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Clinical management of coeliac disease

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Abstract. Ludvigsson JF, Green PH (Örebro University Hospital, Sweden; Clinical Epidemiology Unit, Karolinska University Hospital and Karolinska Institutet, Sweden; and Columbia University College of Physicians and Surgeons, New York, NY, USA). Clinical management of coeliac disease (Symposium). *J Intern Med* 2011; **269**: 560–571.

Objective. To describe the prevalence of Coeliac disease (CD) and its clinical management.

Methods. Narrative review.

Results. Coeliac disease (CD) is an immune-mediated disorder that primarily affects the gastrointestinal (GI) tract. Recent data suggest a prevalence of about 1% in most Western countries, a figure that likely represents an increase in the prevalence of CD. Risk groups include those who are members of families with individuals who have CD as well as those with Type I diabetes and a variety of autoimmune diseases. Whereas biopsy is the gold standard in diagnosis, serological tests are crucial in determining who should undergo endoscopy and biopsy. HLA testing should be used only to rule out CD. Currently, a gluten-free diet is the only available therapy.

Conclusion. In conclusion, CD is one of the most common immune-mediated disorders in the Western world. It should be considered in patients with a number of varying GI and non-GI symptoms, as well as in high-risk groups that include first-degree relatives.

Keywords: autoimmunity, coeliac, gastrointestinal, inflammation.

Abbreviations: BMD, bone mineral density; CD, coeliac disease; EMA, endomysial antibodies; GI, gastrointestinal; IEL, intraepithelial lymphocyte; OR, odds ratio; SIgAD, selective IgA deficiency; T1D, Type 1 diabetes; TTG, tissue transglutaminase antibodies; VA, villous atrophy.

Introduction

Coeliac disease (CD) is an immune-mediated disease associated with villous atrophy (VA) and inflammation of the duodenum or jejunum [1, 2]. It is triggered by gluten in genetically sensitive individuals with HLA-DQ2 or DQ8 [3]. Intestinal tissue transglutaminase (TG2) deamidates gluten peptides and increases the affinity of these peptides to DQ2 and DQ8 [4], thereby generating a stronger T-cell response to gluten. Withdrawal of the triggering agent, gluten, leads to healing of the mucosa, although this may sometimes take several years [5].

Prevalence

Factors influencing the prevalence of CD

The prevalence of CD is generally cited as about 1% of the Western population. Exact figures vary according to population, age, year of measurement and, most importantly, how CD is defined. The established histopathological criterion of CD includes VA with crypt hyperplasia (Marsh III) [6–8]. In some studies, however, prevalence data have been estimated based on the presence of antibodies to TG2 (tissue transglutaminase, TTG), and in some series endomysial antibodies (EMA).

In recent years, changing views on diagnostic practice have meant that some researchers now argue that also minor lesions (Marsh I–II), often called gluten-sensitive enteropathy [9], should be regarded as CD. Including Marsh I and II in prevalence studies leads to higher estimates of the prevalence of CD and may partly explain the increase in CD witnessed in recent years. Further, studies based solely on positive CD serology [10, 11] tend to report higher prevalence rates than studies requesting a positive biopsy for diagnosis [12], as do studies based on members of CD societies [12]. When Dubé *et al.* reviewed 133 studies published until December 2003 [12], they found a trend towards higher prevalence figures in smaller

studies. In larger studies, CD was reported in about 0.5–1.3% of the general population [12].

Unselected populations

The prevalence of CD in an unselected North American population is about 1% [10, 13], although lower figures have been reported [14, 15]. European data suggest a similar [16, 17] or higher prevalence. In 2009, Finnish researchers reported that 2.34% of individuals aged 50 years or above had biopsy-verified CD [18]. Data from other parts of the world with a 'European population' have shown similar levels of CD [19, 20].

Sweden comprises a special case given the 'coeliac epidemic'. A study from Northern Sweden found a prevalence of 1.6% of CD (histological and serological evidence of CD) [21]. In a second study Myleus *et al.* examined Swedish 12-year-olds and found a prevalence of CD of 2.9% [22], but that study may have overestimated the prevalence because patients with already diagnosed CD might have been more likely to have participated in the study. Both these studies [21, 22] accepted high intraepithelial lymphocyte (IEL) counts as proof of CD in patients with positive CD serology. The relationship between high IEL counts and CD however is beyond the scope of this paper [21, 23–29]. Still, changing diagnostic criteria or increased awareness of CD are factors unlikely to fully explain the increase in CD observed since the 1980s. Instead, there is evidence of a true increase in CD as demonstrated in longitudinal studies [30, 31].

Fewer studies have examined the prevalence of CD outside North America and Europe, and most of these studies have examined the prevalence of CD in risk groups (e.g. China [32], India [33] and Tunisia [34]).

In available screening studies of the general population, the prevalence of CD has varied. In Latin America [35], high figures have been found in Mexico (2.7% were TTG+), with lower figures in Brazil: 0.11% [36] and Argentina: 0.60% [37]. In a study of Indian school children, 0.32% had CD, but this may have been an underestimate because only those with symptoms were tested [38]. High levels of CD have also been reported in ethnic Punjabis living in Great Britain [39] and in Iran (positive CD serology with Marsh I-III, 0.96%) [40]. Of special interest is the extremely high prevalence of CD reported from the wheat-consuming Saharawi people in Sahara [41]. In Egypt, more moderate levels have been reported [42].

High-risk groups

First-degree relatives. First-degree relatives are at increased risk of CD [43–45]. When Rubio-Tapia *et al.* screened 344 family members to 111 index cases with CD, 10–11% of the family members suffered from CD [46]. Fasano *et al.*, using EMA positivity as their criterion for CD diagnosis, reported a CD prevalence of 4.5% in first-degree relatives and 2.6% in second-degree relatives [10].

Anaemia. The prevalence of CD in patients with anaemia has varied from 0% [47] to 8.7% [48], with most studies confirming CD through biopsy in about 5% of patients with iron-deficiency anaemia [49, 50].

Osteoporosis. Coeliac disease is associated with osteoporosis [51] both before [52, 53] and after diagnosis of CD [52, 54, 55] (although contradicting reports exist [56, 57]). Some research suggests that more than half of all patients with CD suffer from low 25-(OH)D-vitamin [58].

Autoimmune thyroid disease. A positive association between CD and thyroid disease has been observed both before and after diagnosis of CD [59–70]. Autoimmune thyroid disease occurs in about 3–10% of the CD population [71], and thus patients with CD should be screened for autoimmune thyroid disease. Using National Hospital Discharge data, Swedish researchers estimated the odds ratios (ORs) to be from 2.0 to 4.0 for future CD in patients with thyroid disease: hypothyroidism [odds ratio (OR) = 3.8], thyroiditis (OR = 4.0) and hyperthyroidism (OR = 2.0) [70].

Dermatitis herpetiformis (DH). Dermatitis herpetiformis is a blistering skin condition strongly associated with CD. Autoimmune comorbidity in DH is similar to that noted in CD [72], although a large British study found no increased risk of nonautoimmune morbidity, such as malignancy or fractures [73]. In contrast with CD, DH does not seem to confer an increased risk of mortality [73].

Type 1 diabetes (T1D). Patients with T1D are at increased risk of CD [74], with a prevalence of approximately 3–5% [10, 75, 76] and occasionally more [77, 78]. Positive CD serology in T1D is even more prevalent (Dubé *et al.* report levels up to 12%) [12]. In about 85–90% of patients with both diseases, CD is *pre-*

ceded by T1D [79]. Reasons for the increased risk of CD in patients with T1D include shared HLA [80–82], infant feeding pattern [83–85] and regular screening for CD in patients with T1D, regardless of whether the patients have gastrointestinal (GI) symptoms [86]. Such screening is natural because many patients with T1D and undiagnosed CD lack GI symptoms [87]. Data on metabolic control in patients with both CD and T1D are conflicting [88].

Prolonged fatigue or 'tired all the time' should alert the physician to CD [89–93].

Irritable bowel syndrome (IBS). IBS is a functional bowel disorder of the GI tract that occurs in 5–20% of the general population [94]. A recent meta-analysis suggested that patients with IBS are four times as likely to suffer from CD than the general population [95].

Liver and pancreatic disease. Coeliac disease has also been linked to liver and pancreatic disease. One in 10 patients with cryptogenic hypertransaminasemia suffers from CD [96]. Hypertransaminasemia in patients with *diagnosed CD* often normalizes on a gluten-free diet (GFD) and needs no further investigation. However, investigation for liver complications is warranted in CD patients with persistent liver abnormalities or clinical symptoms of liver disease. In a Swedish study [97], the ORs for having a future CD diagnosis in patients with prior liver disease ranged from about 4 for primary sclerosing cholangitis to 15 for primary biliary cirrhosis. Importantly, Finnish data indicate that CD can contribute to liver failure in individuals with established liver disease and that identification of CD and treatment with GFD can prevent the need for transplantation [98].

Patients with CD are at increased risk of several pancreatic disorders, including pancreatic insufficiency [99, 100], pancreatic cancer [101] and death from pancreatic disorders [102]. Our own paper found a strong association between CD and both acute and chronic pancreatitis [103].

Also in individuals with ataxia [104, 105] and polyneuropathy [106] should CD be ruled out. Gluten ataxia is also commented on by Troncone and Jabri in this issue of Journal of Internal Medicine [107].

Based on available data, we suggest that individuals belonging to the above-mentioned risk groups undergo antibody screening for CD, followed by small intestinal biopsy if CD serology is positive.

Symptoms and signs

The clinical presentation of CD has changed over time. Although classical CD (with GI symptoms such as diarrhoea, abdominal pain, abdominal distension and failure to thrive) still occurs in children (and then most often between 6 and 24 months of age), it has decreased in this age group in the past several decades [108]. The classical diarrhoea-predominant mode of presentation has also diminished in adults [108] and 'coeliac crisis' with sudden severe diarrhoea is uncommon [109]. Other presentations more commonly seen these days are anaemia, osteoporosis, more vague abdominal symptoms (such as abdominal pain, bloating and altered bowel symptoms often labelled as IBS) and neuropathic symptoms [110]. Patients are frequently diagnosed because of their being in high-risk groups [92]. A large percentage of patients are diagnosed because they are family members to patients with CD [10]. Many patients lack GI symptoms.

US data indicate that 2–4% of children with GI symptoms (especially diarrhoea) are positive for EMA [10]. These findings are further supported by British data on 7-year-old children where diarrhoea (odds ratio = 1.96), together with having at least three GI symptoms (OR = 2.45), was statistically significantly associated with later EMA positivity [111]. A Swedish study comparing children with biopsy-verified CD and children with a negative biopsy [112] found that abdominal distension (OR = 22.17), tiredness (OR = 15.43), irritability (OR = 6.50) and thin extremities (OR = 5.89) all predisposed for a later diagnosis of CD. In that study [112], vomiting (OR = 3.04) and diarrhoea (OR = 2.04) were of borderline significance for the risk of having a future diagnosis of CD [112]. The *North American Society for Pediatric Gastroenterology, Hepatology and Nutrition* (NASPGHAN) recommends that CD should be considered in children with failure to thrive, persistent diarrhoea, recurrent abdominal pain, constipation and vomiting [113].

Although sensitivity and specificity of diarrhoea for a diagnosis of CD in adults vary [114], diarrhoea (especially chronic diarrhoea [92]) and other GI symptoms (e.g. constipation and weight loss) should alert the physician to the possibility of CD [114].

Although CD is characterized by inflammatory changes in the small intestinal mucosa, extraintestinal symptoms and signs are also known to occur. In patients with any of the following symptoms screen-

ing for CD may be considered: ataxia [104, 105], neuropathy [106, 115–118], alopecia areata [119], psoriasis [120], depression [121], chronic thrombocytopenic purpura [122] and Addison's disease [123]. Screening could also be considered in patients with certain infections, including tuberculosis [124, 125], pneumococcal infections [126] and sepsis [127]. The increased risk of pneumococcal infection and sepsis may be because of hyposplenism in CD [128]). Given the repeatedly increased relative risk of lymphoproliferative malignancy in CD [129–131], it seems reasonable to also screen patients with lymphoma for CD. In children and adolescents, extraintestinal signs (e.g. short stature and delayed puberty) constitute additional reasons for CD screening [113].

In contrast, infertility is unlikely to be a common sign of CD. Indeed, the two largest cohort studies on CD and fertility to date [132, 133] have not been unable to show an association between CD and infertility, before or after CD diagnosis. This finding does not contradict earlier reports of adverse pregnancy outcome in women with undiagnosed CD [134, 135]. Mothers to preterm children are at increased risk of having undiagnosed CD.

At least three congenital syndromes seem to be associated with CD: Down syndrome, [136–138] Turner's syndrome [139, 140] and Williams syndrome [141], as an example of the great spectrum of clinical presentations of CD. Table 1 represents the modes of presentation in adults and children seen at the Celiac Disease Center at Columbia University in New York.

Table 1 *Mode of presentation of adults and children with coeliac disease*[a]

Symptom	Adults, % (n = 1499)	Children, % (n = 244)
Diarrhoea	40	9
Anaemia	15	3
Bone disease	6	–
Abdominal pain	–	22
Growth issues	–	26
Constipation	–	5
Abdominal distension	–	4
Screening	10	23
Incidental at upper endoscopy	6	–
Other	23	8

[a]Data from the Celiac Disease Center at Columbia University in New York, US.

Serological tests and HLA testing

Whereas biopsy is the gold standard in diagnosis, serological tests are pivotal in determining who should undergo endoscopy and biopsy. The older antigliadin antibodies (IgG and IgA) are no longer used because of their lack of sensitivity and specificity [142], except in younger children. Antigliadin antibodies have been replaced by the more recently developed deamidated synthetic gliadin peptide (often referred to as antigliadin peptide or antideamidated gliadin peptide, anti-DGP) [143]. The EMA remains the most specific test [114, 144]; however, the antibody to its autoantigen, TTG [145], is the most widely used because of its high sensitivity and specificity and ease in performance as an ELISA test [146, 147]. EMA is an immunoflourescent test requiring experience in interpretation and the use of primate tissue [148].

Increasing diagnostic precision through serial testing

The rationale behind serial testing is that one positive test followed by another positive test increases the likelihood of the patient having CD. In turn, several positive tests (TTG+ and EMA+ and biopsy+) as opposed to one (TTG+) decrease the risk that a truly healthy patient is falsely assigned a diagnosis of CD. To illustrate the use of serial testing we describe a large Dutch study [149]. In this study the positive predictive value of TTG alone was 76%. Adding EMA+ increased the positive predictive value to 81%. However, still 3/16 patients with positive TTG and EMA did not have CD in that study. In a large British study of 2000 consecutive patients only 29% of those with positive TTG had CD, further underlining the importance of confirming a CD diagnosis with biopsy [150].

HLA testing

It is estimated that at least 95% of the CD population are positive for HLA-DQ2/DQ8 [151, 152]. At first, this might suggest that positive DQ2/DQ8 could be used to confirm a diagnosis of CD. However, positive DQ2/DQ8 cannot be used to confirm a diagnosis of CD because DQ2/DQ8 is also very common in the general population (of the Western world). Instead, HLA tests should be used to *rule out* the existence of CD (HLA tests have high negative predictive values). Hadithi *et al.* tested 463 patients for CD and found that DQ2/DQ8+ had a positive predictive value of 6% (i.e. 6% of those testing positive had CD) [149]. In contrast, a negative DQ2/DQ8 test carries a lot of information because it will rule

out about 97% of all CD cases (negative predictive value: 96.6%) [149].

IgA deficiency

Individuals with IgA deficiency (IgAD) have decreased levels of IgA [or no IgA at all in the case of selective IgA deficiency (SIgAD)] whilst having normal levels of serum IgG and IgM [153]. SIgAD affects 0.1–0.2% of the general population.

Several studies have indicated a link between SIgAD and autoimmune diseases [154–166]. Although it is more common that SIgAD is diagnosed as part of the screening for CD [167], physicians managing SIgAD patients should be aware of the association with CD [165, 166, 168, 169]. Patients with CD and severe IgAD should undergo testing for anti-immunoglobulin A that may react with plasma IgA in that such anti-immunoglobulins can lead to transfusion reactions in patients receiving blood products.

When testing for IgA EMA or IgA TTG, the physician should always evaluate total IgA levels. In patients with low IgA, IgG against EMA/TTG should instead be measured, although the IgG test has lower sensitivity [147] and specificity than IgA-based tests. Hence, in this patient group, a small intestinal biopsy may be considered independently of CD serology results.

Intestinal biopsy

Intestinal biopsy, though imperfect, is considered the gold standard in the diagnosis of CD [170]. The mucosal changes, as originally classified by Marsh [6], identified in the biopsy of patients with CD consist of a spectrum ranging from prominent intraepithelial lymphocytosis without VA (Marsh I) to total VA (Marsh IIIc) [8]. Figure 1(a) depicts the finger-like villi found in the normal small intestine. In this classification, partial VA is classified as Marsh IIIb (Fig. 1b) and total VA as Marsh IIIc (Fig. 1c).

There is a reluctance to give patients a diagnostic label of CD without the presence of VA. This unwillingness is mainly because there are several other causes of the Marsh I lesion (also known as lymphocytic duodenitis) that include *Helicobacter pylori* gastritis [171], giardiasis and viral gastroenteritis [172].

Because the pathological changes of CD may be patchy, 4–6 biopsy pieces are recommended [173, 174]. In addition, biopsy of the duodenal bulb increases the

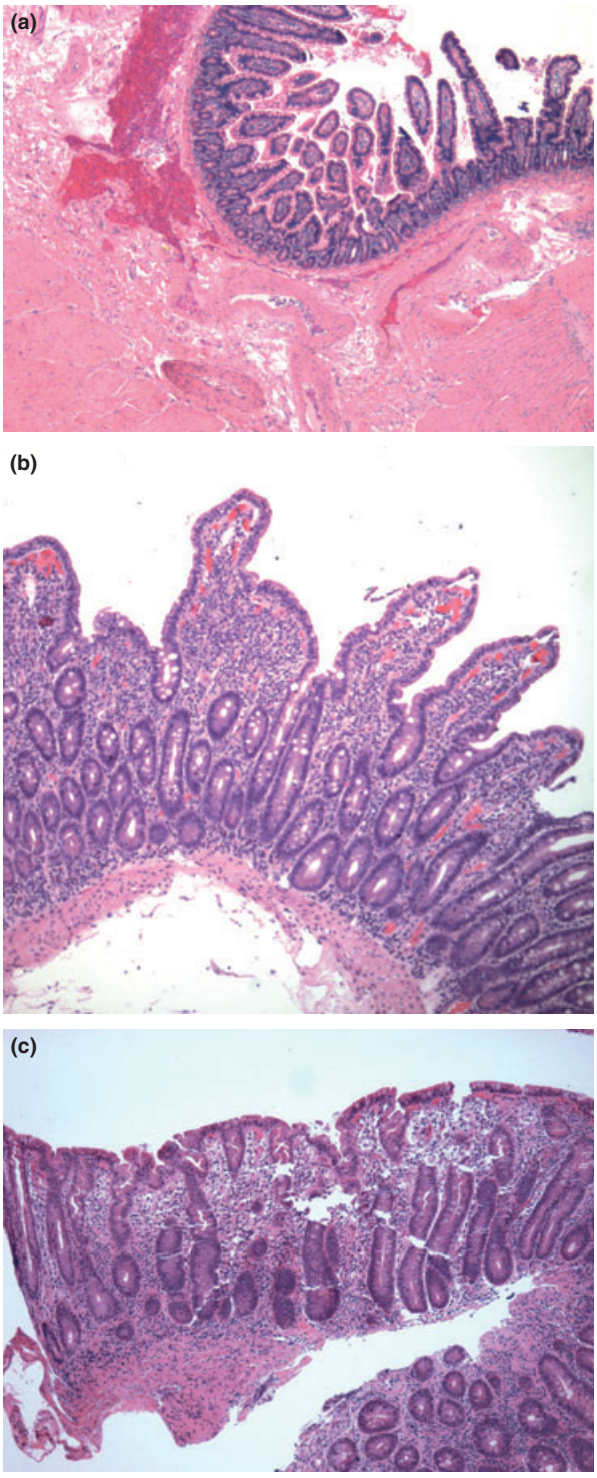

Fig. 1 *(a) Normal small intestine. (b) Partial villous atrophy. (c) Total villous atrophy.*

yield of the presence of VA (in one study by 13%) [175].

Therapy of coeliac disease

A GFD is the only medically accepted treatment for CD. It will improve symptoms and abnormalities in the duodenal biopsy, enhance quality of life in people with symptomatic CD and likely reduce mortality. Consultation with an experienced nutritionist is advised; however, in some countries there are limited recourses to provide this service [176]. The GFD is rigorous, and therefore adherence to it is not consistent [174]. Lactose restriction is not routinely recommended unless symptoms or breath testing suggest the presence of lactose intolerance. Young children with severe CD, however, may benefit from lactose restriction in the first months after CD diagnosis.

After diagnosis

At diagnosis, patients should be assessed for vitamin deficiency with a serum folate, vitamin B12 level [177] and vitamin D (25 hydroxy) and deficiencies corrected by appropriate vitamin supplementation. Vitamin B deficiency is common after an extended period on a GFD [178]; accordingly, all patients are advised to take a gluten-free multivitamin. Mineral status is assessed by measurement of serum iron, ferritin, and possibly, copper and zinc levels. Serum calcium and parathyroid hormones are valuable to assess calcium homeostasis. Hyperparathyroidism, both secondary, which is because of calcium deficiency (the result of calcium malabsorption and possible lactose restriction in the diet), and primary hyperparathyroidism, are increased in CD [179–181].

If neurological symptoms (e.g. neuropathic symptoms, ataxia or memory impairment) were present, we would advice measurement of serum copper, vitamin E, as well as B1, B2, and B6, to exclude deficiency of these nutrients [182, 183].

Fracture risk is increased in CD [52, 184, 185]. Reduced bone density is common, and assessment of bone mineral density (BMD) at diagnosis in adults is well advised [186, 187]. Although BMD may be abnormal in children [188], routine assessment is not appropriate because of lack of standard values. Therapy with calcium and vitamin D to correct vitamin D deficiency and secondary hyperparathyroidism together with a GFD results in improved BMD [187, 188]. Use of bisphosphonates is typically reserved for patients whose BMD does not improve with the GFD and correction of calcium and vitamin D deficiency. Because thyroid disease is common in CD, assessment with a serum TSH level is particularly appropriate [13, 189]. Pneumococcal vaccination is recommended in many countries because of the increased risk of pulmonary diseases [126, 127, 190, 191] and the presence of hyposplenism in patients with CD [128, 192]. Finally, recent data indicate that individuals with CD are at increased risk of influenza [193].

Patients should be encouraged to follow-up with their nutritionist as well as their diagnosing physician. Such follow-up encourages adherence to the diet and allows assessment of response to the GFD. Lately, two instruments have been proposed to measure gluten adherence [194, 195]. Serum antibodies to tTG and DGP should be measured at intervals, possibly at 6 and 12 months, and then annually. They are expected to fall to normal values with a GFD and are valuable as an assessment of dietary adherence [196].

Many patients lack GI symptoms making it difficult to know whether the biopsy abnormalities are healing. In addition, persistent inflammation and villous atrophy are not uncommon in diagnosed CD [197, 198] and probably associated with a poor prognosis, even in the absence of symptoms [197, 199]. We would therefore advocate a follow-up biopsy to document healing after at least 1 or 2 years on the GFD. In small children (below the age of 2 years), repeat biopsy and even a third biopsy may be even more important because cow's milk protein enteropathy and transient gluten intolerance are not uncommon in this age group [200].

Conflicts of interest statement

All authors (JFL and PG) declare that they have no conflicts of interest and therefore nothing to declare.

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