Non-Coeliac Wheat Sensitivity

The dark horse of gluten-related disorders


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Non-coeliac wheat sensitivity (NCWS), also commonly known as non-coeliac gluten sensitivity, is an emerging player in the spectrum of gluten- and wheat-related disorders whose clinical recognition correlates roughly with the explosive popularity of gluten-free diets. Only in the past decade has NCWS come to be recognised widely as a condition distinct from coeliac disease and wheat allergy, as a number of clinical trials and translational studies have begun to validate the condition, characterise its symptom profile, and offer insights into potential molecular triggers, pathogenic mechanism, and biomarkers. Although considerable uncertainty remains about many aspects of the condition, an examination of recent literature points a promising trajectory for progress in the understanding, diagnosis, and treatment of NCWS.

Coeliac disease & wheat allergy

Among conditions that are now referred to as gluten- and wheat-related disorders, coeliac disease and wheat allergy remain the most extensively studied and the best understood. Although an adverse immunologic reaction to specific proteins in wheat and related cereals drives the onset of both conditions, coeliac disease and wheat allergy are characterised by key differences in their susceptibility genes, pathogenic mechanisms, and diagnostic biomarkers.

Coeliac disease is an autoimmune disorder that affects about 1% of the global population. It is characterised by an immune reaction in response to the ingestion of gluten proteins of wheat and related cereals, including rye and barley, in genetically predisposed individuals. Genetic susceptibility is supported by its 10-15% occurrence rate in first-degree relatives, high concordance amongst identical twins, and its strong linkage to human leukocyte antigens (HLA)-DQ2 and -DQ8.[1] The clinical presentation of coeliac disease often includes diarrhoea, bloating, constipation, and abdominal pain, and extraintestinal symptoms can include anaemia, changes in bone mineral density including osteoporosis, and growth retardation in children.[2] The skin manifestation of coeliac disease, referred to as dermatitis herpetiformis, is characterised by itchy blisters and raised skin lesions.[3] The diagnosis of coeliac disease is aided and informed primarily by serological tests for IgA antibodies to the transglutaminase 2 autoantigen. The gold standard for coeliac disease diagnosis involves duodenal biopsy to confirm the associated inflammation and damage to intestinal villi that are triggered by the immune reaction to gluten.[4] Once confirmed, the only effective treatment is strict adherence to a gluten-free diet (GFD), although several therapeutics are in various stages of development and may play a role in treatment in the future. The consequent resolution of symptoms in response to the GFD is a further confirmation of coeliac disease diagnosis.[2]

Wheat allergy, on the other hand, is a food allergy characterised by IgE-mediated immune reactions primarily in response to ingestion or inhalation of wheat proteins. Both the gluten and non-gluten proteins in wheat can trigger wheat allergy, depending on the individual.[5] Affected patients can also be allergic to cereals closely related to wheat, such as rye and barley, due to allergen cross-reactivity.[6] The prevalence of wheat allergy is higher in children (close to 1%), as many outgrow the allergy before adulthood.[6] The associated IgE-mediated responses involve the activation of mast cells and other granulocytic cells and release of various inflammatory mediators, which is characteristic of allergic reactions and typically manifests in a range of symptoms including external swelling, asthma, allergic rhinitis, and anaphylaxis. Diagnosis of wheat allergy is aided by skin prick tests and serologic testing for IgE antibodies to wheat proteins. Similar to coeliac disease, the only known treatment is strict avoidance of wheat allergens, although desensitisation therapies are being studied and may be available in the future.[5]

Non-coeliac wheat sensitivity

The term non-coeliac gluten sensitivity was first used in 1978 by Elias and Linaker in a paper published in The Lancet to describe the successful treatment of gastrointestinal symptoms with GFD in a patient in whom coeliac disease was excluded.[7] Another publication in 1980 detailed eight non-coeliac patients with irritable bowel syndrome (IBS) whose symptoms also resolved on GFD. A focused and concerted examination of NCWS as a potential new clinical entity, however, did not begin until around 2010.[8] Consecutive meetings of expert panels in London, Munich, Salerno, and Merano between 2011 and 2016 helped to define NCWS and provide some guidelines for diagnostic criteria. NCWS is now accepted as a range of gastrointestinal and extra-intestinal symptoms in response to ingestion of gluten-containing foods, and remission of those symptoms on GFD, in the absence of coeliac disease and wheat allergy.[9] Bloating, abdominal pain, and diarrhoea are the more commonly reported gastrointestinal symptoms, while fatigue, headache, anxiety, joint/muscle pain, numbness in arms and legs, and cognitive difficulties feature prominently among the extra-intestinal symptoms.[10] In comparison with coeliac disease and wheat allergy, however, considerably less is known about the aetiology and pathology of NCWS.

Although the term most commonly used to refer to the condition – gluten sensitivity – implicates gluten as the cause, in reality the exact identity of the component(s) of wheat and related cereals that drive NCWS symptoms has not been firmly established. Most double-blind placebo-controlled clinical trials up to now have focused on gluten and nearly all have evidenced its role in NCWS to various degrees.[11] However, while the available evidence is substantial, it is important to consider the limitations of these studies as well. The lack of standardisation of the gluten challenges across studies makes it especially difficult to perform a meta-analysis of the available literature. There is considerable heterogeneity in the gluten vehicle and dosage, placebo, and challenge durations with varying wash-out periods across studies. Recruitment criteria and primary outcomes also differ between studies, thus further contributing to the observed variation in results and making the findings difficult to interpret collectively. These issues need to be overcome in future studies in order to reach a firm conclusion on the molecular triggers of NCWS.

A comparatively small number of clinical trials have also examined fermentable carbohydrates as potential contributors to NCWS symptoms. Carbohydrates make up about 80% of whole wheat grain and of that, approximately 7% is composed of low mass oligosaccharides, including fructan.[12] Wheat fructan and some of the other low mass saccharides are particularly prone to fermentation by gut microbiota and fall into a category of compounds that are now commonly referred to as fermentable oligo-, di-, mono-saccharides, and polyols (FODMAPs).[13] Because they tend to absorb water and ferment in a way that produces excessive gas, FODMAPs can cause gastrointestinal symptoms, particularly bloating and abdominal pain, in individuals who are hypersensitive to luminal distention.[14] However, FODMAPs are not believed to directly lead to immunologic response and inflammation. Clinical trials that have so far examined the relevance of FODMAPs in the context of NCWS support a role for them in contributing to the associated gastrointestinal symptoms in a subset of affected patients.[15, 16] However, similar to trials focusing on gluten, these FODMAP studies are also affected by discordant results and impacted by methodological issues that preclude firm conclusions.[17, 18] Taken together, the collective body of data so far are suggestive of the existence of multiple aetiologic triggers that implicate both gluten and FODMAPs in the heterogenous spectrum of NCWS, as it is currently defined.

Apart from gluten proteins and FODMAPs of wheat, non-gluten proteins have also come to be considered as a potential source of molecular triggers in the pathophysiology of NCWS. In particular, α-amylase/trypsin inhibitor (ATI) proteins of wheat have been proposed as possible contributors due to their observed inflammatory effects in preclinical studies.[19] Capable of inducing innate immune responses through interaction with toll-like receptor 4 (TLR-4), these proteins have been specifically shown to induce intestinal inflammation in the context of animal models of coeliac disease and colitis.[20, 21] However, despite these intriguing findings and the intense speculation that has followed, data to demonstrate a link between ATIs and symptoms of NCWS are not available yet. Clearly, future clinical trials and other studies focused on deciphering the role of wheat components in NCWS will need to account for ATIs and other non-gluten proteins as well.

Although the pathogenic mechanism(s) of NCWS is far from being fully understood, there has been progress on this front as well in recent years, which has also contributed to the identification of potential disease biomarkers.[9] Currently, the most robust scientific evidence for a biological basis of NCWS relates to intestinal barrier dysfunction and systemic immune activation in a significant proportion of patients.[9] The data demonstrate a correlation between increased levels of intestinal fatty acid-binding protein (FABP2), an indicator of increased epithelial cell turnover rate in the small intestine, and serologic markers of immune reaction to microbial and dietary antigens in affected patients.[22] These alterations, which appear to be responsive to dietary restriction of gluten-containing foods in patients, are indicative of a compromised intestinal barrier that leads to microbial translocation into systemic circulation and a systemic inflammatory response. This mechanism would be consistent with the observed rapid onset of NCWS and may also explain the appearance of extra-intestinal symptoms due to the probable activation of inflammatory responses elsewhere in the body.

Another study implicates the large intestine in NCWS pathology as well, as patients were observed to have inflammatory markers not only in their duodenal but also rectal tissues.[23] Patients presented more intraepithelial CD3+ T cells, lamina propria CD45+ cells, and eosinophils compared to controls, evidencing mucosal inflammation and implicating disruption of the colonic epithelium as a possible contributor to NCWS pathology.

Several lines of investigation have also pointed to a strong association between NCWS and elevated levels of IgG antibody to gluten,[22, 24-26] showing them to be comparable in titer to those in coeliac disease and to decline in response to GFD.[22] A newly published study has found that GFD reduces symptoms, particularly diarrhoea, in patients with IBS and elevated IgG antibody to gluten. The results point to the anti-gluten IgG antibody as a possible predictive biomarker. Although increased IgG response to gluten is seen in both coeliac disease and NCWS, another recent study finds these antibodies to be significantly different between the two conditions in their distributions of IgG1, IgG2, IgG3, and IgG4 subclasses.[27] The data point to divergent mechanisms in the B cell immune response to ingested gluten and antibody subclass switching in the two conditions. In addition to offering novel clues into disease pathophysiology, these and other studies of immune activation and intestinal barrier dysfunction in NCWS have provided candidate serologic

biomarkers with potential diagnostic utility to be further assessed and developed. The recent interest in NCWS by the scientific and clinical communities has generated a wealth of data and information that have allowed us to better understand the condition's clinical presentation and biological underpinnings. Double-blind placebo-controlled trials have demonstrated the existence of a condition unique from coeliac disease and wheat allergy, substantiating NCWS as a separate clinical entity. While the molecular triggers remain uncertain, there is promising evidence for the role of gluten and FODMAPs, with the potential for non-gluten proteins, as contributors to the NCWS disease spectrum. Other studies have further supported the recognition of NCWS by evidencing disease mechanisms that are distinct from those of coeliac disease and wheat allergy, particularly via a compromised intestinal epithelial barrier, microbial translocation, and systemic inflammation. In order to further explore NCWS in a more meticulous and robust manner, there is a need for established protocols on dietary challenges and participant recruitment in order to eliminate or reduce potential confounders. As with other diseases linked to the gut, greater consideration of the microbiome is also likely to be revealing and helpful to our understanding of NCWS pathophysiology. For now, the new spotlight and surge of research efforts are also beginning to reveal novel biomarkers that may allow us to more accurately diagnose and appropriately treat NCWS patients. With these details in mind for further focused research, the future for NCWS patients looks auspicious and a comprehensive understanding of the disorder and its novel therapies may be closer than it seems.

A summary of the current state of knowledge regarding gluten- and -wheat-related disorders

	Molecular triggers	Established or suspected mechanism(s)	Diagnostic biomarkers
Coeliac disease (and dermatitis herpetiformis)	Gluten proteins of wheat and related cereals	Mediated by T cells	Anti-transglutaminase or -endomysial IgA antibody; Anti-deamidated gluten IgG antibody; HLA-DQ2/DQ8; Villous atrophy and intraepithelial lymphocytosis on intestinal biopsy
Wheat allergy	Gluten and/or non-gluten proteins of wheat	Mediated by mast cells and IgE antibodies	IgE antibodies to wheat gluten and/or non-gluten proteins; Allergic reaction to skin prick test
Non-coeliac gluten/wheat sensitivity	Triggers are not firmly established: clinical data point to wheat gluten and fermentable carbohydrates as contributors	Linked to intestinal barrier dysfunction, microbial translocation, and systemic immune activation; Gas production and osmotic effects of fermentable carbohydrates	No established diagnostic biomarkers in clinical use yet. Identified candidate serologic markers include those linked. to antibody response to gluten, intestinal barrier dysfunction, microbial translocation, and systemic innate immune activation

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