Extraintestinal manifestations of coeliac disease

Daniel A. Leffler, Peter H. R. Green and Alessio Fasano

Abstract | Coeliac disease is a common disorder that can arise at any age and typically presents with a broad spectrum of symptoms. The disease is thought to be underdiagnosed, in part owing to the fact that coeliac disease is often characterized by associated conditions and extraintestinal manifestations that can misdirect and impede diagnosis. Some of these manifestations are direct consequences of autoimmunity, such as dermatitis herpetiformis or gluten ataxia, whereas others are indirectly related to inflammation and/or malabsorption including anaemia, osteoporosis, short stature and delayed puberty. Any organ from the central nervous system to joints, liver or teeth can be affected. In some cases, extraintestinal symptoms are the only clinical manifestations of coeliac disease or occur in conjunction with diarrhoea and malabsorptive symptoms. An increased awareness among medical practitioners of the variety of extraintestinal manifestations of coeliac disease is essential to improve diagnosis and treatment.

Leffler, D. A. *et al. Nat. Rev. Gastroenterol. Hepatol.* **12**, 561–571 (2015); published online 11 August 2015; doi:10.1038/nrgastro.2015.131

Introduction

Coeliac disease is a systemic immune-mediated disorder triggered by dietary gluten in individuals who are genetically susceptible to the disease. Coeliac disease is further characterized by variable clinical presentation, a specific serum autoantibody response and a variable degree of damage in the small intestinal mucosa. HLA molecules DQ2 (90–95%) and DQ8 (5–10%) are associated with coeliac disease and in the continued presence of gluten the disease is self-perpetuating.[1–3] Until the mid-1970s, coeliac disease was described as a malabsorption syndrome during childhood.[4] However, more in-depth studies and increased awareness have shown that the disease can affect individuals of any age and ethnicity, and any organ in the body. Several reports suggest a major shift in the clinical presentation of coeliac disease with extraintestinal symptoms being more prevalent than classical gastrointestinal symptoms.[3,5–9] This Review provides an overview of the pathogenic mechanisms and a rationale for the development of the extraintestinal manifestations that characterize coeliac disease.

Pathophysiology

The pathophysiology of coeliac disease has been extensively investigated in the past 10–15 years.[10–12] Coeliac disease is a unique autoimmune disease that involves an external trigger (dietary gluten) and leads to changes in intestinal permeability, enzyme modification, HLA recognition and innate and adaptive immune responses to gluten peptides via autoantigens, such as tissue transglutaminase 2 (TG2, also known as protein-glutamine γ-glutamyltransferase). Eventually, these changes can lead to coeliac enteropathy (Figure 1). Although traditionally considered a disease of the adaptive immune system, investigators have presented evidence that IL-15 can mediate a rapid activation of the innate immune system.[12] These reports confirm the key role of IL-15 in intestinal mucosal damage after ingestion of gliadin, a component of gluten.[13] After innate immune activation, deamidated gluten peptides bind to HLA-DQ2 or DQ8, resulting in the activation of T cells in the lamina propria. In the intestinal mucosa, active cytotoxic T cells are responsible for the destructive enteropathy that is a hallmark of coeliac disease, whereas in humoral immunity antibodies are produced that target TG2 and gluten peptides. Some of these activated $CD4^+$ T cells are primed in the gut to express the gut-associated homing molecule α4β7 and receptor CCR9 (also known as C-C chemokine receptor type 9) and have been detected in extraintestinal tissues of patients with coeliac disease.[13] This observation suggests that the pathogenesis of extraintestinal coeliac disease symptoms can, at least in part, be attributed to the spreading of the adaptive immune response to tissues other than the intestinal mucosa. This directly related autoimmunity is most established in dermatitis herpetiformis, but might affect other disorders, including neurological disease and fertility disorders.[14,15] Coeliac disease can also lead to extraintestinal manifestations as a result of nutritional consequences of malabsorption and chronic inflammation (Table 1).

The Celiac Centre at Beth Israel Deaconess Medical Centre, 330 Brookline Avenue, Boston, MA 02215, USA (**D.A.L.**). Celiac Disease Centre at Columbia University, 180 Fort Washington Avenue, HP 934, New York, NY 10032, USA (**P.H.R.G.**). Centre for Celiac Research, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA (**A.F.**).

Correspondence to: A.F. afasano@mgh.harvard.edu

Competing interests
D.A.L. has received funding from Alba Therapeutics, Alvine Pharmaceuticals, Coronado Bioscience, Inova diagnostics, Ironwood Pharmaceuticals, Sidney Frank Foundation and Shire Pharmaceuticals. P.H.R.G. has received funding from Alba Therapeutics, Alvine Pharmaceuticals and Immusan. A.F. has received funding from Alba Therapeutics, Inova diagnostics, Mead Johnson Nutrition and Pfizer Pharmaceutical.

Key points

- Coeliac disease is often accompanied by extraintestinal manifestations, which can be the result of aberrant immune responses but also malabsorption
- These concurrent conditions can affect various systems and organs, and include manifestations in the skin, musculoskeletal and central nervous system
- Anaemia, osteoporosis, dermatitis herpetiformis and gluten ataxia are among the most commonly seen characteristics
- In the paediatric population, coeliac disease can lead to severe growth disorders, such as short stature and delayed puberty due to hypogonadism

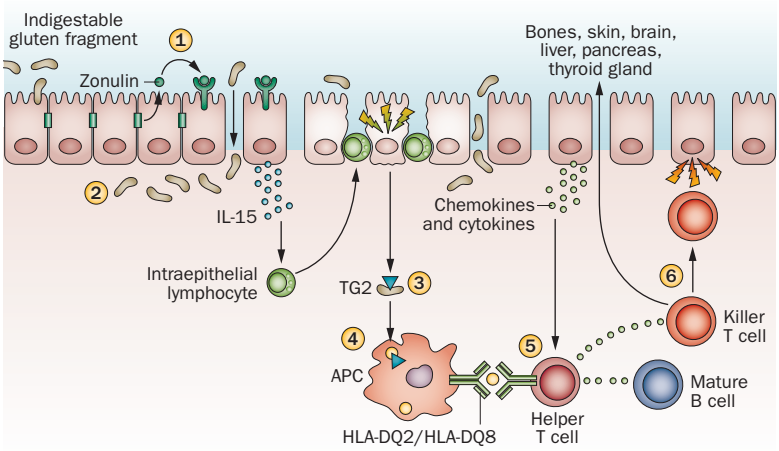

Figure 1 | Extraintestinal manifestations of coeliac disease. Indigestible gluten fragments cause enterocytes to release the protein zonulin, which loosens tight junctions between enterocytes (1). Nonself antigens, including gluten, other food antigens and microorganism components gain access into the lamina propria and activate inflammatory cells to release cytokines (including IL-15) that cause innate immune inflammation (2). The enzyme TG2 released from damaged cells deamidates gluten fragments, making them more adapted to engage HLA DQ2/DQ8 molecules expressed on the surface of antigen presenting cells (3). APCs present the nonself antigens to T_H cells (4). T_H cells initiate killer T cells to directly attack enterocytes (5). Activated inflammatory cells migrate to the intestinal epithelial cells causing local inflammation responsible for gastrointestinal symptoms and/or to other districts where they trigger inflammation responsible for extraintestinal symptoms (6). Abbreviations: APC, antigen-presenting cell; TG2, tissue transglutaminase 2; T_H cells, T helper cells. Permission obtained from Macmillan Publishers Ltd © Fasano, A. *Sci. Am.* **301**, 54–61 (2009).

Extraintestinal manifestations

Anaemia

Anaemia as an extraintestinal manifestation of coeliac disease is the second most frequent mode of presentation in adults, occurring in ~15% of adults with the disorder.[16,17] However, in children (≤18 years of age) coeliac-disease-associated anaemia is less common and accounts for ~3% of individuals, according to a large study conducted in 2011.[18] In this study, recurrent abdominal pain, growth issues and the screening of high-risk groups most commonly led to the diagnosis of coeliac disease in children.[18] In adults, the most common symptom upon presentation is diarrhoea, which develops in ~40% of patients, although some of these patients can have anaemia as well. Overall, ~20% of the patients seen in one centre had anaemia at the time of presentation (17% of men and 22% of women).[19] Iron deficiency is the most commonly recognized cause of anaemia in patients with coeliac disease, followed by folate and vitamin B_{12} deficiencies, which are also common at the time of diagnosis.[19] Each deficiency occurs, in the absence of anaemia, in 33%, 10% and 8% of men and in 19%, 13% and 4% of women, respectively.[19] Macrocytic anaemia is unusual.[19] Malabsorption of nutrients is not the only cause of anaemia in coeliac disease, the chronic inflammatory process in the intestine contributes as well.[20] 'Anaemia of chronic disease' (a form of anaemia associated with inflammation) is seen in ~25% of patients with coeliac disease.[20]

When patients with anaemia as the main reason for presentation in the clinic were compared to those who presented with diarrhoea only, patients with anaemia had evidence of more severe disease.[21] These patients had a higher erythrocyte sedimentation rate, increased anti-TG2 IgA levels, lower cholesterol levels and more severe degrees of villous atrophy and bone disease than patients without anaemia.[21] This finding was surprising because it was expected that those with a diarrhoeal presentation would have a more severe disease. A severity index comparable to the one for IBD is not available for coeliac disease and symptoms such as diarrhoea cannot be used as severity indicators, in contrast to measurable indices such as haemoglobin levels, erythrocyte sedimentation rate and the degree of villous atrophy. Similar findings of severity were reported in a study involving patients with anaemia from India.[22]

The examination of patients with anaemia due to iron deficiency or other nutrient deficiencies for coeliac disease is a useful way to detect the condition, which might otherwise go undiagnosed. In a study from India, 10% of patients with nutritional anaemia had coeliac disease.[23] In the USA, endoscopic evaluation of patients with iron-deficiency anaemia revealed coeliac disease in 8.7% of participants,[24] and in 2.8% in another study.[25] Furthermore, differences are also apparent within populations. For example, coeliac disease is increasingly prevalent in white populations of European descent, as opposed to nonwhite individuals: in one study, 4% of white individuals who were iron-deficient had coeliac disease, compared to none of the iron-deficient, nonwhite individuals.[26]

Guidelines for gastroenterologists in the UK and USA suggest that all patients with iron-deficiency anaemia should be tested for coeliac disease.[27,28] However, no such guidelines have been published for haematologists and a survey revealed little knowledge about the relevance of iron-deficiency anaemia for coeliac disease among haematologists in the USA.[29] Abnormal blood samples with evidence of microcytosis or anisocytosis might prompt a search for iron-deficiency anaemia and coeliac disease. In addition, low levels of HDL or total cholesterol can indicate the presence of coeliac disease in patients with iron-deficiency anaemia.[30,31] Low cholesterol levels probably result from malabsorption, whereas HDL production depends on the generation of apolipoprotein A1 by the intestine, a major protein component of HDL. Another important clue that might indicate the presence of coeliac disease is the failure to respond to oral iron supplementation, compared with a brisk response to intravenous iron supplementation.

Table 1 | Extraintestinal manifestations of coeliac disease

Manifestation	Prevalence	Pathophysiology	Testing and treatment	References
Anaemia	Common	Nutritional deficiencies: iron most frequently followed by folate and vitamin B_{12} Chronic inflammation	Regular testing of haemoglobin and vitamin status recommended	17,19
Reduced bone density	Common	Nutritional, inflammatory, autoimmune	BMD testing recommended within 1 year of diagnosis	30,35
Arthritis	Common	Inflammatory and/or autoimmune	Evaluation of symptomatic individuals	51,52
Dermatitis herpetiformis	Uncommon	Autoimmune: crossreaction of TG2 antibodies with TG3 in skin	Skin biopsy of suspected disease, adjunctive treatment with dapsone	54–56
Eczema or psoriasis	Uncommon	Inflammatory	Consider coeliac disease in severe psoriasis	59,60
Gluten ataxia	Rare	Autoimmune	Coeliac disease testing in idiopathic ataxia	72,74
Autism	Not clearly associated	Unknown	Coeliac disease testing in ASD is reasonable	79,81
Schizophrenia	Not clearly associated	Unknown	Coeliac disease testing not typically recommended	86,90
Peripheral neuropathy	Common	Autoimmune, inflammatory	Coeliac disease testing in unexplained neuropathy	92
Short stature	Common in paediatric populations	Nutritional, hormonal, inflammatory	Coeliac disease testing in growth delay	94,98
Delayed puberty	Uncommon	Nutritional, hormonal, inflammatory	Coeliac disease testing in affected individuals	99
Hepatitis	Common	Inflammatory, autoimmune	LFT testing in patients with coeliac disease, coeliac disease testing in unexplained liver disease	105,106
Cardiovascular manifestations	Not clearly associated	Nutritional, inflammatory	None	119,124
Splenic manifestations	Uncommon	Autoimmune, inflammatory, haemodynamic	Consider vaccination against influenza, pneumococcus	112
Pulmonary manifestations	Rare	Autoimmune	None	114
Renal manifestations	Rare	Autoimmune	None	116
Pancreatic manifestations	Uncommon	Obstructive, inflammatory	Pancreatic exocrine testing in nonresponsive coeliac disease	126,127
Reproductive manifestations including impaired fertility	Uncommon	Nutritional, inflammatory, autoimmune	Coeliac disease testing in unexplained infertility	129,130
Dental	Uncommon	Nutritional, inflammatory	Coeliac disease testing in dental enamel defects	133

Abbreviations: ASD, autism spectrum disorder; BMD, bone mineral density; TG2, tissue transglutaminase 2; TG3, transglutaminase 3; LFT, liver function test.

Musculoskeletal manifestations

Osteopenia and osteoporosis

Reduced bone mineral density is common in both adults and children with coeliac disease, with the exception of those who have been on a gluten-free diet since childhood (Figure 2).[32] This phenomenon occurs in asymptomatic and symptomatic patients,[33] but is more severe in those with gastrointestinal symptoms.[33] Persistent villous atrophy is associated with osteoporosis[34] and an increased fracture risk,[35] although population-based studies in the UK revealed either no[36] or only a minimally increased fracture risk.[37,34] By contrast, the results of a study conducted in the USA indicated an elevated fracture risk in patients with coeliac disease,[38] but in a different study from Argentina fracture was limited to those patients with a classic symptomatic presentation.[39] In a single-centre study, ~10% of patients with coeliac disease were assessed and subsequently diagnosed because of reduced bone density,[17,32] whereas in another study 50% of patients had reduced bone density.[9] The screening of postmenopausal women, who are at high risk of developing reduced bone mineral density, is currently not cost-effective, and an increased incidence of coeliac disease was not evident in this group of individuals in one study.[40] However, we recommend the evaluation of any patient found to have reduced bone mineral density that is not explained by age or other apparent medical conditions. The mechanism of bone

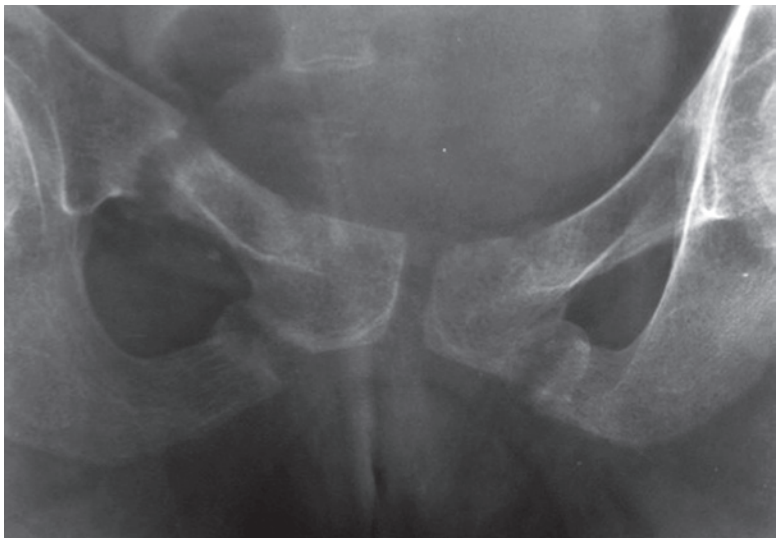

Figure 2 | Osteoporosis as a manifestation of coeliac disease. Radiograph showing classic signs of osteoporosis in a female teenager.

density reduction in coeliac disease is multifactorial. Malabsorption of calcium and vitamin D with associated secondary hyperparathyroidism,[41,42] increased circulating cytokines, misbalanced bone remodelling factors[43] and autoimmune factors might contribute to coeliac-disease-associated reduced bone density.[44,45] The standard treatment for these patients is a gluten-free diet, combined with repletion of calcium and vitamin D to improve bone mass.[46] Data on drug therapies for coeliac disease-related osteopenia are limited but one study suggests that zoledronic acid is not effective as an adjuvant to the gluten-free diet.[47]

Arthritis

Arthritis might be more common in patients with coeliac disease than previously considered.[48] In a study from 1985, an association between seronegative arthritis and coeliac disease was found, based on the observation that patients who initially presented with prominent arthritis markedly improved after coeliac disease had been diagnosed and they commenced a gluten-free diet.[49] Similarly, an association between arthritis in childhood and coeliac disease was demonstrated,[50,51] although not confirmed, in a study from the Netherlands.[52] Among adults, bone scintigraphy detected sacroiliitis in 60% of patients with coeliac disease.[53] In another study that included 200 patients with coeliac disease, arthritis was present in 26% of individuals compared with only 7.5% in a control group, the arthritis being both peripheral and central.[54] More population-based studies are needed to assess the relationship of coeliac disease with arthritis.

Skin manifestations

Dermatitis herpetiformis

Dermatitis herpetiformis was one of the first well-established extraintestinal manifestations of coeliac disease.[55,56] Clinically, dermatitis herpetiformis presents as intensely pruritic papules and vesicles, primarily on extensor surfaces such as elbows, knees and buttocks or the lower back (Figure 3a). Lesions can be limited to small areas or are diffused over the whole body, and can be present only intermittently, such that only excoriations (abrasive skin lesions) in characteristic areas might be present during a clinical exam.[56] For this reason, clinicians should elicit any reports of chronic pruritus from patients with coeliac disease and family members, and recommend dermatological evaluation in these patients. Dermatitis herpetiformis is diagnosed when standard microscopic examination of skin biopsy samples reveals granular IgA deposits (Figure 3b) and neutrophil infiltrates in the papillary dermis.[56] In the exact region of a lesion or excoriated area, the pathological features of dermatitis herpetiformis are disrupted and biopsy samples will only demonstrate nonspecific inflammatory changes, which is a major diagnostic issue. Ideally, a skin biopsy should therefore be performed on normal appearing skin just adjacent to an affected area.[57,58]

Dermatitis herpetiformis is considered to be a directly immune-mediated extraintestinal manifestation of coeliac disease.[56] Active coeliac disease results in the generation of antibodies against the endogenous protein TG2, which is the main intestinal isoform of the TG family of enzymes and closely related to TG3, the primary TG found in the skin.[59] In dermatitis herpetiformis, circulating antibodies, produced by the intestinal immune reaction to gluten, bind to TG3 in the skin; once bound, these antibodies trigger further inflammation, which leads to inflammatory dermatitis (Figure 3).[56] Whereas nearly all individuals with active coeliac disease produce antibodies against TG2, only a minority develops dermatitis herpetiformis—the reasons for this phenomenon are still unclear. Nevertheless, dermatitis herpetiformis should resolve after patients have been treated for coeliac disease by switching to a gluten-free diet and the dermatological response often correlates with a decrease in IgA-TG2 titres.[58] Resolution of dermatitis herpetiformis can take months or longer on a gluten-free diet and pharmacological therapy with dapsone or sulphapyridine is often necessary to rapidly improve symptoms.[58] Even if dermatitis herpetiformis might be the only clinical manifestation of coeliac disease, a gluten-free diet is still considered standard of care and the goal should be to avoid long-term use of medication in patients.[58] If ongoing symptoms prevent the termination of dapsone or sulphapyridine treatment, consistent with nonresponsive coeliac disease, the patient should be evaluated for ongoing gluten exposure.[60]

Eczema and psoriasis

Neither eczema nor psoriasis are considered pathogenically connected with coeliac disease. However, patients with coeliac disease are at a moderately increased risk of psoriasis.[61] In addition, psoriasis activity generally improves in patients with coeliac disease after the adoption of a gluten-free diet.[62–64] No recommendations for coeliac disease screening in individuals with eczema or psoriasis exist to date, but in our opinion, testing

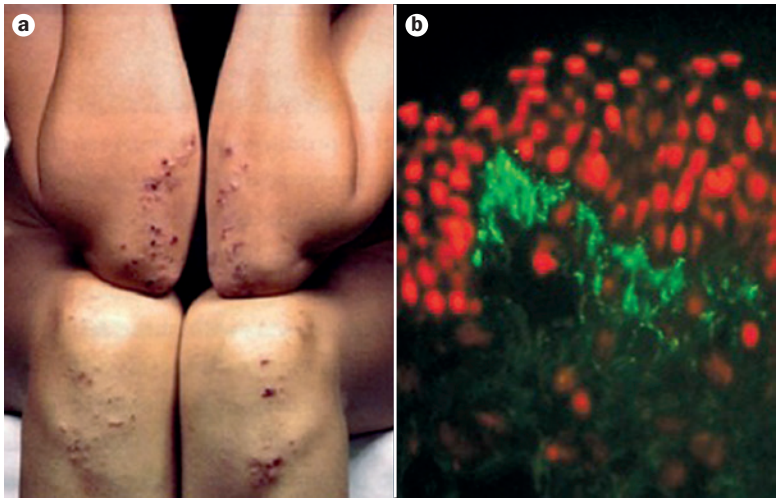

Figure 3 | Dermatitis herpetiformis. **a** | Classical presentation with erythematous or excoriated papules with crusts and urticarial lesions bilaterally distributed on elbows and knees. **b** | Immunofluorescent staining of a lesion. Note the granular deposits of the immunoglobulin A–fluorescein labelled complex (green) at the dermal-epidermal junction of the skin (papillary dermis).

should be considered in patients with unusually severe or difficult-to-treat psoriasis.

Nonspecific skin conditions

Although less well-characterized than other skin disorders, patients with coeliac disease frequently report nonspecific integument issues, including dry skin, easy bruising, brittle nails and thinning hair.[65] These symptoms do not have an obvious autoimmune aetiology but often respond to vitamin supplementation and overall improvement in nutritional status.[66] Iron, zinc and fat-soluble vitamins are most often deficient in patients with newly diagnosed coeliac disease and repletion can accelerate clinical improvement.[66] Alopecia areata can be a separate, coexisting autoimmune disorder in adults and children with coeliac disease, although it is less common.[67] This condition does not typically respond to a gluten-free diet and might be progressive.[68] Consequently, patients with coeliac disease and severe hair loss should be promptly referred to a dermatologist for evaluation.

Neurological or behavioural manifestations

Gluten ataxia

Gluten ataxia, a lack of coordination of muscle movements that can affect balance, gait, extremity and eye movements, is one of the most frequent (~50%) neurological presentations of coeliac disease.[69] Typically, gluten ataxia originates in the cerebellum (cerebellar ataxia), but it might also be encountered in association with myoclonus (sudden muscle contractions). Clinical presentation varies from slow-onset in middle-aged individuals to rapidly progressive forms.[69] Most patients (>60%) with gluten ataxia have gait and limb ataxia, often in combination with nystagmus (involuntary eye movement), which are all common characteristics of cerebellar ataxia.[69] Sensorimotor axonal neuropathy is also frequently found in patients with gluten ataxia (~45%); however, gastrointestinal symptoms are unusual (<10% of patients).[69] Cerebellar atrophy is seen in ~60% of patients, whereas those without atrophy usually have abnormal results upon proton NMR spectroscopy.[69]

Gluten ataxia is now considered an autoimmune condition in the gluten-related spectrum of diseases, whereas several years ago it was classified as idiopathic ataxia.[70] The autoimmune reaction in gluten ataxia is mediated by antibody crossreactivity between Purkinje cells and gluten proteins,[15,71,72] and a widespread perivascular deposition of TG2 antibodies in the brain.[72] Antibodies against TG6, a TG primarily expressed in the brain, have been detected in patients with gluten ataxia.[73–75] In addition, serum from patients with gluten ataxia and anti-TG immunoglobulins, which were derived using phage display technology, can trigger ataxia when injected intraventricularly into mice.[76] After having been diagnosed with gluten ataxia, patients are advised to adhere to a gluten-free diet. However, the improvement of ataxia symptoms can be variable and depends on the duration of the disease, as loss of Purkinje cells and detectable atrophy are not reversible. Early diagnosis and prompt treatment are therefore important to minimize harmful consequences and prevent the progression of the disease. In gluten ataxia, antibodies against TG2 occur in ~50% of patients, often in lower titres than those found in patients with coeliac disease.[76] These antibodies can be of the IgG class. Antibodies against TG2 and TG6 combined are found in 85% of patients with cerebellar ataxia, who are also positive for anti-gliadin antibodies.[77] Further prospective studies are needed to determine the best diagnostic approach for the identification of patients with gluten ataxia.

Currently, we recommend that patients with cerebellar ataxia should be screened for coeliac disease and the presence of anti-gliadin (IgA and IgG) and anti-TG6 antibodies should be assessed. If no other cause of cerebellar ataxia is determined and there is positivity for any of these antibodies, a strict gluten-free diet should be recommended. If patients adhere to the gluten-free diet and antibody titres subsequently decrease in conjunction with marked improvement or stabilization of the ataxia, a diagnosis of gluten ataxia is supported.

Autism

One of the major developmental disabilities in the USA is a group of disorders called autism spectrum disorders (ASD), now affecting as many as 1 in 68 children in the USA, according to the 2012 estimates from the Centre for Disease Control.[78] Typically, these chronic disorders start before the age of 3 years and demonstrate an extensive spectrum of symptoms with repetitive behaviours, social and language impairment. Hyperactivity, aggression, anxiety and depression aggravate the functional disability, which can be irregular, and therapies demonstrate varying success.[79] Case reports have suggested a positive association between coeliac disease and ASD.[80,76] The use of diets that do not contain gluten and casein has, therefore, received increased interest, particularly

among parents of children with ASD. However, aside from individual case studies, systematic research findings have been contradictory and widely challenged,[81–83] and in many studies no association between ASD and coeliac disease has been identified.[82–84] For example, anti-gliadin but not coeliac-specific antibodies have been found in patients with ASD.[85] In 2013, a nationwide review analysis of patients in Sweden with coeliac-disease-associated small intestinal enteropathy and ASD revealed a markedly increased risk of ASD in individuals with a normal mucosa but positive coeliac disease serology test results.[86] However, the investigators did not find an association between prior ASD and subsequent coeliac disease.[86]

Schizophrenia

In the 1960s, investigators suggested an association between schizophrenia and coeliac disease.[87] In a double-blind, controlled trial, individuals with schizophrenia who were based in a secure hospital ward and received gluten-free or gluten-load diets demonstrated changes in the symptoms of their neurological disorder when on a gluten-free diet.[88] In another study conducted in 1981, a 5-week gluten challenge showed no deterioration in clinical status, as measured according to the Brief Psychiatric Rating Scale.[89] In a third study published in 1982, a comparison of gluten-free with gluten-enriched diets discovered no differences in an array of psychological tests.[90]

When serological testing was performed on samples collected and stored from patients in the clinical antipsychotic trials of intervention effectiveness (CATIE), 5.5% of the individuals with schizophrenia had elevated levels of IgA anti-TG2 antibodies (compared with 0.8% in healthy controls).[91] Strikingly, 23% of patients with schizophrenia were found to be positive for anti-gliadin antibodies (native gliadin) compared with 3% in the healthy group.[91] However, the prevalence of coeliac disease among patients with schizophrenia was similar to the general population, which correlates with data published by other researchers.[92] In a follow-up study on the same group of patients, the increase of anti-TG2 antibodies in patients with schizophrenia was mainly associated with the presence of anti-TG6 antibodies.[93] A high prevalence of antibodies against TG and gliadin has been reported in other studies.[92,94] Large, controlled dietary intervention studies need to be performed, especially in those individuals that seem to have mounted an immune response against gluten.

Other neuropsychiatric associations

Anxiety, depression and attention-deficit/hyperactivity disorders have also been associated with coeliac disease.[95,96] However, the cause and magnitude of these associations are unclear and current evidence does not support routine coeliac disease testing in individuals with these disorders. However, health care providers should pay particular attention to symptoms that might suggest concurrent coeliac disease. In addition, patients with coeliac disease often experience symptoms related to peripheral neuropathy. According to a report from 2012,[97] 38.9% of patients with coeliac disease met criteria for peripheral neuropathy, compared with 20.5% in the healthy group ($P<0.001$). In a multiple logistic regression analysis of these data, the odds of peripheral neuropathy after adjusting for age, gender, diabetes, vitamin B_{12} deficiency and cancer history were increased for coeliac disease (OR 2.51, 95% CI 1.82–3.47).[97]

Paediatric extraintestinal manifestations

Short stature

Growth disorders, including short stature, are well-documented manifestations of coeliac disease and might represent the only clinical signs of the disease.[98] Coeliac disease is present in up to 8.3% of children evaluated for short stature.[99,100] The mechanism that leads to short stature in patients with coeliac disease is unclear but considered by most investigators to be multifactorial. Decreases in serum levels of insulin-like growth factor 1 and insulin-like growth factor binding protein have been implicated.[101] Nutritional deficiencies and impaired stimulated growth hormone secretion have also been implicated in coeliac disease.[102] In addition to the involvement of the growth hormone–insulin-like growth factor 1 axis, a role for ghrelin has been proposed.[103] After initiation of a gluten-free diet, a considerable increase in growth velocity might be seen, especially within the first year after diagnosis.[102] Target height is usually reached within 3 years after diagnosis, but some patients do not catch up in growth with healthy children of the same age, possibly related to accelerated bone maturation, which occurs in parallel with rapid increases in growth velocity.[102]

Delayed puberty

In addition to the classic gastrointestinal form, children with coeliac disease can also present with a delayed onset of puberty due to hypogonadism.[104] Delayed menarche has been documented in girls with coeliac disease, but not in those on a gluten-free diet.[104] Androgen resistance, evidenced by reduced serum levels of dihydrotestosterone and increased serum levels of luteinizing hormone has been implicated in the development of coeliac disease in boys.[104] The mechanism underpinning delayed puberty associated with coeliac disease has not been definitely established. Potential explanations include the possibility that autoimmune factors, directed against hormones, receptors or endocrine organs, and the effect of the overall increased inflammatory milieu can delay puberty. In addition, malabsorption of micronutrients that are essential for sex hormone production, carriers or receptors can play a part in the delayed onset.[104]

Organ-specific extraintestinal manifestations

Liver

Hepatitis is commonly associated with active coeliac disease, but in clinical practice often remains unrecognized or is attributed to other causes such as fatty liver disease. In some studies, up to 10% of patients with unexplained or cryptogenic elevations in alanine aminotransferase or aspartate aminotransferase levels had coeliac disease.[105,106] Increased levels of liver function

enzymes can be observed in nearly half of the patients with coeliac disease at diagnosis.[107–112] Although these abnormalities are generally subclinical, coeliac-disease-related liver injury can progress to cirrhosis and liver failure.[113] In epidemiological data, patients with coeliac disease have a twofold to sixfold increased risk of future liver disease, and an eightfold increased risk of death from liver cirrhosis.[111,114] For these reasons, clinical guidelines recommend an initial screening for abnormal liver function in newly diagnosed patients with coeliac disease and routine liver function tests as part of coeliac disease follow-up.[28,115,116] The pathogenesis of coeliac-disease-related liver injury is unclear. Patients with coeliac disease have higher rates of classic autoimmune liver disorders including autoimmune hepatitis and primary biliary cirrhosis than patients without the disease.[96] However, ~75% of patients with elevated liver enzymes in coeliac disease do not have a separate disorder and these individuals respond well to gluten withdrawal.[112] Whether hepatitis in these cases originates from crossreacting autoantibodies (as in dermatitis herpetiformis) or is initiated by a transfer of cytokines and other inflammatory mediators from the small bowel through the portal vein into the liver, is unknown.[117]

Spleen

Active coeliac disease affects the immune system as a whole, a phenomenon most clearly confirmed by evaluation of spleen size and function. The association between coeliac disease and hyposplenism has been recognized since 1970.[118] Up to 30% of patients with coeliac disease are functionally hyposplenic or asplenic at diagnosis.[119] Potential aetiologies of this manifestation include haemodyamic changes, such as higher blood velocity and flow after a meal and generally lower intrasplenic resistance indexes,[120] or might be a sign of general reticular–endothelial dysfunction, especially as the coexistence of other autoimmune disorders increases the risk of impaired spleen function.[119] Impaired spleen function is also assumed to result in an elevated risk of infectious complications, in particular involving encapsulated microorganisms, which are often found in untreated or newly diagnosed patients with coeliac disease.[121] Currently, none of the clinical guidelines recommend the evaluation of spleen function in patients with coeliac disease.[8,28,122] However, vaccination against influenza and pneumonia is generally advised and evaluation should be considered in patients with coeliac disease and a history of major infections.[119]

Lungs

The lungs are rarely involved in coeliac disease but pulmonary manifestations can be life-threatening. The most common pulmonary conditions seen in coeliac disease are of an infectious nature. Unique to coeliac disease is Lane–Hamilton syndrome—a rare and poorly studied condition, in which coeliac disease presents with pulmonary haemosiderosis, generally manifesting as dyspnoea (shortness of breath) and/or haemoptysis (coughing of blood originating from the respiratory tract).[123] Radiological findings typically include dependent opacities and are nonspecific to coeliac disease, as is bronchoscopy.[123] The aetiology of pulmonary manifestations of coeliac disease is unknown but thought to be related to crossreactivity between anti-TG2 antibodies from gut and lungs.[123] Therapy is generally supportive and symptoms can be expected to resolve with time if the patient adheres to a gluten-free diet.[123]

Kidney

Epidemiological data has been interpreted to suggest that coeliac disease is associated with an increased risk of glomerulonephritis and end-stage renal disease.[124,125] However, clinically relevant renal disease is rarely an issue in patients with coeliac disease, except for the frequency of occurrence expected in patients with comorbid type 1 diabetes mellitus.[126] Currently, neither adult nor paediatric clinical guidelines recommend routine renal evaluation in individuals with coeliac disease.[8,122]

Heart

The concept that coeliac disease might modulate cardiovascular disease risk was first raised by Whorwell *et al.*,[127] who found a 40% reduction in mortality owing to ischaemic heart disease in people with diagnosed coeliac disease compared with the general population. This study proposed an apparent protective effect of coeliac disease as a result of malabsorption of dietary lipids. In a population-based study from the UK, the investigators reported lower rates of hypertension and hyperlipidaemia in patients with coeliac disease than in the general population.[128] However, in this study the risk of stroke and coronary artery disease were similar to the control population and the reported prevalence of hypertension and hyperlipidaemia in the control group were substantially higher than age-adjusted rates in populations of the UK and USA.[129] Interestingly, according to a study conducted in the USA, type 2 diabetes mellitus and metabolic syndrome are less prevalent in adults with coeliac disease before and after gluten-free diet initiation, compared with the general population and matched controls, and the risk does not increase after coeliac disease diagnosis, despite a rise in BMI.[130] Although coeliac disease is associated with myocarditis,[131] blood flow alterations[132] and atrial fibrillation[133] in rare cases, the overall cardiovascular risk does not seem to be elevated in coeliac disease.

Pancreas

Coeliac disease has been associated with multiple forms of pancreatic disease, including acute pancreatitis, chronic pancreatitis and pancreatic exocrine insufficiency.[134,135] In multiple case reports and small case studies, coeliac disease has been described as a cause of recurrent acute pancreatitis and often responds to a gluten-free diet.[134,136] The aetiology of recurrent acute pancreatitis in these individuals seems to be related to inflammation of the duodenum resulting in partial or transient sphincter of Oddi obstruction, which can be resolved by a sphincterotomy.[134] Beyond acute pancreatitis, chronic pancreatitis is more common in individuals with coeliac disease,[135]

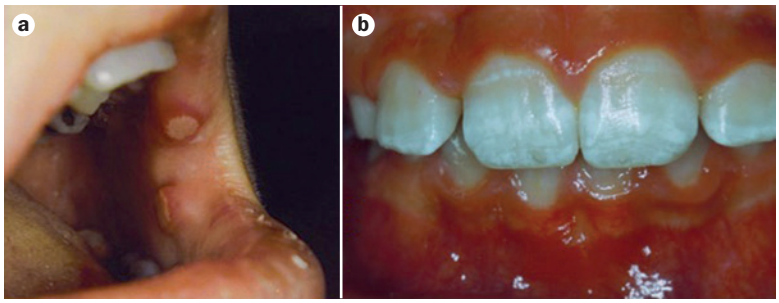

Figure 4 | Oral defects as a manifestation of coeliac disease. **a** | Aphthous ulcers might represent the only visible clinical manifestation of the disease. **b** | Dental enamel defects on permanent teeth are typically symmetric.

although aetiology and clinical relevance of this association remain unclear. Pancreatic exocrine insufficiency has been recognized by clinicians as a potential cause of non-responsive coeliac disease in multiple studies.[137,138] This insufficiency seems to be related to the intestinal para–endocrine function, as faecal elastase levels are decreased in patients with villous atrophy.[138] The prevalence of clinically relevant pancreatic exocrine insufficiency in patients with coeliac disease is unknown, but measurements of faecal elastase levels should be considered in any patient with chronic diarrhoea, after active coeliac disease and microscopic colitis have been excluded.[60]

Reproductive health

The effect of coeliac disease on reproductive health is both diverse and controversial. Studies suggest that anti-TG2 antibodies can directly interact with the placenta, inhibiting placental function and nutrient transfer.[14,139] This effect was perhaps best studied in individuals with IBD, in which chronic inflammation is associated with poor pregnancy outcomes.[140] Moreover, even subtle nutritional deficiencies can have considerable adverse effects on fertility and pregnancy.[131] Although the overall contribution of coeliac disease to reproductive complications is unclear, investigators suggest that women with coeliac disease might have an increased risk of miscarriage (with an OR of up to 1.39).[4]

Oral cavity

The main oral manifestations of coeliac disease include aphthous ulcers (Figure 4a), which are seen in many inflammatory gastrointestinal disorders, and dental enamel defects.[141,142,132] Aphthous ulcers are often present in the setting of active coeliac disease and might be severe, but generally improve with adoption of the gluten-free diet.[143] Defects in dental enamel occur when coeliac disease affects children during dental development; generally before they are 7 years of age (Figure 4b).[141] The aetiology is probably multifactorial owing to immune-mediated damage and nutritional disturbances.[143] Dental enamel defects might be the only clinical manifestation of coeliac disease and therefore should, in an ideal scenario, prompt coeliac disease testing.

Conclusions

The modern definition of coeliac disease was given in 1888 by Samule Gee:[144] "There is a kind of chronic indigestion which is met with in persons of all ages […] Signs of the disease are yielded by the fæces; being loose […] pale in colour, as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; […] the food having undergone putrefaction rather than concoction […] if the patient can be cured at all, it must be by means of diet". This definition outlines malabsorption and gastrointestinal symptoms as the main clinical presentation of coeliac disease. However, coeliac disease is clearly a systemic disorder that does not spare any tissue or organ in the body. The pathogenesis of extraintestinal symptoms can sometimes be explained by malabsorption secondary to the enteropathy that characterized the disease (for example, anaemia), whereas other symptoms (including those involving the skin, brain and musculoskeletal system) can be traced to immune reactions typical for autoimmune processes in coeliac disease. Gaining more insights into the mechanisms that control these symptoms might be instrumental for the prevention of future complications and to further elucidate the processes involved in autoimmune diseases for which no treatment is currently available.

Review criteria

A search for original articles published between 1985 and 2015 and focusing on extraintestinal manifestations of coeliac disease was performed in MEDLINE and PubMed. The search terms used were "coeliac", "celiac", "extraintestinal", "auto-antibodies", "diagnosis" and "systemic", alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

1. Fasano, A. & Catassi, C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* **120**, 636–651 (2001).
2. Green, P. H. & Cellier, C. Celiac disease. *N. Engl. J. Med.* **357**, 1731–1743 (2007).
3. Reilly, N. R., Fasano, A. & Green, P. H. Presentation of celiac disease. *Gastrointest. Endosc. Clin. N. Am.* **22**, 613–621 (2012).
4. Tersigni, C. *et al.* Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms. *Hum. Reprod. Update* **20**, 582–593 (2014).
5. Castillo, N. E., Theethira, T. G. & Leffler, D. A. The present and the future in the diagnosis and management of celiac disease. *Gastroenterol. Rep. (Oxf.)* **3**, 3–11 (2015).
6. Reilly, N. R. & Green, P. H. Epidemiology and clinical presentations of celiac disease. *Semin. Immunopathol.* **34**, 473–478 (2012).
7. Bhattacharya, M., Kapoor, S. & Dubey, A. P. Celiac disease presentation in a tertiary referral centre in India: current scenario. *Indian J. Gastroenterol.* **32**, 98–102 (2013).
8. Bai, J. C. *et al.* World Gastroenterology Organisation global guidelines on celiac disease. *J. Clin. Gastroenterol.* **47**, 121–126 (2013).
9. Volta, U., Caio, G., Stanghellini, V. & De Giorgio, R. The changing clinical profile of celiac disease: a 15-year experience (1998–2012) in an Italian referral center. *BMC Gastroenterol.* **14**, 194 (2014).
10. Fasano, A. Surprises from celiac disease. *Sci. Am.* **301**, 54–61 (2009).
11. Lionetti, E. & Catassi, C. New clues in celiac disease epidemiology, pathogenesis, clinical manifestations, and treatment. *Int. Rev. Immunol.* **30**, 219–231 (2011).
12. Abadie, V., Sollid, L. M., Barreiro, L. B. & Jabri, B. Integration of genetic and immunological insights into a model of celiac disease pathogenesis. *Annu. Rev. Immunol.* **29**, 493–525 (2011).

13. Antvorskov, J. C., Josefsen, K., Engkilde, K., Funda, D. P. & Buschard, K. Dietary gluten and the development of type 1 diabetes. *Diabetologia* **57**, 1770–1780 (2014).
14. Anjum, N., Baker, P. N., Robinson, N. J. & Aplin, J. D. Maternal celiac disease autoantibodies bind directly to syncytiotrophoblast and inhibit placental tissue transglutaminase activity. *Reprod. Biol. Endocrinol.* **7**, 16 (2009).
15. Hadjivassiliou, M. *et al.* Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase. *Ann. Neurol.* **64**, 332–343 (2008).
16. Halfdanarson, T. R., Litzow, M. R. & Murray, J. A. Hematologic manifestations of celiac disease. *Blood* **109**, 412–421 (2007).
17. Rampertab, S. D., Pooran, N., Brar, P., Singh, P. & Green, P. H. Trends in the presentation of celiac disease. *Am. J. Med.* **119**, 355.e9–e14 (2006).
18. Reilly, N. R. *et al.* Celiac disease in normal-weight and overweight children: clinical features and growth outcomes following a gluten-free diet. *J. Pediatr. Gastroenterol. Nutr.* **53**, 528–531 (2011).
19. Harper, J. W., Holleran, S. F., Ramakrishnan, R., Bhagat, G. & Green, P. H. Anemia in celiac disease is multifactorial in etiology. *Am. J. Hematol.* **82**, 996–1000 (2007).
20. Bergamaschi, G. *et al.* Anemia of chronic disease and defective erythropoietin production in patients with celiac disease. *Haematologica* **93**, 1785–1791 (2008).
21. Abu Daya, H., Lebwohl, B., Lewis, S. K. & Green, P. H. Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. *Clin. Gastroenterol. Hepatol.* **11**, 1472–1477 (2013).
22. Singh, P., Arora, S. & Makharia, G. K. Presence of anemia in patients with celiac disease suggests more severe disease. *Indian J. Gastroenterol.* **33**, 161–164 (2014).
23. Kavimandan, A. *et al.* Prevalence of celiac disease in nutritional anemia at a tertiary care center. *Indian J. Gastroenterol.* **33**, 114–118 (2014).
24. Grisolano, S. W. *et al.* The usefulness of routine small bowel biopsies in evaluation of iron deficiency anemia. *J. Clin. Gastroenterol.* **38**, 756–760 (2004).
25. Karnam, U. S., Felder, L. R. & Raskin, J. B. Prevalence of occult celiac disease in patients with iron-deficiency anemia: a prospective study. *South Med. J.* **97**, 30–34 (2004).
26. Murray, J. A. *et al.* Association between celiac disease and iron deficiency in Caucasians, but not non-Caucasians. *Clin. Gastroenterol. Hepatol.* **11**, 808–814 (2013).
27. Goddard, A. F., James, M. W., McIntyre, A. S. & Scott, B. B. Guidelines for the management of iron deficiency anaemia. *Gut* **60**, 1309–1316 (2011).
28. Rubio-Tapia, A. *et al.* ACG clinical guidelines: diagnosis and management of celiac disease. *Am. J. Gastroenterol.* **108**, 656–676 (2013).
29. Smukalla, S., Lebwohl, B., Mears, J. G., Leslie, L. A. & Green, P. H. How often do hematologists consider celiac disease in iron-deficiency anemia? Results of a national survey. *Clin. Adv. Hematol. Oncol.* **12**, 100–105 (2014).
30. Abu Daya, H., Lebwohl, B., Smukalla, S., Lewis, S. K. & Green, P. H. Utilizing HDL levels to improve detection of celiac disease in patients with iron deficiency anemia. *Am. J. Gastroenterol.* **109**, 769–770 (2014).
31. Ciacci, C. *et al.* Low plasma cholesterol: a correlate of nondiagnosed celiac disease in adults with hypochromic anemia. *Am. J. Gastroenterol.* **94**, 1888–1891 (1999).
32. Bianchi, M. L. & Bardella, M. T. Bone in celiac disease. *Osteoporos. Int.* **19**, 1705–1716 (2008).
33. Mazure, R. *et al.* Bone mineral affection in asymptomatic adult patients with celiac disease. *Am. J. Gastroenterol.* **89**, 2130–2134 (1994).
34. Valdimarsson, T., Toss, G., Ross, I., Lofman, O. & Strom, M. Bone mineral density in coeliac disease. *Scand. J. Gastroenterol.* **29**, 457–461 (1994).
35. Lebwohl, B., Michaelsson, K., Green, P. H. & Ludvigsson, J. F. Persistent mucosal damage and risk of fracture in celiac disease. *J. Clin. Endocrinol. Metab.* **99**, 609–616 (2014).
36. Thomason, K., West, J., Logan, R. F., Coupland, C. & Holmes, G. K. Fracture experience of patients with coeliac disease: a population based survey. *Gut* **52**, 518–522 (2003).
37. Logan, R. & West, J. Risk of fracture in coeliac disease. *Gut* **52**, 1532 (2003).
38. Jafri, M. R. *et al.* Long-term fracture risk in patients with celiac disease: a population-based study in Olmsted County, Minnesota. *Dig. Dis. Sci.* **53**, 964–971 (2008).
39. Moreno, M. L. *et al.* Stratification of bone fracture risk in patients with celiac disease. *Clin. Gastroenterol. Hepatol.* **2**, 127–134 (2004).
40. Gonzalez, D. *et al.* Is it necessary to screen for celiac disease in postmenopausal osteoporotic women? *Calcif. Tissue Int.* **71**, 141–144 (2002).
41. Di Stefano, M. *et al.* Bone mass and metabolism in dermatitis herpetiformis. *Dig. Dis. Sci.* **44**, 2139–2143 (1999).
42. Corazza, G. R. *et al.* Bone mass and metabolism in patients with celiac disease. *Gastroenterology* **109**, 122–128 (1995).
43. Larussa, T. *et al.* Bone mineralization in celiac disease. *Gastroenterol. Res. Pract.* **2012**, 198025 (2012).
44. Sugai, E. *et al.* Bone-specific antibodies in sera from patients with celiac disease: characterization and implications in osteoporosis. *J. Clin. Immunol.* **22**, 353–362 (2002).
45. Riches, P. L. *et al.* Osteoporosis associated with neutralizing autoantibodies against osteoprotegerin. *N. Engl. J. Med.* **361**, 1459–1465 (2009).
46. Meyer, D., Stavropolous, S., Diamond, B., Shane, E. & Green, P. H. Osteoporosis in a north american adult population with celiac disease. *Am. J. Gastroenterol.* **96**, 112–119 (2001).
47. Kumar, M. *et al.* Effect of zoledronic acid on bone mineral density in patients of celiac disease: a prospective, randomized, pilot study. *Indian J. Med. Res.* **138**, 882–887 (2013).
48. Ghozzi, M. *et al.* Screening for celiac disease, by endomysial antibodies, in patients with unexplained articular manifestations. *Rheumatol. Int.* **34**, 637–642 (2014).
49. Bourne, J. T. *et al.* Arthritis and coeliac disease. *Ann. Rheum. Dis.* **44**, 592–598 (1985).
50. Lepore, L. *et al.* Prevalence of celiac disease in patients with juvenile chronic arthritis. *J. Pediatr.* **129**, 311–313 (1996).
51. Maki, M. *et al.* Reticulin antibody, arthritis, and coeliac disease in children. *Lancet* **1**, 479–480 (1988).
52. George, E. K. *et al.* Juvenile chronic arthritis and coeliac disease in The Netherlands. *Clin. Exp. Rheumatol.* **14**, 571–575 (1996).
53. Usai, P. *et al.* Adult celiac disease is frequently associated with sacroiliitis. *Dig. Dis. Sci.* **40**, 1906–1908 (1995).
54. Lubrano, E. *et al.* The arthritis of coeliac disease: prevalence and pattern in 200 adult patients. *Br. J. Rheumatol.* **35**, 1314–1318 (1996).
55. Marks, J., Shuster, S. & Watson, A. J. Small-bowel changes in dermatitis herpetiformis. *Lancet* **2**, 1280–1282 (1966).
56. Zone, J. J. Skin manifestations of celiac disease. *Gastroenterology* **128**, S87–S91 (2005).
57. Bolotin, D. & Petronic-Rosic, V. Dermatitis herpetiformis. Part, I. Epidemiology, pathogenesis, and clinical presentation. *J. Am. Acad. Dermatol.* **64**, 1017–1024 (2011).
58. Bolotin, D. & Petronic-Rosic, V. Dermatitis herpetiformis. Part, I. I. Diagnosis, management, and prognosis. *J. Am. Acad. Dermatol.* **64**, 1027–1033 (2011).
59. Jaskowski, T. D. *et al.* IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis and pediatric celiac disease. *J. Invest. Dermatol.* **129**, 2728–2730 (2009).
60. Leffler, D. A. *et al.* Etiologies and predictors of diagnosis in nonresponsive celiac disease. *Clin. Gastroenterol. Hepatol.* **5**, 445–450 (2007).
61. Ludvigsson, J. F., Lindelof, B., Zingone, F. & Ciacci, C. Psoriasis in a nationwide cohort study of patients with celiac disease. *J. Invest. Dermatol.* **131**, 2010–2016 (2011).
62. Michaelsson, G. *et al.* Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet. *Br. J. Dermatol.* **142**, 44–51 (2000).
63. Woo, W. K. *et al.* Coeliac disease-associated antibodies correlate with psoriasis activity. *Br. J. Dermatol.* **151**, 891–894 (2004).
64. Buxton, J. L. *et al.* Multiple measures of adiposity are associated with mean leukocyte telomere length in the northern Finland birth cohort 1966. *PLoS One* **9**, e99133 (2014).
65. Collin, P. & Reunala, T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. *Am. J. Clin. Dermatol.* **4**, 13–20 (2003).
66. Theethira, T. G., Dennis, M. & Leffler, D. A. Nutritional consequences of celiac disease and the gluten-free diet. *Expert Rev. Gastroenterol. Hepatol.* **8**, 123–129 (2014).
67. Corazza, G. R. *et al.* Celiac disease and alopecia areata: report of a new association. *Gastroenterology* **109**, 1333–1337 (1995).
68. Bardella, M. T. *et al.* Alopecia areata and coeliac disease: no effect of a gluten-free diet on hair growth. *Dermatology* **200**, 108–110 (2000).
69. Hadjivassiliou, M. *et al.* Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* **126**, 685–691 (2003).
70. Hadjivassiliou, M. *et al.* Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. *Lancet* **352**, 1582–1585 (1998).
71. Abele, M. *et al.* The aetiology of sporadic adult-onset ataxia. *Brain* **125**, 961–968 (2002).
72. Cooke, W. T. & Smith, W. T. Neurological disorders associated with adult coeliac disease. *Brain* **89**, 683–722 (1966).
73. Hadjivassiliou, M. *et al.* The humoral response in the pathogenesis of gluten ataxia. *Neurology* **58**, 1221–1226 (2002).
74. Korponay-Szabo, I. R. *et al. In vivo* targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. *Gut* **53**, 641–648 (2004).
75. Hadjivassiliou, M. *et al.* Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. *Neurology* **66**, 373–377 (2006).
76. Boscolo, S. *et al.* Gluten ataxia: passive transfer in a mouse model. *Ann. N. Y. Acad. Sci.* **1107**, 319–328 (2007).

77. Hadjivassiliou, M., Sanders, D. S., Woodroofe, N., Williamson, C. & Grunewald, R. A. Gluten ataxia. *Cerebellum* **7**, 494–498 (2008).
78. Centers for Disease Control and Prevention. *Autism Spectrum Disorder (ASD). Prevalence.* [online], http://www.cdc.gov/ncbddd/autism/data.html (2015).
79. Harrington, J. W. & Allen, K. The clinician's guide to autism. *Pediatr. Rev.* **35**, 62–78; quiz 78 (2014).
80. Genuis, S. J. & Bouchard, T. P. Celiac disease presenting as autism. *J. Child. Neurol.* **25**, 114–119 (2010).
81. Barcia, G., Posar, A., Santucci, M. & Parmeggiani, A. Autism and coeliac disease. *J. Autism Dev. Disord.* **38**, 407–408 (2008).
82. Black, C., Kaye, J. A. & Jick, H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. *BMJ* **325**, 419–421 (2002).
83. Pavone, L., Fiumara, A., Bottaro, G., Mazzone, D. & Coleman, M. Autism and celiac disease: failure to validate the hypothesis that a link might exist. *Biol. Psychiatry* **42**, 72–75 (1997).
84. Batista, I. C. *et al.* Autism spectrum disorder and celiac disease: no evidence for a link. *Arq. Neuropsiquiatr.* **70**, 28–33 (2012).
85. Lau, N. M. *et al.* Markers of celiac disease and gluten sensitivity in children with autism. *PLoS ONE* **8**, e66155 (2013).
86. Ludvigsson, J. F., Reichenberg, A., Hultman, C. M. & Murray, J. A. A nationwide study of the association between celiac disease and the risk of autistic spectrum disorders. *JAMA Psychiatry* **70**, 1224–1230 (2013).
87. Dohan, F. C. Is celiac disease a clue to the pathogenesis of schizophrenia? *Ment. Hyg.* **53**, 525–529 (1969).
88. Vlissides, D. N., Venulet, A. & Jenner, F. A. A double-blind gluten-free/gluten-load controlled trial in a secure ward population. *Br. J. Psychiatry* **148**, 447–452 (1986).
89. Potkin, S. G. *et al.* Wheat gluten challenge in schizophrenic patients. *Am. J. Psychiatry* **138**, 1208–1211 (1981).
90. Storms, L. H., Clopton, J. M. & Wright, C. Effects of gluten on schizophrenics. *Arch. Gen. Psychiatry* **39**, 323–327 (1982).
91. Cascella, N. G. *et al.* Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. *Schizophr. Bull.* **37**, 94–100 (2011).
92. Samaroo, D. *et al.* Novel immune response to gluten in individuals with schizophrenia. *Schizophr. Res.* **118**, 248–255 (2010).
93. Cascella, N. G. *et al.* Increased prevalence of transglutaminase 6 antibodies in sera from schizophrenia patients. *Schizophr. Bull.* **39**, 867–871 (2013).
94. Dickerson, F. *et al.* Markers of gluten sensitivity and celiac disease in recent-onset psychosis and multi-episode schizophrenia. *Biol. Psychiatry* **68**, 100–104 (2010).
95. Jackson, J. R., Eaton, W. W., Cascella, N. G., Fasano, A. & Kelly, D. L. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. *Psychiatr. Q.* **83**, 91–102 (2012).
96. Garud, S. *et al.* Interaction between psychiatric and autoimmune disorders in coeliac disease patients in the Northeastern United States. *Aliment. Pharmacol. Ther.* **29**, 898–905 (2009).
97. Shen, T. C. *et al.* Peripheral neuropathic symptoms in celiac disease and inflammatory bowel disease. *J. Clin. Neuromuscul. Dis.* **13**, 137–145 (2012).
98. Iughetti, L. *et al.* Endocrine aspects of coeliac disease. *J. Pediatr. Endocrinol. Metab.* **16**, 805–818 (2003).
99. Queiroz, M. S., Nery, M., Cancado, E. L., Gianella-Neto, D. & Liberman, B. Prevalence of celiac disease in Brazilian children of short stature. *Braz. J. Med. Biol. Res.* **37**, 55–60 (2004).
100. Hyer, W., Cotterill, A. M. & Savage, M. O. Common causes of short stature detectable by a height surveillance programme. *J. Med. Screen.* **2**, 150–153 (1995).
101. Locuratolo, N. *et al.* The circulating insulin-like growth factor system in children with coeliac disease: an additional marker for disease activity. *Diabetes Metab. Res. Rev.* **15**, 254–260 (1999).
102. Peracchi, M. *et al.* Abnormal growth hormone responsiveness to stimuli in women with active celiac sprue. *Am. J. Gastroenterol.* **87**, 580–583 (1992).
103. Meazza, C. *et al.* Short stature in children with coeliac disease. *Pediatr. Endocrinol. Rev.* **6**, 457–463 (2009).
104. Bona, G., Marinello, D. & Oderda, G. Mechanisms of abnormal puberty in coeliac disease. *Horm. Res.* **57**, 63–65 (2002).
105. Volta, U. *et al.* Coeliac disease hidden by cryptogenic hypertransaminasaemia. *Lancet* **352**, 26–29 (1998).
106. Bardella, M. T. *et al.* Chronic unexplained hypertransaminasemia may be caused by occult celiac disease. *Hepatology* **29**, 654–657 (1999).
107. Bardella, M. T. *et al.* Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. *Hepatology* **22**, 833–836 (1995).
108. Bonamico, M. *et al.* [Hepatic damage in celiac disease in children]. *Minerva Pediatr.* **38**, 959–962 (1986).
109. Vajro, P., Paolella, G., Pisano, P. & Maggiore, G. Hypertransaminasemia and coeliac disease. *Aliment. Pharmacol. Ther.* **35**, 202–203; author reply 203–204 (2012).
110. Sainsbury, A., Sanders, D. S. & Ford, A. C. Meta-analysis: coeliac disease and hypertransaminasaemia. *Aliment. Pharmacol. Ther.* **34**, 33–40 (2011).
111. Ludvigsson, J. F., Elfstrom, P., Broome, U., Ekbom, A. & Montgomery, S. M. Celiac disease and risk of liver disease: a general population-based study. *Clin. Gastroenterol. Hepatol.* **5**, 63–69 (2007).
112. Castillo, N. *et al.* Prevalence of abnormal liver function tests in celiac disease and the effect of the gluten free diet in the US population. *Am. J. Gastroenterol.* http://dx.doi.org/10.1038/ajg.2015.192.
113. Kaukinen, K. *et al.* Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. *Gastroenterology* **122**, 881–888 (2002).
114. Peters, U., Askling, J., Gridley, G., Ekbom, A. & Linet, M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch. Intern. Med.* **163**, 1566–1572 (2003).
115. Silvester, J. A. & Rashid, M. Long-term follow-up of individuals with celiac disease: an evaluation of current practice guidelines. *Can. J. Gastroenterol.* **21**, 557–564 (2007).
116. Pietzak, M. M. Follow-up of patients with celiac disease: achieving compliance with treatment. *Gastroenterology* **128**, S135–S141 (2005).
117. Rubio-Tapia, A. & Murray, J. A. The liver in celiac disease. *Hepatology* **46**, 1650–1658 (2007).
118. Ferguson, A., Hutton, M. M., Maxwell, J. D. & Murray, D. Adult coeliac disease in hyposplenic patients. *Lancet* **1**, 163–164 (1970).
119. Di Sabatino, A., Brunetti, L., Carnevale Maffe, G., Giuffrida, P. & Corazza, G. R. Is it worth investigating splenic function in patients with celiac disease? *World J. Gastroenterol.* **19**, 2313–2318 (2013).
120. Magalotti, D. *et al.* Splanchnic haemodynamics in patients with coeliac disease: effects of a gluten-free diet. *Dig. Liver Dis.* **35**, 262–268 (2003).
121. Ludvigsson, J. F., Olen, O., Bell, M., Ekbom, A. & Montgomery, S. M. Coeliac disease and risk of sepsis. *Gut* **57**, 1074–1080 (2008).
122. Husby, S. *et al.* European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J. Pediatr. Gastroenterol. Nutr.* **54**, 136–160 (2012).
123. Hendrickx, G. F., Somers, K. & Vandenplas, Y. Lane-Hamilton syndrome: case report and review of the literature. *Eur. J. Pediatr.* **170**, 1597–1602 (2011).
124. Welander, A., Prutz, K. G., Fored, M. & Ludvigsson, J. F. Increased risk of end-stage renal disease in individuals with coeliac disease. *Gut* **61**, 64–68 (2012).
125. Ludvigsson, J. F. *et al.* Coeliac disease and risk of renal disease—a general population cohort study. *Nephrol. Dial. Transplant.* **21**, 1809–1815 (2006).
126. Ismail-Beigi, F. *et al.* Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* **376**, 419–430 (2010).
127. Whorwell, P. J., Alderson, M. R., Foster, K. J. & Wright, R. Death from ischaemic heart-disease and malignancy in adult patients with coeliac disease. *Lancet* **2**, 113–114 (1976).
128. West, J., Logan, R. F., Card, T. R., Smith, C. & Hubbard, R. Risk of vascular disease in adults with diagnosed coeliac disease: a population-based study. *Aliment. Pharmacol. Ther.* **20**, 73–79 (2004).
129. Wolf-Maier, K. *et al.* Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* **289**, 2363–2369 (2003).
130. Kabbani, T. A. *et al.* Body mass index and the risk of obesity in coeliac disease treated with the gluten-free diet. *Aliment. Pharmacol. Ther.* **35**, 723–729 (2012).
131. Frustaci, A. *et al.* Celiac disease associated with autoimmune myocarditis. *Circulation* **105**, 2611–2618 (2002).
132. Addolorato, G. *et al.* Regional cerebral hypoperfusion in patients with celiac disease. *Am. J. Med.* **116**, 312–317 (2004).
133. Emilsson, L., Smith, J. G., West, J., Melander, O. & Ludvigsson, J. F. Increased risk of atrial fibrillation in patients with coeliac disease: a nationwide cohort study. *Eur. Heart J.* **32**, 2430–2437 (2011).
134. Patel, R. S., Johlin, F. C., Jr & Murray, J. A. Celiac disease and recurrent pancreatitis. *Gastrointest. Endosc.* **50**, 823–827 (1999).
135. Sadr-Azodi, O., Sanders, D. S., Murray, J. A. & Ludvigsson, J. F. Patients with celiac disease have an increased risk for pancreatitis. *Clin. Gastroenterol. Hepatol.* **10**, 1136–1142 (2012).
136. Rodrigo, L. *et al.* [Relapsing acute pancreatitis associated with gluten enteropathy. Clinical, laboratory, and evolutive characteristics in thirty-four patients]. *Rev. Esp. Enferm. Dig.* **100**, 746–751 (2008).

137. Abdulkarim, A. S., Burgart, L. J., See, J. & Murray, J. A. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am. J. Gastroenterol.* **97**, 2016–2021 (2002).
138. Walkowiak, J. & Herzig, K. H. Fecal elastase-1 is decreased in villous atrophy regardless of the underlying disease. *Eur. J. Clin. Invest.* **31**, 425–430 (2001).
139. Shah, S. & Leffler, D. Celiac disease: an underappreciated issue in women's health. *Womens Health (Lond. Engl.)* **6**, 753–766 (2010).
140. De Felice, K. M. & Kane, S. V. Inflammatory bowel disease in women of reproductive age. *Expert Rev. Gastroenterol. Hepatol.* **8**, 417–425 (2014).
141. Rashid, M., Zarkadas, M., Anca, A. & Limeback, H. Oral manifestations of celiac disease: a clinical guide for dentists. *J. Mich. Dent. Assoc.* **93**, 42–46 (2011).
142. Cheng, J., Malahias, T., Brar, P., Minaya, M. T. & Green, P. H. The association between celiac disease, dental enamel defects, and aphthous ulcers in a United States cohort. *J. Clin. Gastroenterol.* **44**, 191–194 (2009).
143. Pastore, L. *et al.* Oral manifestations of celiac disease. *J. Clin. Gastroenterol.* **42**, 224–232 (2008).
144. Losowsky, M. S. A history of coeliac disease. *Dig. Dis.* **26**, 112–120 (2008).

Author contributions
The authors contributed equally to all aspects in the production of this article.