

Celiac disease and non-celiac gluten sensitivity

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Cite this as: *BMJ* 2015;351:h4347
doi: 10.1136/bmj.h4347

ABSTRACT

Celiac disease is a multisystem immune based disorder that is triggered by the ingestion of gluten in genetically susceptible individuals. The prevalence of celiac disease has risen in recent decades and is currently about 1% in most Western populations. The reason for this rise is unknown, although environmental factors related to the hygiene hypothesis are suspected. The pathophysiology of celiac disease involves both the innate and adaptive immune response to dietary gluten. Clinical features are diverse and include gastrointestinal symptoms, metabolic bone disease, infertility, and many other manifestations. Although a gluten-free diet is effective in most patients, this diet can be burdensome and can limit quality of life; consequently, non-dietary therapies are at various stages of development. This review also covers non-celiac gluten sensitivity. The pathophysiology of this clinical phenotype is poorly understood, but it is a cause of increasing interest in gluten-free diets in the general population.

Introduction

Celiac disease occurs in about 1% of the population worldwide, although most people with the condition are undiagnosed.¹ It can cause a wide variety of symptoms, both intestinal and extra-intestinal because it is a systemic autoimmune disease that is triggered by dietary gluten. Patients with celiac disease are at increased risk of cancer, including a twofold to fourfold increased risk of non-Hodgkin's lymphoma and a more than 30-fold increased risk of small intestinal adenocarcinoma, and they have a 1.4-fold increased risk of death.²

Studies of stored serum show that the prevalence of celiac disease has increased fourfold to fivefold over the past 50 years, and the reason for this rise is unknown, although it may relate to aspects of the hygiene hypothesis (exposure to micro-organisms and antibiotics).³ Despite advances in our understanding of its pathophysiology and improved diagnostic tools, the rise in celiac disease has been a largely silent epidemic, with undiagnosed patients going untreated and at increased risk of morbidity from intestinal and extra-intestinal symptoms, as well as the risks of cancer and mortality mentioned above.

Interest in gluten as a determinant or contributing factor in a variety of conditions has also increased, with many people identifying themselves as being gluten sensitive in the absence of celiac disease. The biological basis of gluten induced symptoms in the absence of celiac disease is largely unknown but may be related to immune responses to components of wheat apart from gluten. This review covers celiac disease and non-celiac gluten sensitivity because they are considered part of a spectrum of gluten related disorders.^{4, 5}

Sources and selection criteria

We identified relevant publications by searching PubMed

using the terms “c(o)eliac disease”, “c(o)eliac sprue”, and “gluten” from the year 2000 to 31 January 2015. We also identified publications by searching the bibliographies of relevant articles, as well as abstracts from Digestive Disease Week conferences for the years 2011-14 and the biennial International Coeliac Disease Symposium in 2011 and 2013. The literature review included randomized controlled trials, cohort studies, case-control studies, and cross sectional analyses. A few studies were randomized controlled trials, and those pertaining to celiac disease or non-celiac gluten sensitivity of adequate size and quality were included. Most studies were well designed non-randomized controlled trials or observational studies with controls. We included all relevant randomized trials on the subjects of celiac disease and non-celiac gluten sensitivity, and included other studies on the basis of relevance, sample size, quality, and outcomes.

Prevalence worldwide

Celiac disease currently occurs in about 1% of the general population worldwide.⁴ In Sweden this prevalence was first noted 15 years ago,⁶ and similar levels were subsequently reported elsewhere¹; even higher levels have sometimes been reported in young (12 year olds in Sweden) and older people (aged 52-74 in Finland).^{7, 8} In general, prevalence studies based on serology only (tissue transglutaminase (TTG) and endomysial (EMA) antibodies) report higher prevalence than screening that requires confirmation through small intestinal biopsy.^{9, 10}

Prevalence by country

The differences in prevalence between countries cannot be fully explained by diagnostic criteria. Two recent studies indicate a biopsy verified prevalence of 0.7-0.8%

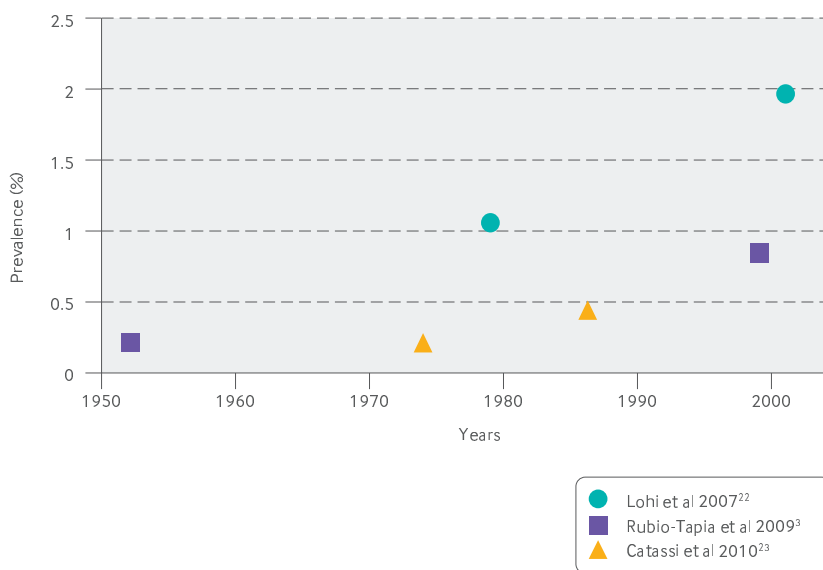


Fig 1 | Increasing prevalence of celiac disease over time as illustrated by screening studies

in the United States,^{1–11} which is consistent with earlier data from North America.¹² The disease seems to be more common in white people than in African-Americans or Hispanics in the US.^{1–13}

Data from Europe vary widely, with the United Kingdom and Germany having a low prevalence,^{14–15} while Sweden and Finland have perhaps the highest prevalence rates reported to date (2–3%).^{7–8}

Reports on the prevalence of celiac disease outside of Europe and the US are less abundant. The prevalence of celiac disease in China is low (probably because of the scarcity of the necessary HLA haplotypes, DQ2 and DQ8, in the Chinese population).¹⁶

The prevalence of biopsy verified celiac disease in the Indian Punjab region, where wheat is a staple food, is 1%.¹⁷ The disease is rare in people from sub-Saharan Africa—none of 600 people in Burkina Faso who were screened were positive for EMA or TTG antibodies.¹⁸

Prevalence by age

Because celiac disease can develop at any age¹⁹ and the absolute mortality rate after diagnosis is low,^{2–20} it might be expected that the prevalence of disease would be higher in older age groups. The similar prevalence in children and adults is therefore surprising.¹⁰ The conspicuous lack of a higher prevalence in adults may partly be the result of cohort effects. For instance, the incidence of celiac disease increased dramatically among young children during an approximately 10 year period in Sweden that began in the late 1980s, and the prevalence of celiac disease in those who were born during that period remains raised.²¹ Screening studies of unselected people have shown an increase in the prevalence of celiac disease over time—both undiagnosed plus diagnosed disease^{22–23} and undiagnosed disease only (fig 1).³

First degree relatives of people with the disease form a special high risk group. The lifetime risk of celiac disease in these people has been estimated at 4–17%.^{12–24} First degree relatives who are homozygous for HLA DQ2

are at particularly high risk, with about a 26% chance of developing celiac disease during childhood.^{25–26} Second degree relatives are also at increased risk, although the risk is smaller.¹²

Incidence of diagnosed celiac disease

Several studies suggest that the incidence of diagnosed celiac disease is increasing. Data from a North American county have shown a continuous rise in incidence since the 1950s,²⁷ reaching 17 per 100 000 person years in 2008–2011.²⁸ Similar data were recently reported from the UK,¹⁴ where the incidence in an unselected population reached 19 per 100 000 person years in 2010 and 2011.

The prevalence and incidence of celiac disease are dependent on several factors:

- Underlying genetics of the population (a prerequisite for diagnosis)
- Gluten exposure and possibly infant feeding patterns
- Other environmental risk factors
- Awareness of disease (among patients and physicians)
- Method and frequency of testing.

Although the rise in the prevalence of celiac disease may be partly due to changing diagnostic criteria (serology *v* histological examination), this is unlikely to be the only reason for the increase. Thus, other factors must be sought to explain these higher rates.

Environmental risk factors

Even in monozygotic twins, concordance is only about 85%.²⁹ The lack of concordance suggests that non-genetic factors are crucial in the development of celiac disease. The most obvious risk factor is gluten exposure. In settings with a high gluten load (such as refugee camps of the Saharawi people in Africa³⁰ and formula fed Swedish infants born in the early 1990s²¹) well over 1% of the population was affected.

Infant feeding patterns

Given that an epidemic of celiac disease in Swedish infants coincided with a change in infant feeding recommendations,²¹ the timing of gluten introduction, quantity of gluten at introduction, and breastfeeding patterns in relation to gluten introduction had long been assumed to affect the development of celiac disease.³¹ However, three recent prospective observational studies have failed to confirm an association between breastfeeding patterns and later celiac disease.^{32–34} This lack of association was corroborated by two multicenter randomized clinical trials in 2014, which found no link between age of gluten introduction, ongoing breast feeding, and the development of celiac disease.^{25–26} Nevertheless, data on the importance of the amount of gluten given at introduction and whether a gradual increase in gluten exposure will protect against celiac disease need to be examined further.

Perinatal exposure

A Swedish study of prospectively collected data on perinatal risk factors in more than 11 000 people with celiac

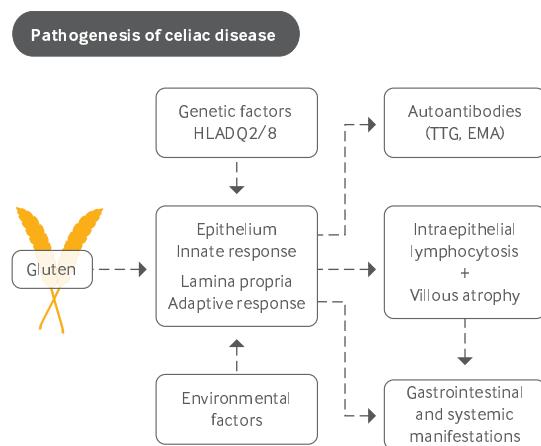


Fig 2 | The pathogenesis of celiac disease involves a triad of predisposing genes (HLA-DQ2 and HLA-DQ8 haplotypes), dietary gluten, and other less well defined environmental factors. Innate and adaptive immune responses to gluten fragments at the small intestinal epithelium result in characteristic autoantibodies, histologic changes (intraepithelial lymphocytosis and villous atrophy), and clinical symptoms (such as diarrhea or iron deficiency anemia). Adapted, with permission, from Green and colleagues⁴⁹

disease found no association between any cesarean section and later celiac disease (odds ratio 1.06, 95% confidence interval 0.99 to 1.13) but did find a small increased risk in those undergoing elective cesarean section (1.15, 1.04 to 1.26).³⁵ This might be because the baby does not enter the birth canal during elective cesarean section. This would have an effect on the baby's bacterial gut flora and could potentially mediate celiac disease.³⁵

Infection

As with other immune mediated diseases, such as type 1 diabetes,³⁶ viral infections have sometimes been linked to celiac disease,³⁷ but the evidence for an underlying viral trigger is inconclusive. Exposure to gastrointestinal infection during early life and adulthood seems to be linked to the development of celiac disease,^{33 38 39} but study shortcomings (potential recall bias,⁴⁰ lack of significance,³³ and data being significant only when analyzed for trend³⁸) make the interpretation of data difficult. One cross sectional study from the US suggests that gastric colonization with *Helicobacter pylori* may protect against the development of celiac disease.⁴¹

Smoking

Data on smoking are inconsistent and inconclusive. In the UK and elsewhere,⁴²⁻⁴⁴ smoking seems to protect against celiac disease. By contrast, other studies have found little association with smoking.⁴⁵ Population based prospectively recorded data on smoking are probably needed to determine whether smoking influences the risk of developing celiac disease.

Drugs

Drugs such as proton pump inhibitors and antibiotics have been linked to the development of celiac disease,^{46 47} but these data should be interpreted with caution because

some of these drugs may have been given in response to symptoms caused by undiagnosed celiac disease rather than triggering its development.

Pathophysiology

Celiac disease results from the interaction of environmental factors, mainly gluten, with immune and genetic factors (fig 2). For immunological reasons, the disease almost exclusively occurs in people with the DQ2 or DQ8 HLA haplotype.⁴⁸

Gluten is the term for the storage proteins of the cereal grains wheat, rye, and barley. Gluten proteins are rich in glutamines and prolamines and are therefore incompletely digested by gastric, pancreatic, and brush border peptidases, leaving large peptides up to 33 amino acids long.⁵⁰ These peptides pass through the epithelial barrier of the intestine and enter the lamina propria through a transcellular or paracellular route.^{51 52} The relative importance of each route in the pathogenesis of celiac disease is unclear.

The immune response to gluten involves both the adaptive and innate immune systems. Within the lamina propria an adaptive immune reaction occurs. TTG deamidates gliadin, and this increases its immunogenicity by altering the charge of the gliadin fragments that facilitate binding to the HLA DQ2 or DQ8 molecule on antigen presenting cells. Gliadin reactive CD4 positive T cells recognize gliadin peptides presented by these antigen presenting cells and subsequently produce proinflammatory cytokines,⁵³ especially interferon γ .⁵⁴ During the inflammatory cascade, the release of metalloproteinases and other tissue damaging mediators induces tissue injury.⁵⁵ During this process TTG antibodies are formed through unclear mechanisms. The role of these TTG antibodies in disease modulation is uncertain; however, they may contribute to systemic manifestations of celiac disease such as dermatitis herpetiformis.⁵⁶

The presence of increased intraepithelial lymphocytes (IELs) reflects the role of the innate immune system in celiac disease because IELs express the natural killer (NK) T cell receptors, NKG2D and CD9/NKG2A, which recognize the products of stress induced genes *MICA* and *MICB* and the protein HLA-E on epithelial cells.⁵⁷ Interleukin 15 (IL-15) plays a central role in upregulating NK receptors on these cytotoxic epithelial cells.⁵⁸ The mechanism of the interaction between the processes in the epithelium and lamina propria has not been elucidated. Recently non-gluten wheat proteins have been suggested to be responsible for the innate epithelial cell damage.⁵⁹

Clinical presentations and the role of screening

Celiac disease can present at any age, although nowadays rarely presents as a malabsorption syndrome with diarrhea, edema, and wasting.⁶⁰

Children

The major modes of presentation in children are recurrent abdominal pain, growth problems (failure to thrive and short stature), and the screening of high risk groups.⁶¹

A diarrhea predominant presentation currently occurs in only 10% of children and tends to be most prominent

in those who are very young at diagnosis.^{61 62} Those detected at screening have family members with the disease or have an autoimmune disease such as type 1 diabetes or thyroid disease. Children may be overweight or obese at diagnosis.⁶¹

Adults

Although diarrhea remains one mode of presentation that prompts testing for celiac disease in adults, most patients with the disease do not have diarrhea. Instead, most adults have one of the many “non-classic symptoms” such as anemia (usually as a result of iron deficiency, although it may be caused by chronic disease⁶³); osteoporosis; and various other presentations, including dermatitis herpetiformis, abdominal pain,⁶⁴ neurological or psychiatric problems,⁶⁵ infertility, aphthous stomatitis,⁶⁶ and vitamin deficiencies.⁶⁷

Screening

Patients may be diagnosed as a result of screening of high risk groups or incidental discovery at endoscopy, which is typically performed for reflux disease.⁶⁸ Most newly diagnosed patients have a normal body mass index, with 15% being underweight and a similar proportion being overweight or obese.^{69 70} The diagnosis is made more often in women than in men and is rarely made in young men.⁷¹

In adults, as with children, screening of at risk groups involves family members of people with celiac disease, as well as people with type 1 diabetes, other autoimmune disorders, and Down’s syndrome. Although celiac disease fulfils some of the World Health Organization criteria for general population screening, such screening is currently not recommended. Screening for celiac disease is controversial, with some authorities advising this practice in high risk groups,⁷² and others not.⁷³ Recent British Society of Gastroenterology (BSG) guidelines advise screening people at high risk, including those with a family member who has the disease.⁷⁴

Mortality and cancer in people with celiac disease

Mortality

Most studies indicate that celiac disease is associated with an increased risk of mortality^{2 75} and cancer.^{76 77} However, as shown in a meta-analysis, excess mortality is low,⁷⁸ and one British study published in 2015 even suggests that patients have no increased risk of death.²⁰ Different risk estimates may mirror country specific factors (such as disease management), but they may also depend on how disease is defined and how patients in each study are identified. The absolute risk of death is low. In the largest study so far the excess risk (attributable risk) beyond one year after diagnosis was 0.2 per 1000 person years in children (≤ 20 years) and 8.2 per 1000 in adults aged over 60 years at diagnosis.² In that study the risk of the most common causes of death (cardiovascular disease and cancer) was similar to that seen in the general population.

Cancer

Non-Hodgkin’s lymphoma has attracted most attention in celiac disease. Earlier reports of a 10-fold increased

risk in patients with celiac disease have been dramatically reduced to relative risks between two and four, with one study reporting an absolute excess risk of 40 per 100 000 person years.⁷⁷⁻⁷⁹ The risk of both T cell and B cell non-Hodgkin’s lymphoma is increased. The future risk of non-Hodgkin’s lymphoma is dependent on mucosal healing.⁸⁰ Of the gastrointestinal cancers, the largest relative increase is that for small intestinal adenocarcinoma (hazard ratio 31.0) although the absolute risk of that rare cancer is low (10 instances in 28 882 patients), and the absolute excess risk of any gastrointestinal cancer was two per 100 000 person years.⁸¹

Patients with celiac disease do not seem to be at increased risk of prostate cancer and breast cancer, which are common in the general population.^{82 83}

Other comorbidities and complications associated with celiac disease

Many of the conditions associated with celiac disease share a common genetic basis.⁸⁴ The genetic overlap does not only involve HLA genes but also non-HLA genes, such as those encoding CTLA-4 and myosin 1XB. *IL2* and *IL21* genes have also been linked to celiac disease.⁸⁵ However, considering the overwhelming importance of the HLA system, it is not unexpected that diseases that are associated with the same HLA haplotypes as celiac disease (such as type 1 diabetes and autoimmune thyroid disease) have been linked to celiac disease.⁸⁶

Autoimmune diseases

The prevalence of celiac disease approaches 5% in many autoimmune diseases. The association with celiac disease is often bi-directional—people with celiac disease are at increased risk of immune mediated diseases both before and after the diagnosis of celiac disease.^{87 88} One rationale for diagnosing minimally symptomatic celiac disease is that this may reduce the risk of developing other autoimmune diseases, although the results of studies on such a protective effect are conflicting.⁸⁹

Gastrointestinal disease

Celiac disease has also been linked to gastrointestinal disorders such as liver disease and pancreatic disease.⁹⁰⁻⁹³ The spectrum of disease varies from an asymptomatic increase in serum transaminases,⁹⁴ to liver failure,⁹¹ liver cancer,⁸¹ and pancreatic cancer.⁸¹ For several gastrointestinal cancers, particularly small intestinal adenocarcinoma, the relative risks are strikingly high in the first year after the diagnosis of celiac disease, suggesting that part of the increased risk may be due to ascertainment bias or confounding by indication.

The highest relative risks for liver disease in celiac disease have been seen in primary biliary cirrhosis.⁹⁵ Although cost effectiveness analyses have not been performed on this subject, it seems prudent to test for celiac disease in patients with raised transaminases of unclear cause and in patients with primary biliary cirrhosis.

Cardiovascular disease

Of particular interest has been the risk of ischemic heart disease because study results have been contradictory.

Sources of dietary gluten**Primary sources**

Wheat (triticale, semolina, spelt, khorasan wheat)
Rye
Barley (malt)

Hidden sources

Oats (unless harvested separately from wheat)
Sauces (marinades, soy sauce)
Drug fillers (prescription and over the counter items, including dietary supplements)
Shared food preparation equipment (pasta pot, toaster, deep fryer)
Processed meats

In general, Nordic studies have reported a positive association,⁹⁶⁻⁹⁸ whereas most British studies have noted an inverse association.^{20 98-100} This difference in relative risk for cardiovascular disease may reflect underlying factors, such as socioeconomic status and smoking, which seem to differ between countries.

Pregnancy

Unlike diagnosed celiac disease, undiagnosed disease has repeatedly been linked to adverse pregnancy outcomes, including spontaneous abortion.¹⁰¹⁻¹⁰⁴ However, in large scale studies, both diagnosed and undiagnosed celiac disease do not seem to be major risk factors for congenital malformations.¹⁰⁵ Recent data also indicate that infertility is rare in women with the disease.¹⁰⁶

Assessment and importance of healing of the intestinal mucosa**Persistent intraepithelial lymphocytosis**

After celiac disease is diagnosed and a gluten-free diet is started the intestinal mucosa usually starts to heal. This is a gradual process, and the median time to achieve a normal villous height was estimated to be 3.8 years in one study of 241 adults who underwent serial follow-up biopsy.¹⁰⁷ In some patients villous height normalizes but intraepithelial lymphocytosis persists. The implications of this are uncertain, but one study that compared 96 patients with persistence versus 74 patients with completely normal small intestinal histology found no difference in the risk of cancer or quality of life, although the study may have been underpowered for either of these two outcome measures.¹⁰⁸ Patients with persistent intraepithelial lymphocytosis were more likely to be regular consumers of oats, although this finding did not translate into clinical significance.¹⁰⁸

Persistent villous atrophy

By contrast, persistent villous atrophy has been linked to clinically important outcomes. A population based study of patients in Sweden who underwent follow-up biopsy found that 44% had persistent villous atrophy.¹⁰⁹ However, there was no difference between groups in overall mortality,¹¹⁰ cardiovascular outcomes,¹¹¹ or obstetric complications (in women who were pregnant within five years of follow-up biopsy),¹¹² although those with persistent villous atrophy were found to have a higher risk of lymphoproliferative disorders than those with mucosal

healing (hazard ratio 2.25, 1.18 to 4.34; absolute excess risk 57 per 100 000 person years).⁸⁰ Patients with persistent villous atrophy also had a higher risk of hip fracture and other fractures that were probably caused by osteoporosis than those with mucosal healing.¹¹³

Follow-up biopsy

Results of the follow-up biopsy correlate with adherence to a gluten-free diet and seem to be more sensitive as a marker of gluten exposure than normalization of TTG antibodies.¹¹⁴ Follow-up biopsy can therefore help discern the cause of persistent or recurrent symptoms and is crucial for the diagnosis of refractory disease. However, it is unclear whether a follow-up biopsy is needed in all patients. Management guidelines note that practitioners disagree about the need for routine follow-up biopsy in patients who become asymptomatic after starting a gluten-free diet, so it is not universally recommended in this setting.^{74 115} But the link between persistent villous atrophy and long term morbidity (specifically the risk of lymphoproliferative cancers and osteoporotic fractures) provides support for its role as a risk stratifying tool. Those with persistent villous atrophy, even if asymptomatic, may be appropriate targets for more intensive education with a dietitian; such an approach has been shown to improved histologic outcomes.¹¹⁴

Treatment**Diet**

The only known treatment is adherence to a lifelong strict gluten-free diet. Such a diet results in the normalization of symptoms in most patients, with a mean resolution of four weeks.¹¹⁶ Symptom improvement (resolution of diarrhea or abatement of abdominal pain) typically precedes serologic normalization of TTG antibodies (which can take months to more than a year) and is then followed by normalization (or at least improvement) of histologic results. As noted above, intestinal healing is not universal. In a population based study of Swedish patients, lower educational attainment was associated with an increased risk of persistent villous atrophy, which probably reflected poorer adherence to a gluten-free diet.¹⁰⁹

Limitations of a gluten-free diet

Although a gluten-free diet is effective when implemented correctly, many patients find it unsatisfactory. It is expensive, with bread and pasta substitutes costing substantially more than their gluten-containing counterparts.¹¹⁷ It can be socially isolating in settings such as communal celebrations, religious rituals, and dining out. Strict avoidance of gluten can be a challenge because of hidden sources of gluten (box). Potential hidden gluten in drugs or sauces is a legitimate source of anxiety for patients, including those who have minimal acute symptoms on exposure to gluten and so remain unsure of the safety of their daily practices. Given these everyday worries about gluten exposure, it is perhaps not surprising that patients' self rated treatment burden from adhering to a gluten-free diet was similar to that of patients with end stage renal disease in one questionnaire study.¹¹⁸ The shortcomings of this diet are also underscored by the fact that about

20% of patients report persistent or recurrent symptoms after diagnosis, and the most common cause of these symptoms is gluten exposure.¹¹⁹ (Other causes of persistent or recurrent symptoms in celiac disease, once the initial diagnosis is verified, include concomitant irritable bowel syndrome, additional food intolerances, microscopic colitis, and small bacterial overgrowth.)

Because of these problems with gluten-free diets, most patients are interested in non-dietary treatments for celiac disease.¹²⁰

Non-dietary treatments

Categories for drug therapy include the detoxification of ingested gluten (glutenases); the enhancement of tight junctions in the intestinal epithelium; a vaccine to induce gluten tolerance; and blockers of immune activation, such as inhibitors of the HLA DQ2 and DQ8 proteins or TTG.¹²¹

To date, two drugs have been evaluated in phase II studies. Larazotide acetate is an oral peptide that modulates tight junctions, enhancing the epithelial barrier to prevent immune activation in the lamina propria. In two randomized studies (270 patients) involving a gluten challenge, larazotide acetate did not differ significantly from placebo regarding the outcome of intestinal permeability (as measured by the lactulose to mannitol urinary excretion ratio). However, symptoms were attenuated ($P=0.013$) and the rise in TTG levels was blunted ($P=0.01$) compared with placebo.^{122 123} In another phase II study, a combined oral endopeptidase and endoprotease (ALV003) was compared with placebo in 34 patients with celiac disease who were undergoing gluten challenge. Those randomized to ALV003 had no significant reduction in villous height on intestinal biopsy, whereas those taking placebo had the expected gluten induced mucosal injury.¹²⁴ Subsequent trials of both of these drugs are planned.

Non-celiac gluten sensitivity

Worldwide there is a great interest in gluten-free diets, and many people have adopted such a diet in the absence of a diagnosis of celiac disease or clear health benefit.

The term non-celiac gluten sensitivity (NCGS) was coined to encompass those people who report symptoms that respond to withdrawal of gluten from the diet in the absence of celiac disease and wheat allergy.^{4 125} Perhaps a more accurate term for this condition is people who avoid gluten. It is not clear how common this condition is, or whether all those buying gluten-free food are on a strict gluten-free diet. However, data on this subject are available from several countries.

Prevalence of people who avoid gluten

In a population based questionnaire of 1002 people from the UK, 13% reported gluten sensitivity, with 3.7% claiming to be on a gluten-free diet.¹²⁶ In a similar random sampling of Australians ($n=1184$), 7.3 % reported adverse effects from wheat ingestion but most had had no formal medical assessment.¹²⁷ An analysis of population based data in the US (from the National Health and Nutrition Examination Survey) found that 0.55-0.63% of people

were adherent to a gluten-free diet in the absence of celiac disease, a prevalence similar to that of celiac disease (diagnosed and undiagnosed combined).^{1 128} Women and older people predominated.¹²⁸ A multicenter study from Italy ($n=12\ 255$) found that non-celiac gluten sensitivity was only slightly more common than celiac disease.¹²⁹ Some population groups seem to be especially wed to the gluten-free diet, with nearly 50% of 910 athletes (including world class and Olympic medalists) adhering to a gluten-free diet, mainly because of the perceived health and energy benefits.¹³⁰

Diagnosis

The concept of NCGS is not new—reports from the 1970s and 1980s describe patients who had a symptomatic response to wheat or gluten withdrawal in the absence of celiac disease.^{131 132} However, today NCGS is typically a self diagnosis or a diagnosis made by alternative health practitioners, with patients reporting both gastrointestinal and extra-intestinal symptoms.^{129 133 134} After gluten exposure those with NCGS report more symptoms than those with celiac disease.¹³⁵ People who avoid gluten rarely have celiac disease excluded before adopting a gluten-free diet,¹³⁴ and when evaluated alternative diagnoses such as fructose intolerance or small bowel bacterial overgrowth may be identified.¹³³

Association with irritable bowel syndrome

Some patients with irritable bowel syndrome improve when gluten is restricted. This was demonstrated in an Australian double blind randomized trial of 34 self identified gluten sensitive patients who experienced more symptoms when exposed to gluten compared with placebo (68% v 40%, $P=0.0001$).¹³⁶ In another randomized controlled trial in 45 patients with diarrhea predominant irritable bowel syndrome, a gluten containing diet was associated with increased bowel movements ($P=0.04$) and small bowel permeability ($P=0.028$), especially in those positive for HLA DQ2 or DQ8.¹³⁷ A subsequent study of 37 patients found that the effect of gluten exposure in patients with gluten sensitive irritable bowel syndrome was nullified by the use of a diet low in FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), indicating that other dietary products may be important in some people with NCGS.¹³⁸ That study raised the possibility that a large proportion of patients with apparent NCGS are instead sensitive to FODMAPs. Most recently, a randomized crossover trial of 61 patients found a significant increase in intestinal and extra-intestinal symptoms in patients exposed to gluten compared with placebo. However, most patients showed no significant difference and the positive result was driven by a large effect of gluten in three patients.¹³⁹

Pathophysiology

The pathophysiology of NCGS is unclear. Increased permeability of the small intestine was noted in two studies,^{137 140} but not in a third.¹⁴¹ Gut mucosal immune activation seems to be present, with increased CD3 positive intraepithelial lymphocytes compared with patients with celiac disease who are maintained on a gluten-free

diet,^{135 141} evidence of an adaptive immune response,¹⁴¹ and increased interferon γ response to a gluten challenge.¹³⁵

Interest has recently developed in the non-gluten components of wheat.¹⁴² These include the amylase trypsin inhibitors, which seem to activate the innate immune system,⁵⁹ and have been suggested to have a role in both celiac disease and NCGS. By definition those with NCGS lack celiac disease specific antibody markers, but some have antibodies to native gliadin, which are thought to have low specificity for celiac disease. In some patients with NCGS and antibodies to gliadin (especially IgG ones), the antibodies disappear and symptoms improve after a gluten-free diet is started.¹⁴³

Neuropsychiatric disorders

Gluten has been proposed to be involved in various neuropsychiatric disorders including schizophrenia, autism, peripheral neuropathy, and ataxia. Associations have been reported between these conditions, especially schizophrenia¹⁴⁴ and peripheral neuropathy,¹⁴⁵ and celiac disease. However, studies using larger databases and stored serum from patients with schizophrenia show a high incidence of anti-gliadin antibodies,¹⁴⁶⁻¹⁴⁸ rather than the more celiac disease specific antibodies, indicating a closer association with NCGS. The clinical significance of these anti-gliadin antibodies is not clear.

Similarly about 20% of people with autism spectrum disorder had antibodies to gliadin, specifically IgG anti-gliadin antibodies rather than the celiac disease specific antibodies to TTG or deamidated gliadin.¹⁴⁹ The largest study so far in this field, a population based cohort study of 26 995 patients with celiac disease, found no association between autism and biopsy verified celiac disease but did find a positive association between autism and positive serology, primarily the less specific gliadin antibodies (IgA and IgG).¹⁵⁰ Although the importance of these observations needs to be determined, future randomized studies of a gluten-free diet in people with various psychiatric disorders should be targeted at those with a measurable immune response to gluten.

Management

Because NCGS currently has no firm biologic basis, the approach to patients on a self prescribed gluten-free diet is uncertain. Measures should be taken to determine whether the patient has celiac disease, because this has implications for long term dietary guidance and monitoring of complications. It is sometimes necessary to determine the patient's HLA haplotype in this setting because those negative for DQ2 and DQ8 will not have celiac disease. A focused evaluation for alternative causes of symptoms (such as irritable bowel syndrome or other food intolerances, including intolerance to FODMAPs) is also warranted. Finally, it is advisable to have a frank discussion with patients about the limited current understanding of non-celiac gluten sensitivity, offering guidance on medical and dietary follow-up to guide symptom control.

Future areas of research

Gluten exposure

The prevention of celiac disease in at risk people requires further investigation. The negative results of two recent randomized trials evaluating early low dose gluten exposure at four months after birth²⁵ or delayed gluten exposure until 12 months²⁶ have led to speculation about why these interventions failed and whether celiac disease can be prevented at all.¹⁵¹ Nonetheless, these trials did provide evidence that the number of copies of the HLA DQ2 gene effectively stratifies patients with regard to subsequent risk of celiac disease. In both trials, more than 25% of infants who were homozygous for HLA DQ2 developed the disease,^{25 26} indicating that this high risk group may be of particular interest when studying future interventions. However, most of those who develop celiac disease do not have a family history and are therefore not in this high risk group.

Although studies into the dose or duration of gluten exposure in infancy may prove useful, further study is needed into exposure in adults. Because celiac disease can develop at any age, studies of dietary habits or drug use in adults may produce insights into the triggers of celiac disease.¹⁵²

Microbiome

The duodenal and colonic microbiome may prove to be an important mediator in the loss of gluten tolerance in at risk people. Patients with celiac disease have distinct duodenal microbial populations at diagnosis compared with non-celiac controls, with more abundant *Bacteroides* spp and *Escherichia coli*, and this normalizes after starting a gluten-free diet.¹⁵³ One study showed that the microbiome may contribute to, and not be a mere consequence of, the loss of gluten tolerance.¹⁵⁴ The study stratified infants of age 1 month who had a first degree relative with celiac disease by risk of celiac disease according to HLA haplotype. Those with an at risk (DQ2) gene had higher proportions of firmicutes and proteobacteria and lower proportions of actinobacteria in their feces than those who were negative for HLA DQ2 and DQ8. Because all of these infants had been vaginally delivered and exclusively breast fed (not yet exposed to gluten), the results indicate that these gut microbial characteristics are a consequence of HLA genotype and may contribute to the pathogenesis of celiac disease.

Reintroduction of gluten

Although there is a need to study prevention strategies for celiac disease, future research should focus on the re-induction of tolerance to gluten after diagnosis. Transient celiac autoimmunity, in which a person develops TTG antibodies that normalize with ongoing gluten ingestion, has been noted in children,¹⁵⁵ and it has been documented in one adult.¹⁵⁶ This provides proof of concept evidence that the development of celiac disease can be halted, although it is not known whether there is any step beyond which the path is irreversible.

A vaccine is being developed that consists of select immunogenic gluten peptides, and parenteral administration has been shown to mobilize gluten specific peripheral T cells in people with celiac disease who are adhering to a gluten-free diet.¹²¹ It remains to be seen whether the

QUESTIONS FOR FUTURE RESEARCH

Why is celiac disease increasing in incidence, and what environmental triggers can be modified so as to prevent its development?

What causes intestinal symptoms (abdominal pain and altered bowel habits) in patients with celiac disease and why do some patients have no symptoms?

Is the loss of tolerance to gluten irreversible or can tolerance be regained through immunotherapy?

Is there a biomarker that can distinguish patients with non-celiac gluten sensitivity from those with celiac disease and those with functional gastrointestinal disorders?

immune activation induced by this method can be manipulated into a way to re-induce tolerance.

Diagnosis and follow-up

In addition to efforts to prevent or reverse celiac disease, research is under way to improve diagnosis and follow-up. Point of care kits for diagnosis have been developed with the rationale that ease of testing will improve the problem of underdiagnosis.¹⁵⁷ One potential setting for such testing is in patients undergoing upper gastrointestinal endoscopy for any reason, because many of these patients do not undergo duodenal biopsy, so celiac disease may be missed.¹⁵⁸ Another potentially useful technology for patients adhering to a gluten-free diet is a consumer friendly detector of gluten in food. When developing such technology, ease of use, portability, speed, and accuracy would need to be optimized.

Biomarkers are also needed for the follow-up of patients with celiac disease. Assessment of symptoms, evaluation by a dietitian, serological test results, and follow-up histologic examination are currently used to assess adherence and response to a gluten-free diet. Efforts are under way to identify biomarkers that correlate more closely than TTG antibody titer with follow-up intestinal histology.

Intestinal fatty acid binding protein is one such candidate. In one study of patients with newly diagnosed celiac disease and patients adhering to a gluten-free diet for various durations, concentrations of this protein correlated with the degree of villous atrophy at diagnosis and on follow-up, and it was raised in those with normalized TTG antibody titer but persistent villous atrophy.¹⁵⁹ After further validation, this biomarker may be useful for the regular assessment of the patients with celiac disease. A marker of incompletely digested gluten, that is measurable in the stool as partial epitopes of a 33-amino acid chain, may also prove to be clinically useful when assessing adherence to a gluten-free diet.¹⁶⁰

A marker of celiac disease that remains present regardless of the duration of adherence to a gluten-free diet would be particularly useful when evaluating those people who avoid gluten who have not yet been tested for celiac disease, but such a marker has not yet been identified. A marker that can predict the degree of sensitivity to gluten is also needed. The minimum amount of ingested gluten that induces symptoms or villous atrophy varies substantially,¹⁶¹ and future biomarkers, such as those that could identify patients at high risk of complica-

tions or refractory disease, might enable a personalized approach, rather than the current blanket mandate of total gluten avoidance.

Education

Improvements in the diagnosis and treatment of patients with celiac disease are crucially dependent on the education of healthcare providers regarding the condition. Even in countries with a high rate of diagnosis patients may have symptoms for a long time before a diagnosis is made.¹⁶² There is a paucity of publications on celiac disease relative to its prevalence and compared with other gastrointestinal diseases, although the general quality is high,^{163 164} indicating that exposure to the disease among non-experts may not be great. Knowledge that celiac disease can be a cause of iron deficiency was poor in a recent survey of hematologists in the US,¹⁶⁵ and erratic screening practices in patients with diabetes reflect a lack of and inconsistent guidelines.¹⁶⁶ The development of national guidelines in Finland resulted in an increase in the diagnosis of celiac disease.^{162 167} Importantly, these guidelines had input from and targeted primary care physicians, a group that has first contact with patients and the potential to increase the rate of diagnosis.¹⁶⁸ Guidelines need to be developed that are consistent and applicable to the physician population who come into contact with patients with possible celiac disease.

Guidelines

Numerous societies have published guidelines on the diagnosis and management of celiac disease, including the British Society of Gastroenterology⁷⁴; the American College of Gastroenterology¹¹⁵; the World Gastroenterology Organisation¹⁶⁹; the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition⁷²; and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).¹⁷⁰ Broad areas of agreement include the need for active case finding to identify patients with celiac disease and for a strict gluten-free diet and assessment by a dietitian. All guidelines mandate a duodenal biopsy for diagnosis, except for ESPGHAN, which allows for the diagnosis to be made in certain scenarios on the basis of symptoms, the presence of high titers of celiac disease specific antibodies, and a compatible HLA haplotype.

Conclusion

Celiac disease is an increasingly common autoimmune condition that affects the intestine and has multiple systemic manifestations. Despite the increase in rates of diagnosis, most people with celiac disease remain undiagnosed. This must be remedied by appropriate testing and correct interpretation of serologic and histologic results. The availability of expert dietitians must be increased to improve the care of patients who strive to avoid hidden sources of gluten while maintaining a healthy diet. With knowledgeable patients and healthcare providers, advances in celiac disease will translate into symptom control, reduced morbidity, and improved quality of life.

Despite interest in the health effects of gluten in peo-

ple without celiac disease, the biology underlying NCGS is unclear. As such, future research should focus on the identification of biomarkers to better characterize what is probably a heterogeneous group of disorders. Evaluation of the innate immune response to gluten in people with NCGS, as well as long term natural history studies, will inform the management of these patients. Despite our lack of knowledge about the epidemiology, pathophysiology, and natural course of NCGS, the approach to people who avoid gluten should involve ruling out celiac disease, assessing for other disorders, and providing symptom based medical and dietary treatment.

Contributors: All three authors participated in all four components of authorship: the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PHRG is guarantor.

Funding: BL: National Center for Advancing Translational Sciences, National Institutes of Health (UL1 TR000040). JFL: Örebro University Hospital, Karolinska Institutet, the Swedish Society of Medicine, the Swedish Research Council—Medicine (522-2A09-195), and the Swedish Coeliac Society.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: PHRG serves on the scientific advisory boards of Alvine Pharmaceuticals and ImmusanT. The other authors have no competing interests.

Provenance and peer review: Commissioned; externally peer reviewed.

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