

PRACTICE

UNCERTAINTIES PAGE

Does gluten sensitivity in the absence of coeliac disease exist?

Imran Aziz *clinical research fellow in gastroenterology*¹, Marios Hadjivassiliou *consultant neurologist*², David S Sanders *professor of gastroenterology*¹

¹Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK; ²Department of Neurology, Royal Hallamshire Hospital, Sheffield

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com.

Coeliac disease is a chronic inflammatory disorder of the small bowel which affects 1% of the population.¹ The condition can be defined as a state of heightened immunological responsiveness to ingested gluten (from wheat, barley, or rye) in genetically susceptible individuals.² The gold standard diagnosis of coeliac disease is by the demonstration of villous atrophy on duodenal biopsies, with coeliac serology (endomysial and tissue transglutaminase antibodies) playing a supportive role.^{2,3} The cornerstone of treatment for coeliac disease is lifelong adherence to a strict gluten-free diet, which leads to improvements in clinical outcome, psychological wellbeing, and quality of life for most patients.²

However, the number of patients consuming a gluten-free diet seems greatly out of proportion to the projected number of patients with coeliac disease. Marketers have estimated that 15-25% of North American consumers want gluten-free foods,^{4,5} although recently published data from the United States and New Zealand suggest this may be an overestimation.^{6,7} Nevertheless, this is now “big business,” with Reuters projecting an increased revenue in the US gluten-free food market from \$1.31bn for the year 2011 to \$1.68bn by 2015.⁸ In tandem, a growing problem encountered in clinical practice is the diagnosis and management of patients complaining of gluten related symptoms in the absence of diagnostic markers for coeliac disease, such as negative coeliac serology and normal duodenal biopsies. These patients pose a clinical dilemma to gastroenterologists, general practitioners, and dietitians and in the past have been described as belonging to a “no man’s land” because of the diagnostic uncertainty.⁹

What is the evidence of the uncertainty?

A search of PubMed (“coeliac disease”) yielded over 18 000 citations, with only 170 PubMed citations to papers on gluten sensitivity in the absence of coeliac disease. We limited our search to systematic reviews, case series, case-control studies, and randomised controlled clinical trials conducted in adults.

Gluten related symptoms in patients without coeliac disease

Observational data exists of patients reporting gluten related symptoms but without evidence of coeliac disease. For instance in a prospective series of 94 adults who reported abdominal symptoms after cereal ingestion, 63% of study participants did not have either coeliac disease or cereal allergy on histological or immunological testing.¹⁰ Despite this, these individuals symptomatically benefited from a gluten-free diet, although the diet was not tested in a separate group of 30 controls.

Historically, it has also been noted that there seems to be an increased prevalence of antigliadin antibodies in those complaining of gluten related symptoms (40%)¹⁰ and in patients with irritable bowel syndrome (17%)¹¹ in comparison with healthy controls (12%),¹ despite the exclusion of coeliac disease through normal duodenal biopsies and negative tests for endomysial and tissue transglutaminase antibodies. A large, double blind, placebo controlled, crossover study has recently demonstrated the existence of wheat sensitivity in patients without coeliac disease: 920 patients with symptoms of irritable bowel syndrome undertook a standard four week elimination diet (wheat, cow’s milk, eggs, tomato, chocolate, plus any other known food hypersensitivities), then a two week crossover challenge with a one week washout period.¹² A third of patients (n=276) showed clinical and statistically significant sensitivity to wheat and not placebo, with worsening abdominal pain, bloating, and stool consistency. The evidence therefore suggests that, even in the absence of coeliac disease, gluten based

products can induce abdominal symptoms which may present as irritable bowel syndrome.

The recognition that reactions to gluten are not limited to coeliac disease has led to the development of a consensus document in 2012 among a panel of 15 international experts. A new nomenclature and classification was suggested, with three gluten induced conditions—coeliac disease, wheat allergy, and non-coeliac gluten sensitivity.¹³ The definition of coeliac disease is mentioned earlier. Wheat allergy is defined as an adverse immunologic reaction to wheat proteins that is IgE mediated—it can present as respiratory symptoms (baker's asthma or rhinitis, more common in adults), food allergy (gastrointestinal symptoms, hives, angio-oedema, or atopic dermatitis; mainly in children) and contact urticaria. Testing for wheat allergy includes IgE serum assay or skin prick test to wheat. Non-coeliac gluten sensitivity is a form of gluten intolerance when both coeliac disease and wheat allergy have been excluded.¹³ The prevalence of non-coeliac gluten sensitivity was reported at 6% based on the Maryland clinic experience (where, between 2004 and 2010, 5896 patients were seen, with 347 fulfilling the criteria for non-coeliac gluten sensitivity).¹³ However, the true prevalence in the general population is unknown. Furthermore, currently there are no specific biomarkers to identify non-coeliac gluten sensitivity, and the long term outcome for these patients is unknown.

Non-coeliac gluten sensitivity is an umbrella term and may incorporate a wide range of possible clinical features.¹⁴ Data from the Maryland clinic (n=347)¹³ and an evaluation of 78 Italian patients with non-coeliac gluten sensitivity¹⁵ show that subjects may associate gluten ingestion with intestinal symptoms such as abdominal discomfort, bloating, pain, and diarrhoea (also consistent with irritable bowel syndrome) or with a variety of extra-intestinal symptoms such as headaches, "foggy mind," depression, fatigue, musculoskeletal pains, and skin rash. Some investigators have suggested that, whereas patients with coeliac disease demonstrate both an innate (non-specific) and adaptive (specific, T cell mediated and antibodies) immune response to gluten exposure, those with non-coeliac gluten sensitivity seem to show only an innate response.^{16 17} The table¹ summarises the spectrum of gluten related disorders.

Gluten versus other wheat components

There is also uncertainty as to whether it is the withdrawal of gluten specifically that benefits patients or whether another component of wheat is the culprit. Expert opinion^{8 18} and a double blind, randomised, placebo controlled, re-challenge trial¹⁹ suggest that fermentable fructans (carbohydrates present in wheat) may provoke gastrointestinal symptoms in patients with irritable bowel syndrome. Thus, withdrawal of gluten might inadvertently be reducing the ingestion of fructans, which interplay with gut microbiota, gas production, and fermentation.^{8 18 19} Current evidence to support the withdrawal of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) for irritable bowel syndrome may overlap with a gluten-free diet.^{20 21}

Recently, a double blind, randomised, placebo controlled, re-challenge trial evaluated 34 patients with irritable bowel syndrome in whom coeliac disease was excluded and who had been symptomatically controlled on a gluten-free diet. Over a six week period, significantly more of the group exposed to products containing gluten but specifically prepared free of FODMAPs (and thus of fructans) reported a clinically significant deterioration in symptoms including abdominal pain, bloating, satisfaction with stool consistency, and tiredness.²² Individuals

showed no evidence of intestinal inflammation or damage while being challenged with gluten, and thus no clues to the pathophysiological mechanism involved were elicited. Although the number of participants in this study was small, the results suggest that gluten itself may induce gastrointestinal symptoms in individuals with non-coeliac gluten sensitivity. Larger multicentre studies would help to substantiate these findings and perhaps further delineate patients' sensitivity to gluten and fructans

Is ongoing research likely to provide relevant evidence?

A search of the metaRegister of Controlled Trials (www.controlled-trials.com/mrct/) and the US ClinicalTrials.gov database (www.clinicaltrials.gov/) found one relevant study—a multicentre trial currently recruiting gluten sensitive subjects without coeliac disease. Patients receive a gluten-free diet for two weeks and will then be randomised (double blinded) to a two week diet with either gluten or placebo, followed by a gluten-free diet for another two weeks. The primary outcomes are global symptom scores, while secondary outcomes are possible markers that may differentiate non-coeliac gluten sensitivity from coeliac disease (serological, gut barrier function, immunological, and expression of tight junction constitutive proteins). Recommendations for future research are listed in the box.

What should we do in the light of uncertainty?

With the increasing worldwide consumption of the "Mediterranean diet," it is apparent that physicians are increasingly being exposed to patients with gluten related disorders. For patients who report wheat intolerance or gluten sensitivity, exclude coeliac disease (with endomysial and/or tissue transglutaminase antibodies and duodenal biopsies on a gluten containing diet) and wheat allergy (IgE serum assay or skin prick test to wheat). Those patients with negative results should be diagnosed with non-coeliac gluten sensitivity. These patients benefit symptomatically from a gluten-free diet. They should be told that non-coeliac gluten sensitivity is a newly recognised clinical entity for which we do not yet fully understand the natural course or pathophysiology.

Contributors: All authors wrote the manuscript and approved the final version. DSS is guarantor for the article.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; DSS has received an unrestricted educational grant from Dr Schär (a gluten-free food manufacturer) to undertake research on gluten sensitivity; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

- 1 Sanders DS, Patel D, Stephenson TJ, Ward AM, McCloskey EV, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol* 2003;15:407-13.
- 2 Hopper AD, Hadjivassiliou M, Butt S, Sanders DS. Adult coeliac disease. *BMJ* 2007;335:558-62.
- 3 Hopper AD, Cross SS, Hurlstone DP, McAlindon ME, Lobo AJ, et al. Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. *BMJ* 2007;334:729.
- 4 Painter K. Gluten-free diets gaining in popularity. *USA Today* 2008 Aug 17.

Recommendations for future research

- Population prevalence and natural history of gluten related disorders
- Identification of serological biomarkers for non-coeliac gluten sensitivity
- Comparison of symptoms and quality of life between patients with coeliac disease and those with non-coeliac gluten sensitivity
- Are there long term complications associated with non-coeliac gluten sensitivity that are comparable to coeliac disease?

- 5 Di Sabatino A, Corazza GR. Nonceliac gluten sensitivity: sense or sensibility? *Ann Intern Med* 2012;156:309-11.
- 6 Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol* 2012;107:1538-44.
- 7 Tanpowpong P, Ingham TR, Lampshire PK, Kirchberg FF, Epton MJ, et al. Coeliac disease and gluten avoidance in New Zealand children. *Arch Dis Child* 2012;97:12-6.
- 8 Ferch CC, Chey WD. Irritable bowel syndrome and gluten sensitivity without celiac disease: separating the wheat from the chaff. *Gastroenterology* 2012;142:664-6.
- 9 Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* 2009;104:1587-94.
- 10 Kaukinen K, Turjanmaa K, Mäki M, Partanen J, Venäläinen R, et al. Intolerance to cereals is not specific for coeliac disease. *Scand J Gastroenterol* 2000;35:942-6.
- 11 Sanders DS, Carter MJ, Hurlstone DP, Pearce A, Ward AM, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. *Lancet* 2001;358:1504-8.
- 12 Carroccio A, Mansueto P, Iacono G, Soresi M, D'Alcamo A, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol* (forthcoming).
- 13 Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012;10:13.
- 14 Volta U, De Giorgio R. New understanding of gluten sensitivity. *Nat Rev Gastroenterol Hepatol* 2012;9:295-9.
- 15 Volta U, Tovoli F, Cicola R, Parisi C, Fabbri A, Piscaglia M, et al. Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol* 2012;46:680-5.
- 16 Sapone A, Lammers KM, Mazzarella G, Mikhailenko I, Carteni M, et al. Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. *Int Arch Allergy Immunol* 2010;152:75-80.
- 17 Sapone A, Lammers KM, Casolaro V, Cammarota M, Giuliano MT, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Med* 2011;9:23.
- 18 Pimentel M, Chang C. Inflammation and microflora. *Gastroenterol Clin North Am* 2011;40:69-85.
- 19 Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* 2008;6:765-71.
- 20 Biesiekierski JR, Rosella O, Rose R, Liels K, Barrett JS, Shepherd SJ, et al. Quantification of fructans, galacto-oligosaccharides and other short-chain carbohydrates in processed grains and cereals. *J Hum Nutr Diet* 2011;24:154-76.
- 21 Barrett JS, Gibson PR. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and nonallergic food intolerance: FODMAPs or food chemicals? *Therap Adv Gastroenterol* 2012;5:261-8.
- 22 Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011;106:508-14.

Accepted: 13 November 2012

Cite this as: *BMJ* 2012;345:e7907

© BMJ Publishing Group Ltd 2012

Table

Table 1 | The spectrum of gluten related disorders include coeliac disease, wheat allergy, and non-coeliac gluten sensitivity.¹³ In all three conditions symptoms improve on the withdrawal of gluten

Investigation	Coeliac disease* (adaptive immune response)	Wheat allergy† (allergic immune response)	Non-coeliac gluten sensitivity‡ (innate immune response)
Coeliac serology (endomysial and tissue transglutaminase antibodies)	Positive	Negative	Negative
Duodenal biopsies	Villous atrophy	Normal	Normal or near normal with raised intraepithelial lymphocytes
IgE serology or skin prick test to wheat	Negative	Positive	Negative

*Coeliac disease has the presence of positive coeliac serology and shows villous atrophy on duodenal biopsies.

†In wheat allergy there is the presence of positive IgE serology or skin prick test to wheat.

‡In non-coeliac gluten sensitivity there is negative coeliac serology (except possibly a positive gliadin antibody), negative wheat allergy testing, and normal to near normal duodenal biopsies (with raised intraepithelial lymphocytes only).¹⁵