

What's in a name? 'Non-coeliac gluten or wheat sensitivity': controversies and mechanisms related to wheat and gluten causing gastrointestinal symptoms or disease

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INTRODUCTION

The global population has more than doubled over the past 40 years, supported by the 'green revolution' in agriculture producing high-yield grain varieties, including wheat, that are central to the modern diet.¹ Wheat covers more than 200 million hectares of land,² is the third most produced cereal behind rice and maize,³ and is responsible for one-fifth of the world's calorific input.² Wheat contains gluten proteins, predominantly made of equal parts of glutenins and gliadins, which are resistant to digestion, and their partially digested epitopes are immunogenic and central to the process that leads to coeliac disease,^{3,4} an autoimmune condition characterised by an aberrant immune response to ingested gluten in genetically susceptible individuals, which results in small bowel inflammation, enteropathy and potential malabsorption.⁵ The prevalence of coeliac disease in the past 50 years has risen to approximately 0.7%–2%, a phenomenon attributed to increased awareness and detection, as well as a true increase in prevalence.^{6,7} The sole and current only curative treatment, a life-long gluten-free diet, considered central to the management of coeliac disease has also seen increasing popularity in the general population; there is a widespread underlying belief that a gluten-free diet may be 'healthier', despite a lack of evidence to support this notion and even evidence that it may be harmful to the non-coeliac population.⁸ This has seen the gluten-free food industry boom to an estimated US\$6 billion per year industry.⁵

NON-COELIAC GLUTEN SENSITIVITY: THE CURRENT PARADIGM

Gluten, or more generally wheat, has also been associated with other GI disease. In the absence of coeliac disease and under the guise of the increasingly fashionable but controversial label 'non-coeliac gluten/wheat sensitivity' (NCG/WS), gluten has been popularised in the press as a potential cause of almost all possible conceivable physiological complaints, ranging from GI to neurological, dermatological, psychological and musculoskeletal symptoms.^{9,10} The phenomenon of self-reported gluten or wheat sensitivity has reached such proportions that 15% of Australians believe their chronic GI symptoms are due to gluten or wheat,¹¹ with similar numbers reported in other international studies,¹¹ some of whom may have true undiagnosed coeliac disease.¹²

NCG/WS in the scientific literature is currently defined by stricter consensus criteria.¹⁰ Potential subjects (after coeliac disease and wheat allergy are excluded) undertake a gluten-free diet, and if any symptom (GI or otherwise) is responsive, then rechallenge with gluten and placebo is undertaken to see whether a reaction occurs confirming a formal diagnosis of NCG/WS.^{4,10} Due to the range of physiological complaints linked to NCG/WS,⁹ the consensus criteria allow for a total of 24 possible symptoms to be associated with the gluten challenge.¹⁰ A minority who self-report wheat sensitivity are shown to have reliable and reproducible symptoms when put through the formal diagnostic process.¹³

Using these criteria, the pathophysiology of the disorder has begun to be unravelled, including a landmark study in this journal by Uhde *et al*¹⁴ which described significantly increased serum levels of soluble CD14 and lipopolysaccharide-binding protein (LPS) in patients with NCGS made by strict consensus criteria. However, this study, like most in the field, allowed for a myriad of symptoms

(in this case 10) to define the disease, thus assuming that a single disorder underpins several separate clinical syndromes. This reflects a baseline assumption that those who have, for instance, a headache after ingestion of wheat or gluten are suffering from the same disease process as those who have diarrhoea and bloating, or constipation or 'brain-fog'. This reasoning is arguably akin to grouping all smoking-related respiratory symptoms under a common disease heading such of 'chronic smoking-related respiratory disease' to explain the fact that smokers can experience shortness of breath, cough and haemoptysis, all true but overlooking the fact that these smoking-related symptoms can be caused by several very distinct disease processes, with different treatments and outcomes.

This current NCG/WS criteria may also mistakenly include some with latent or subclinical coeliac disease as having NCG/WS. Observations such as those from Rosinach *et al*,¹⁵ demonstrating mucosal anti-tissue transglutaminase deposits and gamma delta T cells, highly sensitive markers for a diagnosis of coeliac disease, in patients fulfilling criteria for NCG/WS, or those from Vazquez-Roque *et al*,¹⁶ demonstrating higher symptomatic responses to a gluten containing diet in HLA-DQ2 or 8 positive IBS patients, support this notion. The current NCG/WS criteria may therefore need further refinement.

Defining a disease is not simple,¹⁷ but it is reasonable to base a definition on a set of highly specific clinical features, preferably related to an underlying pathological mechanism. However, without a definable symptom cluster linked to a clear pathological or immunological mechanism, we believe that the concept of 'non-coeliac gluten/wheat sensitivity' is unlikely to aid researchers to dissect the role of gluten or wheat in chronic unexplained GI or somatic symptoms. Gluten and wheat may very well be central in the pathogenesis of yet partially or unexplained disease processes. We believe an approach more likely to uncover the aetiological mechanisms behind these relationships is to ask whether gluten or wheat is a contributing or causal factor in more specific disease processes or symptom complexes. This approach has already been fruitful in linking gluten with psoriasis and neurological symptoms in preliminary studies^{18,19} and should be applied to GI disorders. The remainder of this article will illustrate this approach by focusing on already defined GI disorders in which gluten or wheat may play a causal role.

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IRRITABLE BOWEL SYNDROME

Patients with both self-reported and formally diagnosed NCG/WS predominantly complain of IBS type symptoms such as abdominal pain or discomfort, bloating and diarrhoea.⁹ Indeed, one of the first descriptions of NCGS was in a group of eight female patients with abdominal pain and diarrhoea, describing jejunal biopsies with normal architecture and mild lymphocytic infiltrates and increased intraepithelial lymphocytes which responded to a gluten free diet (GFD).²⁰ Patients with IBS often associate symptoms with the ingestion of food, and the elimination of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) has rapidly become standard of care.²¹ Gluten-free diets have also been trialled in IBS with some success. Multiple cohort studies and double-blind randomised placebo-controlled dietary trials have associated symptom improvement with a gluten-free diet in patients with IBS in both the short^{13,22} and long term.²³ These improvements have been associated with lower small bowel permeability, possibly implicating gluten in barrier disruption in IBS.¹⁶ However, a gluten-free diet is also low in FODMAPs, leading some investigators to consider whether the inadvertent lowering of these carbohydrates associated with a gluten-free diet are responsible for symptom relief, rather than removal of gluten itself. Biesiekierski *et al*²⁴ were not able to demonstrate reproducible symptoms triggered by gluten using a dietary crossover trial methodology in patients with IBS who had also been placed on a low FODMAP diet in addition to a gluten-free diet. A more recent study by Skodje *et al*²⁵ demonstrated fructan (a FODMAP carbohydrate) but not gluten responsiveness in 59 participants (of whom 18 fulfilled criteria for Rome III IBS) who had self-instituted a gluten-free diet for gut symptoms and were subsequently challenged with gluten, fructan and placebo. Although these were small studies, with short challenge durations and limited washout periods, their observations suggest that with IBS, or IBS-like symptoms, it is more likely to be FODMAP components in wheat, rather than gluten that induces symptoms. Other wheat-based compounds, such as amylase trypsin inhibitors (ATIs),²⁶ may contribute to IBS-like symptoms in a small subset, as ATIs have been shown to activate the innate immune system through Toll like receptor (TLR) signalling. Wheat-based foods may affect the intestine through

more than one pathway and induce symptom complexes mislabelled as NCG/WS.

FUNCTIONAL DYSPESIA

Functional dyspepsia (FD), characterised by early satiety, postprandial fullness or epigastric pain, in the absence of obviously definable pathology at gastroscopy, has been associated with wheat-based foods in observational studies.²⁷ Dyspeptic symptoms are also often linked with NCG/WS,⁹ although only one study specifically enrolled patients with FD and found that postprandial fullness and early satiety were significantly responsive to gluten elimination and rechallenge.²⁸ Duodenal eosinophilia has been observed in a major subset with the postprandial distress syndrome subtype of functional dyspepsia, a finding that has been linked to impaired duodenal barrier function and defective neuronal signalling.²⁹ Duodenal eosinophilia has also been demonstrated in NCG/WS³⁰ and so it is conceivable given the overlap between the two conditions that one of the antigenic triggers in functional dyspepsia may be gluten or other compounds in wheat. Randomised controlled trials are required to further explore this hypothesis.

EOSINOPHILIC GI DISEASES

Eosinophilic oesophagitis (EoE) is a Th2-mediated chronic inflammatory disease of the oesophagus characterised by eosinophilic infiltration (oesophageal mucosal eosinophilia of ≥ 15 eosinophils per high power field), which leads to dysphagia and food bolus obstruction in adults.^{31,32} A major trigger for this inflammatory response is believed to be food allergens, supported by multiple observations that the condition responds to food elimination diets.³² The six-food elimination diet removes the most commonly identified allergenic foods (wheat, milk, soy, nuts, eggs and seafood)³¹ and has been shown to alleviate the symptoms and histological changes of EoE.³³ Milk and wheat are the most commonly identified single food triggers.³²

Gladin has recently been implicated in the pathogenesis of EoE. Marietta *et al*³⁴ reported significantly higher levels of oesophageal gliadin deposits in active EoE as compared with inactive disease, EoE treated with a gluten-free diet and healthy controls. Subsequent perfusion with soy sauce (an undigested wheat source) in patients with EoE on a gluten containing diet did not increase gliadin staining levels suggesting that only partially digested

gluten epitopes are deposited in the mucosa.

Diets excluding wheat have also been effective in the treatment of eosinophilic diseases distal to the oesophagus, including eosinophilic gastroenteritis and colitis, but again research elucidating the specific dietary antigens are lacking.²⁹

INFLAMMATORY BOWEL DISEASE

Epidemiological studies have implicated several dietary factors in the pathogenesis of IBD.³⁵ Removal of all dietary antigens with exclusive enteral nutrition has been shown in multiple studies to be as effective as corticosteroids for remission induction in children with Crohn's disease.³⁶ More recently, an exclusion diet in conjunction with partial enteral nutrition, eliminating gluten as well as other potentially proinflammatory foods such as animal fats, sulphites and emulsifiers, was observed to induce clinical remission in 62% of patients in a cohort of 21 adults and children refractory to biologic therapy with antitumour necrosis factor agents but there was no control group.³⁷ In a mouse model of Crohn's disease, early feeding with a semisynthetic diet was shown to prevent ileitis; however, fortification of this experimental diet with gluten did not prevent ileitis, despite not causing T cell activation, implicating gluten in the pathogenesis.³⁸

Self-reported wheat sensitivity has been reported in 25%–28% of patients with IBD.^{39,40} In Crohn's disease, this observation has been linked with higher disease activity,³⁹ stricturing disease,^{39,40} recent flares³⁹ and extraintestinal manifestations.⁴⁰ Many with IBD turn to a GFD for control of symptoms, with 19% previously trying a gluten-free diet and 8% currently adherent to a gluten-free diet in one survey.⁴¹ The alternative hypothesis is that gluten-free diets benefit the not inconsiderable subset of patients with IBD with concurrent IBS⁴² secondary to the lowering of FODMAP content as discussed above. Randomised studies are needed, examining the endpoint of mucosal healing, if we are to ascertain if gluten is a causal trigger of symptoms or disease flares.

DYSBIOSIS AND GLUTEN-RELATED GI PATHOLOGY

While gluten is likely involved in the exacerbation of multiple GI disorders, even within patients with coeliac disease, the presence of gluten alone cannot fully account for the disease, as the prevalence of susceptibility genes far exceed the

prevalence of coeliac disease.⁴³ A common observation across GI diseases is an altered composition of the intestinal microbiota (dysbiosis), often associated with reduced diversity and changes in microbial carbohydrate metabolism.⁴⁴ Dysbiosis recently also been demonstrated in patients with functional dyspepsia, with significantly higher relative abundance of *Streptococcus* compared with controls and lower relative abundance of *Prevotella*, *Veillonella* and *Actinomyces*.⁴⁵ While it is unclear whether these changes are causal or are a result of the GI disorder, there is sufficient evidence to suggest that the microbiome can contribute to disease and in many cases, such as with IBD, the altered microbiome persists during remission.⁴⁶ Notably in patients with coeliac disease, the microbiota does not normalise even with adherence to a gluten-free diet.⁴⁷

Important in this context is the fact that gluten and gluten-derived immunogenic peptides are relatively resistant to degradation by small intestinal digestive enzymes, but can be degraded by enzymes of bacterial and fungal origin.^{48,49} Thus, a common role for gluten across the pathology of GI disorders may lie in an altered capacity of the microbiota to digest gluten peptides, leading to an excess of immunogenic gluten-derived peptides (figure 1). This hypothesis would explain the importance of partially digested epitopes in EoE.³⁴ In addition, dysbiosis has been strongly implicated in the development of food allergies and murine models of dysbiosis suggesting alterations in intestinal innate immune status and increased uptake of food antigens.⁵⁰ A combination of altered microbial digestion and an increased intestinal permeability common to many GI

disorders may result in increased immune involvement observed in gluten-related GI disease.

THE WAY FORWARD

We believe that the current concept of non-coeliac gluten or wheat sensitivity may hinder our understanding of whether gluten or other compounds found in wheat are in fact causally related to unexplained GI disease. Inappropriately combining groups of patients with disparate and unrelated symptoms is unlikely to clarify our understanding of the likely complex interactions between specific dietary components, the host-genetic makeup and microbiome and resultant illnesses that may develop. Unravelling these complex mechanisms needs to start with meticulous phenotyping of patients based on specific and reproducible clinical

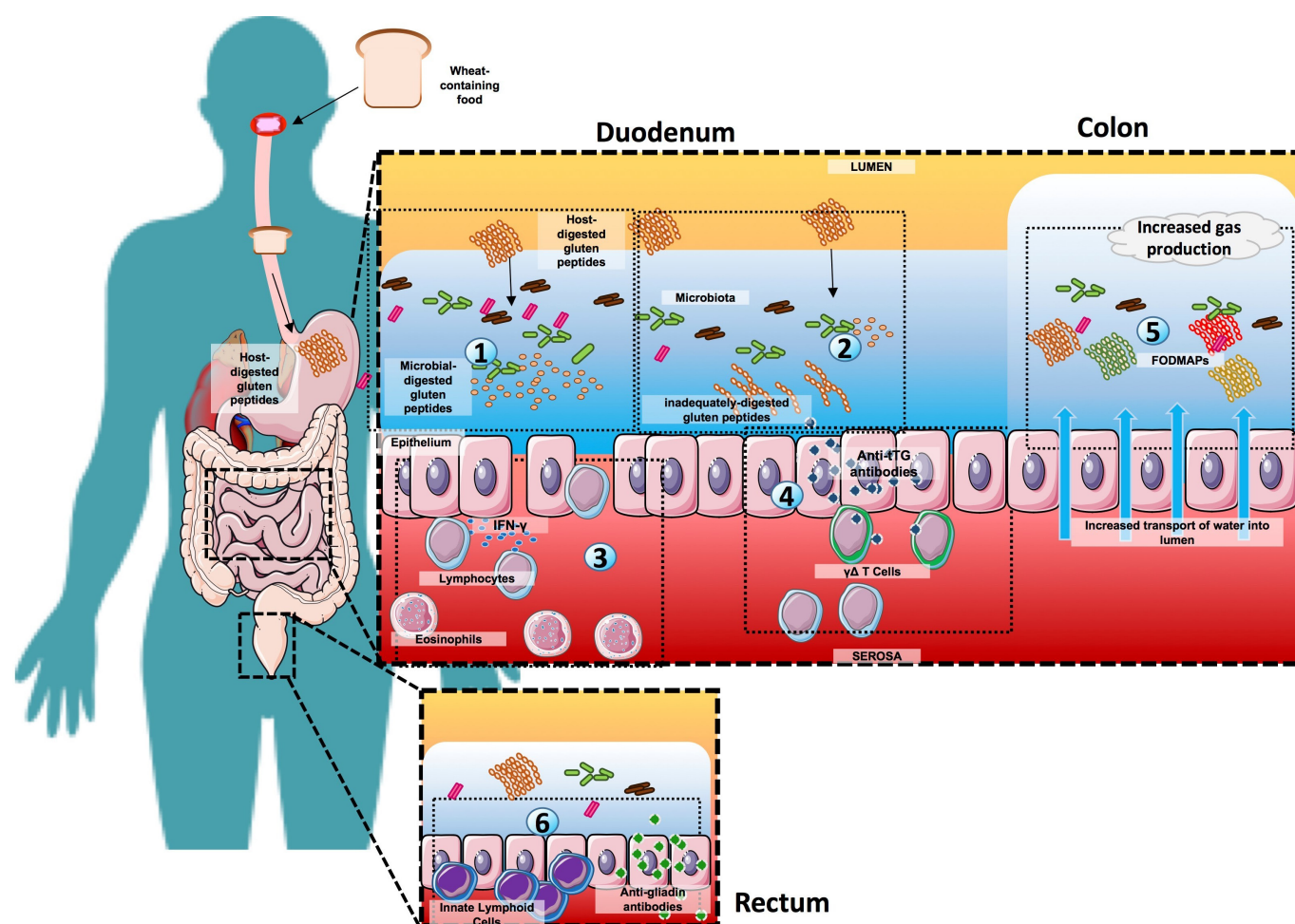


Figure 1 Potential pathways by which gluten may induce intestinal inflammation in GI disease. (1) Microbe and yeast-derived enzymes are required for complete proteolytic digestion of gluten peptides. (2) Dysbiosis may lead to incomplete digestion of gluten peptides increasing the concentration of immunogenic gluten-derived peptides in the gut. (3) Innate immune response to gluten peptides: increased small bowel (SB) permeability, IFN-γ, duodenal eosinophilia, lymphocytic duodenitis. (4) 'Coeliac like' mucosal deposits of anti-tTG, lymphocytic duodenitis with γδ T cells. (5) Poor absorption of carbohydrates (FODMAPs): increase in SB water volume, colonic gas production and altered intestinal motility. (6) Mucosal Th1 type response: rectal innate lymphoid cells, antigliadin antibodies. FODMAP, fermentable oligosaccharides, disaccharides, mono saccharides and polyols; IFN, interferon; tTG, tissue transglutaminase.

characteristics, such as those described in the Rome criteria, or based on already definable clinicopathological definitions such as are used in eosinophilic GI diseases or IBD, including biopsy. Using this as a starting point, then applying rigorous dietary studies which remove wheat and FODMAPs from the diet and then reintroduce specific compounds such as gluten, ATIs and FODMAPs and assess the mucosal response and immune activation is much more likely to uncover the true role of wheat or gluten in unexplained GI disease.

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