ORIGINAL ARTICLE

The Oslo definitions for coeliac disease and related terms

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ABSTRACT

Objective The literature suggests a lack of consensus on the use of terms related to coeliac disease (CD) and gluten.

Design A multidisciplinary task force of 16 physicians from seven countries used the electronic database PubMed to review the literature for CD-related terms up to January 2011. Teams of physicians then suggested a definition for each term, followed by feedback of these definitions through a web survey on definitions, discussions during a meeting in Oslo and phone conferences. In addition to 'CD', the following descriptors of CD were evaluated (in alphabetical order): asymptomatic, atypical, classical, latent, non-classical, overt, paediatric classical, potential, refractory, silent, subclinical, symptomatic, typical, CD serology, CD autoimmunity, genetically at risk of CD, dermatitis herpetiformis, gluten, gluten ataxia, gluten intolerance, gluten sensitivity and gliadin-specific antibodies.

Results CD was defined as 'a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals'. Classical CD was defined as 'CD presenting with signs and symptoms of malabsorption. Diarrhoea, steatorrhoea, weight loss or growth failure is required.' 'Gluten-related disorders' is the suggested umbrella term for all diseases triggered by gluten and the term gluten intolerance should not to be used. Other definitions are presented in the paper.

Conclusion This paper presents the Oslo definitions for CD-related terms.

Significance of this study

What is already known on this subject?
- There is a lack of consensus on the use of terms related to coeliac disease (CD) and gluten.
- Variability in the use of terminology has led to difficulty when comparing and evaluating clinical studies and research findings.

What are the new findings?
- The panel reached agreement on the definition of terms related to CD and/or gluten currently in use in clinical practice and research.
- Some terms in current use should be abandoned because they are outdated or misleading.

How might it impact on clinical practice in the foreseeable future?
- Uniform definitions for common terms relating to CD will improve communication among researchers, clinicians and the general public, and will ensure that research is conducted and reported in a consistent manner.

INTRODUCTION

Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed people. Although symptoms and signs of CD have been recognised for more than 100 years, it was in the 1940s that the Dutch paediatrician Dicke established a link between the protein component of wheat (gluten) exposure and CD.[1] CD and related diseases are now common chronic diseases in children and adults, and increased diagnosis has led to a proliferation of research activities. As with many other chronic conditions, the boundaries of CD are not always clear, with the consequence that there is considerable confusion and a lack of consensus regarding diagnostic criteria of CD and related conditions.

The first consensus definition of CD was published in *Acta Paediatrica* in 1970.[2] This publication defined CD as a permanent condition of gluten intolerance with mucosal flattening that reversed on a gluten-free diet (GFD) and then relapsed on re-introduction of gluten. Although the definition of CD has undergone minor changes since 1970,[3 4] consensus definitions have been restricted to CD. However, the scientific community has come to recognise that there is a spectrum of disorders related to gluten ingestion.

Due to a lack of common definitions for the spectrum of terms and disorders related to CD, a multidisciplinary task force of 16 physicians from seven countries with particular expertise in diagnosis and treatment of CD proposes the following definitions for the variety of vague and often confusing terms currently in use in the literature. These definitions are based on thorough literature reviews (table 1), a discussion in Oslo at the 14th International Coeliac Disease Symposium in June 2011, and agreement on consensus statements by a web survey and phone conferences. We refer to our definitions as the 'Oslo definitions'.

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Table 1 Terms evaluated for this review

Term	PubMed hits until January 2011*
Defined	
Coeliac disease (CD)†	14 843
Asymptomatic CD	39
Classical CD	10
Paediatric classical CD†	–
Non-classical	3
Potential CD	33
Refractory CD	109
Subclinical CD	43
Symptomatic CD	26
CD autoimmunity‡	16
Genetically at risk of CD†	–
Dermatitis herpetiformis†	2759
Gluten†	8879
Gluten ataxia	28
Non-coeliac gluten sensitivity	85
Gliadin-specific antibodies§	5
Overt CD	10
Gluten-related disorders	12
Discouraged	
Atypical CD	13
Latent CD	78
Typical CD	11
Gluten intolerance	244
Gluten sensitivity	241
Silent CD	80
CD serology¶	15

*We searched PubMed for the period 1 January 1900 to 31 January 2011. Individual authors then examined papers deemed most relevant. When the phrase 'coeliac disease' is part of the definition, we searched PubMed for the relevant term *and* coeliac disease (British and American spelling). For example, 'silent coeliac disease' [All Fields] OR 'silent coeliac disease' [All Fields] AND ('1900/01/01' [PDAT]: '2011/01/31' [PDAT]).
†For these terms, our literature review was entirely based on expert consensus of the literature because it was beyond the scope of this paper to review all papers identified through PubMed (or as in the case of 'paediatric classical CD' there were no hits).
‡We searched for 'coeliac disease autoimmunity' and 'coeliac autoimmunity' (British and American spelling).
§A search for 'gluten and antibodies' yielded 2529 hits.
¶Although we discourage the use of the term 'CD serology', we have provided a definition for this term.

The purpose of our recommended definitions is to create a foundation for clinical management and research. Clear definitions will allow more efficient and generalisable advances in CD research relating to aetiology, incidence, prevalence, complications and treatment of patients with CD and other gluten-related disorders.

METHODS

Task force constitution

Members of this collaborative effort were invited to participate by two of the authors (DAL and CC). The constitution of the group reflects the wide variety of disciplines to which CD may present in practice: gastroenterology, histopathology, paediatrics, neurology and dermatology. Members of the task force were from Sweden, the USA, Argentina, Italy, the UK, Finland and Norway. Four of the five physicians from the USA had trained elsewhere (two in Ireland, one in Australia and one in Italy).

Literature review

Teams of three or four physicians were assigned between one and four CD-related terms. Each team carried out a literature search (table 1) of the entire electronic database PubMed up to January 2011 using the terms as key words. These terms included CD and the following descriptors of CD: asymptomatic, atypical, classical, latent, non-classical, overt, paediatric classical, potential, refractory, silent, subclinical, symptomatic, typical, CD serology, CD autoimmunity, genetically at risk of CD, dermatitis herpetiformis, gluten, gluten ataxia, gluten intolerance, gluten sensitivity and gliadin-specific antibodies.

The literature review was mostly restricted to original papers and reviews. Most papers had been published after 1990. The teams then suggested definitions for each term.

Web survey

A web survey was then conducted and all suggested definitions were listed and subjected to peer review (online appendix).

Comments and feedback from the web survey were taken into account when creating a second set of definitions.

Discussions and phone meetings

The revised definitions and appending comments were then discussed in Oslo at the 14th International CD Symposium in June 2011. This discussion was followed by two phone conferences in which the remaining definitions were discussed until consensus was achieved. We did not grade the evidence underlying each definition because that was not the purpose of the task force and this review did not deal with clinical management. For the convenience of readers, each definition given in the Results section below is followed by a short literature review of each term. Two terms were added after the initial web survey and the meeting in Oslo: 'dermatitis herpetiformis' and 'CD autoimmunity', which were discussed through email.

RESULTS

Coeliac disease

Coeliac disease is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.

CD is triggered by the ingestion of gluten (definition below), the protein component of wheat, rye, barley, but not oats.[5 6] Such exposure results in a variable degree of intestinal damage.[7] In most patients with CD, the enteropathy will reverse on a GFD.[2–4] According to the suggested definition, CD is a chronic disease, but as the discussion of the terms potential CD and latent CD will show, there are reports of transient CD.[8]

Although CD is the most common cause of enteropathy in the western world and enteropathy is a prerequisite for CD, it should be noted that other diseases may cause small intestinal inflammation but do not qualify as CD.[9] Typically, the inflammation in CD includes an increased intraepithelial lymphocyte (IEL) count, most often >25/100 cells.[9 10] Another feature of CD is that it incorporates an adaptive T-cell-mediated response (to gluten) and that it occurs in people who are DQ2–DQ8 positive.[11 12] Increasingly, the presence of specific endomysial antibodies (EMA, also called AEA), anti-tissue transglutaminase antibodies (TTG, a-tTG, TTA), and/or deamidated antigliadin antibodies (DGP) plays an important role in the serological work-up for CD. These antibodies strongly support the diagnosis of CD, but by themselves are not confirmatory.

To confirm a diagnosis of CD, biopsies of the duodenum must be taken when patients are on a gluten-containing diet. Consensus states four to six biopsies are necessary for diagnosis,[13] including from the duodenal bulb.[14 15]

Three histological classifications of CD are used: Marsh,[7] Marsh–Oberhuber[16] and Corazza.[10] A comparison of these classifications is shown in table 2.

Table 2 Comparison of histopathological classifications

Morphology of duodenal mucosal biopsy	Classification		
	Marsh* [7]	Marsh-Oberhuber[16]	Corazza[10]
Normal	Type 0	Type 0	Normal
Normal architecture and increased intraepithelial lymphocytes ≥25/100 enterocytes	Type 0	Type 0	Grade A
Normal architecture and increased intraepithelial lymphocytes ≥40/100 enterocytes	Type 1	Type 1	Grade A
Normal architecture and increased intraepithelial lymphocytes ≥40/100 enterocytes with crypt hyperplasia	Type 2	Type 2	Grade A
Partial villous atrophy and increased intraepithelial lymphocytes ≥40/≥25/100 enterocytes	Type 2 hyperplastic lesion Crypt hyperplasia, increased crypt height and influx of inflammatory cells	Type 3 destructive	Grade B1 atrophic, villous to crypt ratio is <3:1
		Type 3a partial villous atrophy; villi blunt and shortened with a villous:crypt ratio, 1:1	
		Type 3b subtotal villous atrophy; villi atrophic but still separate and recognisable	
Total villous atrophy intraepithelial lymphocytes ≥40/≥25/100 enterocytes	Type 3 destructive severe inflammation, flat villi; hyperplastic crypts	Type 3c total villous atrophy; villi rudimentary or absent; mucosa resembles colonic mucosa	Grade B2 atrophic, villi are no longer detectable
Atrophic hypoplastic lesion: flat mucosa, normal crypt height, no inflammation with normal intraepithelial lymphocyte counts	No equivalent	Type 4	No equivalent

*Marsh initially explored the association of mucosal damage with a progressively increased gluten intake in treated patients with celiac disease. This staging has since been used as a classification.

Historically, CD has been equivalent to sprue, coeliac sprue, gluten-sensitive enteropathy and gluten intolerance. In the past the terms non-tropical sprue and idiopathic steatorrhoea were used.[17 18] None of these terms are currently recommended.

Gluten

Gluten is the commonly used term for the complex of water insoluble proteins from wheat, rye and barley that are harmful to patients with CD.

The major seed proteins in cereals are the alcohol-soluble prolamins, a complex group of alcohol-soluble polypeptides that make up about half of the protein in the mature grain. The term gluten indicates a broad group of prolamins (gliadins and glutenins) found in wheat. Other prolamins showing similar immunogenic properties are also found in rye (secalins), barley (hordeins) and other closely related grains.[13 19] The major prolamins of the more distantly related maize (zeins) seem to have evolved independently and show no harmful effects in patients with CD. Oats have also been shown to be non-immunogenic in most patients with CD.[20] A GFD usually indicates a diet free from wheat, rye, barley, triticale, kamut and spelt.

Gluten is poorly digested in the human intestine with or without CD. Gluten peptides cross intact into the submucosa of the small intestine. In the submucosa of the small intestine the human enzyme transglutaminase 2 also referred to as tissue transglutaminase (tTG) deamidates gluten peptides, which allows for high-affinity binding to human leucocyte antigen (HLA) DQ2 and HLA DQ8 molecules, subsequently triggering an inflammatory reaction in patients with CD.[12]

Gluten content in food is regulated by the *Codex Alimentarius* (http://www.codexalimentarius.net). This codex (CODEX STAN 118–1979 revised in 2008) states that gluten-free foods are foods or ingredients naturally free of gluten, in which the measured gluten level is ≤20 mg/kg in total, or processed to <100 mg/kg. According to the current Codex, foods meeting these criteria may be labelled as a 'gluten-free food'.

Asymptomatic CD

Asymptomatic CD is not accompanied by symptoms even in response to direct questioning at initial diagnosis.

Individuals with asymptomatic CD do not manifest any symptoms commonly associated with CD and have no symptoms that respond to gluten withdrawal, even in response to direct questioning. These patients are often diagnosed through testing of populations enrolled in screening programmes or in case-finding strategies for detecting CD in patients with disorders that are associated with a high risk for CD.[21–33] Many of these patients suffer from decreased quality of life. Sometimes minor symptoms (eg, fatigue) are only recognised after the introduction of a GFD;[34] such patients do not suffer from true asymptomatic CD and should be reclassified as having subclinical CD.

Typical CD

Historically, typical CD has denoted a gluten-induced enteropathy presenting with signs or symptoms of malabsorption/global malabsorption (such as diarrhoea or malnutrition) or a malabsorption syndrome (indicated by weight loss, steatorrhoea and oedema secondary to hypoalbuminemia). The above use is questionable in that the clinical presentation of CD has changed over time,[35–37] and the word 'typical' implies that this form is the most frequently encountered form of CD. In contrast, many current patients have symptoms such as anaemia,[38–40] fatigue[41 42] and abdominal pain.[43]

We therefore discourage the use of the term typical CD.

Atypical CD

Atypical CD can only be used in reference to typical CD. Historically, atypical CD has been used to describe patients with gluten-induced enteropathy who have no weight loss but present with any of the following symptoms or signs: gastrointestinal symptoms,[44] including symptoms suggestive of irritable bowel syndrome[45 46] and liver dysfunction[47 48]; extraintestinal manifestations, such as metabolic disease/

symptoms (failure to thrive, thyroid dysfunction (hypo/hyper))[49 50]; neurologic findings,[51–53] including depression[54] and gluten ataxia[55]; reproductive disease,[56–58] including abnormalities in menarche and menopause[58 59]; oral/cutaneous disease,[60–64] including dermatitis herpetiformis (DH);[65] and skeletal findings.[66] Atypical CD has also been used to denote patients with a gluten-induced enteropathy and significant nutritional deficiencies (such as iron deficiency). We argue that the term atypical CD should not be used. Some patients previously described as having atypical CD may fulfil the requirements for non-classical CD (see below).

Classical CD

Classical CD presents with signs and symptoms of malabsorption. Diarrhoea, steatorrhoea, weight loss or growth failure is required.

Classical and typical CD have traditionally been similar concepts defining the presence of a gluten-induced enteropathy presenting with diarrhoea, malnutrition or a malabsorption syndrome (indicated by weight loss, steatorrhoea and oedema secondary to hypoalbuminemia).[7 67–74] While recognising that these symptoms are not specific to CD, we encourage the use of classical CD, as defined above, because the term 'classical' does not imply that this type of CD is more common than CD without clinical malabsorption. Examples of classical CD are patients with diarrhoea and weight loss but also patients with weight loss and anaemia.

Paediatric classical CD is the paediatric equivalent of classical CD. These children are often characterised by failure to thrive, diarrhoea, muscle wasting, poor appetite and abdominal distension.[75–79] Many children with classical CD and malabsorption also show signs of emotional distress ('change of mood') and lethargy.[72]

Non-classical CD

Non-classical CD presents without signs and symptoms of malabsorption.

In non-classical CD the patient does not suffer from malabsorption (eg, a patient with constipation and abdominal pain but no malabsorption). Patients with monosymptomatic disease (other than diarrhoea or steatorrhoea) usually have non-classical CD.

Silent CD

Silent CD is equivalent to asymptomatic CD. We discourage the use of the term silent CD.

Subclinical CD

Subclinical CD is below the threshold of clinical detection.

The term subclinical has often been used to denote silent CD[80–82] or patients with CD and extraintestinal symptoms (and no gastrointestinal symptoms).[83] The term has also been used for patients with CD who have clinical or laboratory signs (iron deficiency anaemia, abnormalities in liver function tests, enamel defects, incidental endoscopic features, osteoporosis, etc) but no symptoms.[84]

As understanding of CD has advanced, new disease associations have been regularly found and populations tested for CD have changed in response. For this reason, what is 'subclinical' has changed over time. To provide a stable definition, we specified subclinical CD to be disease that is below the threshold of clinical detection without signs or symptoms sufficient to trigger CD testing in routine practice.

Symptomatic CD

Symptomatic CD is characterised by clinically evident gastrointestinal and/or extraintestinal symptoms attributable to gluten intake.

The clinical manifestations of CD vary from none (asymptomatic CD) to a wide spectrum of symptoms. The vast majority of authors describing symptomatic CD do not distinguish between CD with gastrointestinal symptoms and CD with extraintestinal symptoms.[85–98]

What was previously called overt CD should be considered part of symptomatic CD.

Overt CD

Overt CD has most often been characterised by clinically evident gluten-related symptoms, either gastrointestinal (dyspepsia, diarrhoea and bloating) or extraintestinal (neurological symptoms and fatigue).[99 100] We recommend that the term overt CD should not be used; symptomatic CD is the preferred term.

Refractory CD

Refractory CD (RCD) consists of persistent or recurrent malabsorptive symptoms and signs with villous atrophy (VA) despite a strict GFD for more than 12 months.

Although definitions of RCD differ slightly,[101–118] most expert-opinion-based definitions include persistence or recurrence of malabsorptive symptoms and signs (eg, diarrhoea, abdominal pain, involuntary loss of weight, low haemoglobin and hypoalbuminemia) associated with persistent or recurrent VA despite a strict GFD for more than 12 months (or severe persistent symptoms independently of the duration of GFD) in the absence of other causes of VA or malignant complications[119] and after the confirmation of the initial diagnosis of CD.

Generally, most patients are negative for EMA and TTG at the time of RCD diagnosis, but the presence of persisting elevated titres of circulating EMA and/or TTG does not necessarily rule out RCD, though this should lead to questions about dietary adherence. In all cases, a careful dietary interview should be performed to exclude gluten exposure before diagnosing RCD.[120] Not all dietary non-responsive CD is RCD.[121–123]

RCD is divided into two categories[111 115]: type I, in which a normal IEL phenotype is found; and type II, in which there is a clonal expansion of an aberrant IEL population. The abnormal phenotype is supported by loss of normal surface markers CD3, CD4 and CD8 with preserved expression of intracytoplasmic CD3 (CD3ϵ) in >50% of IELs as evaluated by immunohistochemistry or >20% as determined by flow cytometry, and by detection of clonal rearrangement of T-cell receptor chains (γ or δ) by PCR.[104 107 108 115 116]

Latent CD

The literature reveals at least five definitions of latent CD: positive CD serology in patients with normal mucosa or absence of VA;[124–129] and normal mucosa in patients who are on a gluten-containing diet, but have had an earlier or will have a later flat mucosa when they eat gluten.[130–134] To some physicians latent CD is simply equivalent to undiagnosed CD,[135 136] whereas others refer to latent CD as CD preceded by another autoimmune disease (eg, type I diabetes or thyroid disease). Finally, latent CD is sometimes used to denote normal mucosa with non-serological abnormalities, such as an increased number of γ or δ cells, or increased mucosal permeability.[137] Considering that the terms potential CD and latent CD have

often been used interchangeably, resulting in confusion, we discourage the use of the term latent CD.

Potential CD

Potential CD relates to people with a normal small intestinal mucosa who are at increased risk of developing CD as indicated by positive CD serology.

Potential CD is also often used with different meanings. For some, potential CD means that the patient has an increased number of IELs in the villi[138] or increased expression of γ or δ cells.[139] To others, potential CD describes people with normal mucosa but positive CD serology.[140 141] Adding to this is the suggestion by Ferguson *et al* that all first-degree relatives to patients with CD have potential CD.[142]

We recommend that the term potential CD be used for people with normal small intestinal mucosa who are at increased risk of developing CD as indicated by positive CD serology. A difficulty in the definition of this group is variability in the adequacy of the biopsies that were taken to exclude the diagnosis of active CD, especially with the current knowledge that at least four biopsies need to be taken[143] and the bulb may be the only location of VA.[15]

CD autoimmunity

CD autoimmunity relates to increased TTG or EMA on at least two occasions when status of the biopsy is not known. If the biopsy is positive, then this is CD, if the biopsy is negative than this is potential CD.

The term 'coeliac disease autoimmunity' or 'coeliac autoimmunity' has been used to describe: individuals with positive TTG,[144–147] positive EMA,[148] positive EMA with positive/borderline TTG,[149] positive TTG on at least two occasions,[150] and positive TTG on two occasions or a positive small bowel biopsy after only a single positive TTG.[151]

We defined CD autoimmunity as positive TTG or EMA on at least two occasions. In a clinical setting this will lead to a small intestinal biopsy, and patients can then be classified as either CD (positive biopsy) or potential CD (negative biopsy), but in a research setting there are circumstances when small intestinal biopsy has not been performed. The term CD autoimmunity should then be used. When TTG or EMA has only been tested on one occasion, it is preferable to refer to patients as TTG positive or EMA positive.

Genetically at risk of CD

Family members of patients with CD that test positive for HLA DQ2 and/or DQ8 are genetically at risk of CD.

CD is a multifactorial condition with unparallelled evidence of the pivotal role of HLA-DQA1*05-DQB1*02 (DQ2) and DQA1*03-DQB1*0302 (DQ8) in disease predisposition.[152 153] DQ2 and DQ8 are major risk factors carried by almost all patients with CD. Interestingly, when carried in *trans* on DR5/DR7 (ie, *DQA1*05-DQB1*0301/DQA1*0201-DQB1*02*) or DR3/DR7 (ie, *DQA1*05-DQB1*02/DQA1*0201-DQB1*02*) genotypes, the risk of CD in southern Europeans is higher than when the alleles are carried in *cis* on DR3 (ie, *DQA1*05-DQB1*02*) alone, suggesting that additional factors in the region may be influencing disease propensity.

Non-HLA genes together contribute more to genetic susceptibility (approximately 65%) than the HLA genes (the remaining 35%), but the contribution from each single, predisposing non-HLA gene appears to be modest.[154]

At the moment, the concept of genetically at risk for CD should be limited to family members (of patients with CD) who test positive for HLA-DQ2 or HLA-DQ8, with the understanding that the risk varies between 2% and 20%, depending on the degree of the relative with CD and the number of copies of HLA-DQ2 genes. However, people who harbour these genes are at risk of developing CD.

Gluten intolerance

The term gluten intolerance has been used as a synonym of CD and to indicate that a patient experiences a clinical improvement after starting a GFD, even when they do not have CD.[8 76 122 155–166] However, we believe the term gluten intolerance is non-specific and carries inherent weaknesses and contradictions. Although gluten intolerance could be a consequence of poor digestion, it could also be the effect of some lectin-like properties of gluten or foods generated from gluten that cause gastrointestinal upset. Another problem is that gluten intolerance may not truly reflect intolerance to gluten but to other wheat components.[156] Because of these contradictions, we recommend that the term gluten intolerance should not be used and that gluten-related disorders be used instead.

Gluten-related disorders

Gluten-related disorders is a term used to describe all conditions related to gluten.

We recommend that this term is used to describe all conditions related to gluten. This may include disorders such as gluten ataxia, DH, non-coeliac gluten sensitivity (NCGS) and CD.[115 167 168]

Gluten sensitivity

In some papers the term gluten sensitivity is used synonymously with CD.[7] Other papers used the concept of gluten sensitivity as an umbrella term to include CD and other conditions related to gluten ingestion, such as DH,[169] gluten ataxia[170] and NCGS.[156] Most recently,[157 171–174] several authors employed the term gluten sensitivity to describe a condition in which symptoms are triggered by gluten ingestion, in the absence of TTG or EMA antibodies and enteropathy, with variable HLA status and variable anti-gliadin (AGA) presence. It is important to distinguish CD from less well characterised diseases related to gluten ingestion. We therefore recommend that the term gluten sensitivity should not be used and that NCGS be used instead.

Non-coeliac gluten sensitivity

The term NCGS relates to one or more of a variety of immunological, morphological or symptomatic manifestations that are precipitated by the ingestion of gluten in people in whom CD has been excluded.

NCGS is a condition in which gluten ingestion leads to morphological or symptomatic manifestations despite the absence of CD.[172–176] As opposed to CD, NCGS may show signs of an activated innate immune response but without the enteropathy, elevations in tTG, EMA or DGP antibodies, and increased mucosal permeability characteristic of CD.[173] Recently, in a double-blind randomised trial, Biesiekierski *et al* showed that patients with NCGS truly develop symptoms when eating gluten.[156] It is unclear at this time what components of grains trigger symptoms in people with NCGS and whether some populations of patients with NCGS have subtle small intestinal morphological changes. While there is currently no standard diagnostic approach to NCGS, systematic evaluation should be conducted, including exclusion of CD and other inflammatory disorders.

Gliadin-specific antibodies

These are AGAs of IgA and IgG subclass recognising the gliadin moiety of wheat. Antibodies recognising native gluten are now rarely used for diagnostic purposes because they lack general specificity. Antibodies recognising DGP demonstrate high specificity and sensitivity. They can also be used for measurement of gluten in foodstuffs.

Use of the term gliadin-specific antibodies generally refers to antibodies directed against the gliadin moiety of wheat prolamins. The following four aspects of these antibodies are relevant to the spectrum of gluten-induced disease.

Diagnostic value

After introduction in the 1980s, IgA antibodies against wheat gliadin (AGAs) served as the best serological test for CD for some years.[177 178] However, the low positive predictive value[179] meant that this test has since been abandoned for the investigation of CD,[13 179] except for in children younger than 18 months, in whom IgA AGA seems to have high sensitivity.[180] Recently, assays for IgA and IgG antibodies against DGP have been introduced[181] and perform similarly to TTG-based tests.[179]

Increased gut permeability

Elevated levels of AGAs have also been used for the investigation of possible increased gut permeability, but this use in clinical practice lacks a strong scientific background.

Disorders beyond the classical enteropathy

AGAs are also relevant to gluten-induced disorders beyond the classical enteropathy. The most well known example is gluten ataxia. Patients with this disorder may have CD or only elevated levels of IgA or IgG AGAs[55] (see gluten ataxia).

Measurement of gluten in foods

Gluten-specific antibodies have a clear role in the food industry in that they are indispensable for measurement of gluten in foods. More recently, an assay using a monoclonal antibody recognising a major coeliac toxic epitope has been developed.[182] This assay is now the preferred method for gluten analysis in food.[183]

Coeliac disease serology

Coeliac disease serology is a term that includes endomysium, transglutaminase, deamidated gliadin antibodies, and in small children also gliadin antibodies for the assessment of CD.

Since the introduction of AGAs, antibodies have become an important means to diagnose CD. Serological testing has been used routinely in the investigation of CD since the 1980s. Whereas AGA tests were common in the 1980s and 1990s,[184] laboratories have since gradually shifted to EMA and TTG tests.[185–187] In most patient groups with suspected CD, EMA and TTG tests have a higher sensitivity and specificity than the AGA test.[188] We defined CD serology as an all-encompassing term that includes all available tests which have been shown in clinical studies to be sensitive for assessment of CD. Accordingly, we discourage the use of the term CD serology in that it is preferable to specify the antibody tests used because sensitivity and specificity differ substantially. We have nevertheless suggested a definition of this term because it is extensively used.

Gluten ataxia

Gluten ataxia can be defined as idiopathic sporadic ataxia and positive serum antigliadin antibodies even in the absence of duodenal enteropathy.

Gluten ataxia is one of a number of neurological manifestations attributed to CD. Defining criteria for gluten ataxia[170 189 190] include otherwise idiopathic sporadic ataxia in association with positive AGA with or without enteropathy on duodenal biopsy. Most reports (22 of 35 reports) after 1998 have used the same definition, that is, idiopathic sporadic ataxia with positive AGA (IgG or IgA, or both). However, a number of reports refer to patients with established CD (13 of 35 reports) without always providing serological information on these patients other than stating that the patient had CD (taken to imply the presence of enteropathy).[170 191–199]

One report examined the presence of IgA deposits on duodenal biopsies and found that all 10 patients with gluten ataxia (without enteropathy) had such deposits.[195] One study has identified a novel transglutaminase (TTG6) as a potential new serological marker for gluten ataxia,[192] but currently the most appropriate definition for gluten ataxia remains that of idiopathic sporadic ataxia with positive AGA.

Dermatitis herpetiformis

DH is a cutaneous manifestation of small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten. It is characterised by herpetiform clusters of pruritic urticated papules and vesicles on the skin, especially on the elbows, buttocks and knees, and IgA deposits in the dermal papillae. DH responds to a GFD.

DH is characterised by the presence of IgA deposits in the skin,[200–202] is strongly linked to an immune-mediated enteropathy precipitated by gluten,[65 203–205] and responds to a GFD.[206–209] A study from the USA in 1992 documented a prevalence of 11.2 per 100 000 people and an incidence of 0.98 per 100 000 people per year.[210] These rates are comparable to earlier studies of prevalence of DH in northern Europe.[205]

VA will be revealed by a single intestinal biopsy in two-thirds of patients, and by multiple biopsies in 95%. The enteropathy is variable in severity, but even in the presence of normal villous architecture, elevated levels of γδ T lymphocytes in the intestinal mucosa, elevated IEL counts and induction of VA are noted on gluten challenge, and these patients are very likely to reflect the entire spectrum of histological and clinical CD in adults.[65 211] The association with HLA is the same as in CD: 90% of patients have HLA DQ2 and almost all the remainder have HLA DQ8.[212] The skin lesions clear with gluten withdrawal but may also require treatment by the neutrophil inhibitor dapsone.[207 208 213] In the long term, adherence to a strict GFD shows 47% of patients can stop drug treatment completely; however 15% will not be able to reduce the dose of dapsone.[214]

DISCUSSION

This review was based on PubMed literature searches and expert meetings. We aimed to define key concepts relevant to CD and related disorders. The character of the current paper implies that we did not pool any data or use any statistical tools. Instead, we assembled an international team of recognised experts in CD research, discussed definitions and tried to reach a consensus. This approach is similar to that of previous papers on definitions of CD.[2–4] As opposed to previous studies,[2–4] however, we did not limit ourselves to 'CD only' but defined a large number of concepts. In addition, we provide guidance to the scientific and clinical community as to which terms should be used and which should be abandoned.

Overall, we evaluated more than 300 papers in detail and all authors participated in the discussion leading to consensus

definitions. We tried to avoid cumbersome definitions and have mostly avoided the inclusion of specific techniques, antibodies and measurements or units in these definitions. Cumbersome definitions are rarely used in practice and because of the progress in the CD research field, statements on specific tests may rapidly become obsolete.

Our research team was multidisciplinary and was composed of specialists from gastroenterology, pathology, paediatrics, neurology and dermatology. We hope that our definitions will be acceptable to all specialties dealing with CD and gluten-related disorders and anticipate that they will facilitate both research and clinical management of patients with these disorders.

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