies could thus be hypothesized as another mechanism for the steatosis in CeD. Finally, the GFD is richer in saturated fatty acids and caloric density than a gluten-containing diet, which may predispose to weight gain and obesity^{185, 186}. It is thus difficult to assess if untreated CeD associated steatosis improves on a GFD.

Other complications related to systemic inflammation

Similarly to other inflammatory bowel diseases, active CeD may be a risk factor for atherosclerosis, arterial thrombosis and venous thromboembolism. Potential mechanisms are linked to hyperhomocysteinemia, thrombophilia, circulating cytokines and deficiencies in protein C and S^{122, 187}.

Stroke—Individuals with untreated asymptomatic CeD, as well as CeD in the first year following diagnosis may be at increased risk for stroke¹⁸⁸. Some have suggested to screen for CeD among those with cryptogenic strokes, especially children¹⁸⁹. The risk of atrial fibrillation is increased in CeD, both before and after diagnosis, which is an additional risk factor for cerebrovascular accident¹⁹⁰.

Ischemic heart disease—Untreated CeD is associated with an increased risk of atherosclerosis, even in childhood^{191, 192}. Altered cholesterol metabolism and inflammation (increased erythrocyte sedimentation rate, hyperhomocysteinemia) are cardiovascular risk factors that tend to improve on a GFD¹⁹¹; however, there is limited evidence that an increased risk of incident ischemic heart disease persists for more than a year after CeD diagnosis^{193, 194}. This may be explained by the GFD leading to a higher intake of saturated fatty acids and caloric load, being a risk factor for obesity^{185, 186}.

Thrombocytosis—Thrombocytosis may be common at the time of CeD diagnosis, particularly in association with iron-deficiency anemia; however, this phenomenon is mostly reported in older studies, such as a pediatric study from India fifteen years ago showing a prevalence of 60%¹⁹⁵. It is unclear nowadays how frequent thrombocytosis is at the time of CeD diagnosis¹⁹⁶, but it may still be a marker of ongoing inflammation with untreated CeD.

Thrombosis—In addition to atherosclerosis, both arterial and venous thrombosis may occur in undiagnosed CeD, without any other identifiable risk factors¹⁸⁷. Individuals with CeD are at increased risk of venous thromboembolism¹⁹⁷ and silent CeD may be unmasked by pulmonary embolism¹⁸⁷. Other examples of venous thrombosis may involve the hepatic, mesenteric¹⁹⁸, portal, splenic, retinal¹⁹⁹ and cerebral veins²⁰⁰. CeD has been identified as the cause of Budd-Chiari in 11.4% of the cases in a study from North Africa²⁰¹. As for active inflammatory bowel disease or cancer, RCD lead to a higher risk of thromboembolism, with deep vein thrombosis involving the superior mesenteric vein, the superior vena cava, pulmonary veins as well as central vein catheters²⁰². Moreover, increased levels of thrombin-activatable fibrinolysis inhibitor (TAFI) have been reported among newly diagnosed CeD, which could be an additional risk factor for venous thromboembolism²⁰³. There is no existing data about the duration of anticoagulation in the context of venous thrombosis with no risks factors other than CeD or among well-established treated CeD¹⁸⁷.

Common coexisting conditions

Many other autoimmune diseases are associated with CeD without being gluten-responsive (Table 2). Putative mechanisms include common genetic predisposition, shared immune pathways and potential triggers (virus, microbiota, environment), increased intestinal permeability and molecular mimicry (especially with primary biliary cholangitis)²⁰⁴. The risk of auto-immune disorders increases with age and possibly also the duration of gluten exposure, especially when signs and symptoms are present more than ten years before diagnosis^{205, 206}. Other risk factors for coexisting auto-immune disorders include a family history of auto-immune disorders and being overweight at the time of CeD diagnosis²⁰⁶.

Sjogren syndrome, systemic sclerosis, rheumatoid arthritis and idiopathic inflammatory myopathies may also be associated with CeD, but well-designed population or case-control studies are lacking^{98, 111, 207}. This also applies to autoimmune hepatitis (AIH) as although single center studies have shown an increased prevalence of CeD among individuals with AIH^{208, 209}, population studies with well-characterized AIH and CeD are lacking.

Conclusion

The discovery of tissue transglutaminase as a target of autoantibodies associated with CeD and the development of various assays for TTG antibodies have liberalized screening for this condition. However, even in Europe and North America, diagnostic delays of more than three years persist, especially among individuals without GI complaints ^{5, 222, 223, 224}. Contrary to previous belief, CeD is a multisystem disease, and physicians from all fields should be aware of the various presentations of CeD and consider it in the diagnostic algorithm of many conditions. Furthermore, most of the EIM of CeD improve with the GFD; other specific diagnoses should be considered among non-responders. EIM should be taken into account in the drug development for CeD.

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Take-home messages:

- Headaches are frequent in the CeD population and may be associated with gluten exposure
- Gluten ataxia must be recognized and GFD initiated early may avoid permanent sequelae.
- Peripheral neuropathy is also frequently reported in the CeD population but may not always improve with the GFD.
- Gluten-induced cognitive impairment is increasingly reported by individuals with CeD and may be associated with gluten exposure.

Take-home messages:

- Fatigue is fairly common among individuals with CeD and is multifactorial; screening for depression, sleep disorders, and thyroid disease is advised, especially if there is no improvement on the GFD.

Take-home messages:

- Dermatitis herpetiform is the most frequent dermatologic manifestation of CeD
- Diagnosis of DH requires skin biopsy for histology and direct IgA immunofluorescence.
- Skin rashes are frequent among individuals with CeD (Table 2). Some may respond to the GFD, but a dermatology evaluation is advised.

Take-home messages:

- Oral manifestations of CeD are mostly related to nutritional deficiencies (Table 1).
- Recurrent aphthous stomatitis occurs more frequently among children, and recurrence may be a sign of gluten exposure.
- Dental enamel defects should prompt to testing for CeD.

Take-home messages:

- Low bone density is frequent among individuals with CeD and a DEXA scan is recommended after one year of GFD, or sooner among males, those older than 45 years, underweight or with severe histological damage (Marsh 3c)
- Myalgia and arthralgia are common at the time of CeD diagnosis. Failure to improve with a GFD should prompt rheumatology evaluation to rule out other associated conditions.

Take-home messages:

- Cardiac manifestations are rare, but screening for CeD is suggested among individuals with idiopathic or dilated cardiomyopathy.

Take-home messages:

- CeD may be a risk factor for diabetic nephropathy in type I diabetes.
- Testing for CeD should be considered in those with:
 - IgA nephropathy, especially males
 - Oxalate kidney stones in the absence of inflammatory bowel disease

Take-home messages:

- Evaluation for CeD is suggested in cases of unexplained infertility or frequent miscarriages
- The risk of obstetrical complications or fetal bad outcomes is similar to the general population among treated CeD women

Take-home messages:

- Evaluation for CeD must be part of the work-up of iron deficiency anemia
- Lack of improvement of iron deficiency anemia on a GFD should lead to investigations for other causes of anemia
- CeD may be an indication for pneumococcal vaccination
- Untreated CeD may be associated with poor response to HBV vaccine; the booster should be administered during treatment with a GFD.

Take-home messages:

- Mild elevation of serum transaminases is present in about 40% at the time of CeD diagnosis and usually resolves on a GFD ¹⁷⁵. Persistent elevated liver enzymes should be further investigated.
- Evaluation for CeD should be performed among individuals with unexplained elevated liver enzymes or steatosis.

Take-home messages:

- Untreated CeD may be a risk factor for early atherosclerosis, but dietary guidance should also be given to avoid excessive weight gain on a GFD.
- Venous thrombosis at many locations have been associated with CeD, and investigation for CeD should be part of the work-up of a venous thrombosis of unknown etiology.

Figure 1:
Main Extraintestinal Manifestations Associated with Celiac Disease

Table 1:

Nutritional deficiencies associated with CeD and their related clinical manifestations

Nutritional deficiency	Most frequent signs and symptoms
Iron ^a	Hypochromic, microcytic anemia, glossitis, koilonychia, fatigue, pallor, cognitive impairment ⁹
Folate	Megaloblastic anemia, glossitis, diarrhea, cognitive impairment ¹⁰
Vitamin B12	Megaloblastic anemia, posterior columns syndrome, dementia, depression, psychosis
Vitamin D	Osteomalacia (deformity of bone, pathologic fractures), osteoporosis, cognitive impairment ¹¹ , secondary hyperparathyroidism ^{12, 13}
Zinc	Growth retardation, hypogonadism, infertility, dysgeusia, poor wound healing, diarrhea, dermatitis on the extremities and periorificial, glossitis, alopecia, corneal clouding
<i>Less frequently occurring</i>	
Protein	Edema, muscular atrophy
Vitamin B1 (thiamine)	Irritability, fatigue, headaches, peripheral neuropathy, wet Beriberi: congestive heart failure; Wernicke: nystagmus, ophthalmoplegia, ataxia; Korsakoff: hallucinations, impaired short-term memory and confabulation
Vitamin B3 (niacin)	Pellagra: diarrhea, dementia, pigmented dermatitis; Glossitis, stomatitis, vaginitis, vertigo, burning dysesthesias
Vitamin B6 (pyridoxine)	Stomatitis, angular cheilosis, glossitis, irritability, depression, confusion, normochromic normocytic anemia
Vitamin A	Follicular hyperkeratosis, night blindness, conjunctival xerosis, keratomalacia
Vitamin E	Hemolytic anemia, peripheral neuropathies, ophthalmoplegia, posterior columns syndrome
Vitamin K	Easy bleeding

^aIron deficiency is very common among individuals with CeD and may be the leading manifestation in up to 46% of subclinical or asymptomatic cases¹⁴.

Table 2:

Association between CeD and other conditions

System	Disease	Odds ratio or Hazard ratio
Endocrine	Hypothyroidism	OR 3.38(95% CI 2.88–6.56) ²¹⁰ HR 4.4 (95% CI 3.4–5.6) ²¹¹
	Hyperthyroidism	OR 1.28 (95% CI 0.37–4.46) ²¹⁰ HR 2.9 (95% CI 2.0–4.2) ²¹¹
	Type 1 diabetes	HR 2.4 ^a (95% CI 1.9–3.0) ²¹²
	Addison's disease	HR 11.4 (95% CI 4.4–29.6) ²¹³
Renal	Diabetic nephropathy among type 1 diabetes	HR 1.36 (95% CI 1.23–1.50) ¹²⁸
Skin	Psoriasis	OR 1.64 (95%CI 1.40–1.92) ⁵⁹ OR 3.09 (95% CI 1.92 – 4.97) ⁷⁹
	Urticaria	HR 1.51 (95%CI 1.36 – 1.68) ⁸¹
	Chronic urticaria ^b	HR 1.92 (95% CI 1.48 – 2.48) ⁸¹
	Atopic dermatitis	OR 3.17 (95% CI 1.02–9.82) ²¹⁴
	Rosacea	HR 1.46 (95%CI 1.11–1.93) ²¹⁵
Liver	Primary biliary cholangitis	HR 10.16 (95% CI 2.61–39.49) ²¹⁶
	Primary sclerosing cholangitis	HR 4.46 (95%CI 2.50–7.98) ²¹⁶
Immunology	Selective IgA deficiency	10–20 fold increased risk ^{c217}
Lung	Chronic obstructive pulmonary disease	HR 1.24 (95%CI 1.10–1.38) ¹²¹
Connective tissue disorders	Systemic lupus erythematosus	HR 3.49 (95% CI 2.48 – 4.90) ²¹⁸
	Ehlers-Danlos syndrome	HR 2.43 (95%CI 1.20–4.91) ²¹⁹
Genetic syndromes	Turner syndrome	OR 3.29 (95%CI 1.94–5.56) ²²⁰
	Down's syndrome	OR 6.15 (95%CI 5.09–7.43) ²²¹

^a Risk of subsequent type I diabetes among children and adolescent diagnosed with CeD^b Duration 6 weeks^c 13% of a cohort with CeD and selective IgA deficiency had subclinical CeD