Non-Celiac Gluten Sensitivity and Irritable Bowel Disease: Looking for the Culprits

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ABSTRACT

During the last 30 y, a gluten-free diet has been classified among the most popular fad diets mainly due to the ambiguous notion that gluten avoidance promotes health. Gluten intolerance has been implicated in non-celiac gluten sensitivity (NCGS) and irritable bowel syndrome (IBS), 2 disorders with overlapping symptoms and increasing trend. Together with gluten, other wheat components; fermentable oligo-, di-, monosaccharide, and polyols (FODMAPs); and amylase trypsin inhibitors (ATIs), are implicated in the pathogenesis of both disorders. Gut microflora alterations in IBS and NCGS have been described, while microbiota manipulations have been shown to be promising in some IBS cases. This literature review summarizes our current knowledge on the impact of wheat ingredients (gluten, FODMAPs, and ATIs) in IBS and NCGS. In both disorders, FODMAPs and ATIs trigger gut dysbiosis, suggesting that gluten may not be the culprit, and microbiota manipulations can be applied in diagnostic and intervention approaches. *Curr Dev Nutr* 2020;4:nzaa176.

Keywords: non-celiac gluten sensitivity, irritable bowel syndrome, gluten-free diet, microbiota, gluten, FODMAP, ATIs

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Abbreviations used: ATI, α-amylase/trypsin inhibitor; CD, celiac disease; DBPCFC, double-blind placebo-controlled food challenge; FODMAPs, fermentable oligo-, di-, monosaccharide, and polyols; FOS, fructo-oligosaccharides; GFD, gluten-free diet; GFP, gluten free product; GOS, galacto-oligosaccharides; IBS, irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, mixed IBS; GOS, galacto-oligosaccharides; NCGS, non-celiac gluten sensitivity; TGOS, *trans*-GOS; TLR, Toll-like receptor; WA, wheat allergy.

Introduction

During the last 30 y, the consumption of gluten-free products (GFPs) has become increasingly common, resulting in often being included in the list of fad diets with a great impact on the sales market of the Western world (1). The therapeutic role of a gluten-free diet (GFD) is undisputed in wheat allergy (WA) and celiac disease (CD), in which the reactions to gluten are mediated by the adaptive immune system (2). Nevertheless, the prevalence of these diseases is low, accounting for only 1% for CD and 0.1% for WA, and cannot justify the exponential rise in popularity of GFPs (3).

To date, 2 syndromes with unclear pathogenesis, diagnostic criteria, and epidemiology have been included under the umbrella of gluten-related disorders: non-celiac gluten sensitivity (NCGS) and irritable bowel syndrome (IBS), both having gluten among the causative agents of induction of their symptoms (4–9). Self-reporting of the implicated foods into symptom development is an integral part of diagnosis of both disorders, after the exclusion of CD and WA (4, 10), as a genetic predisposition has not yet been identified, nor damage to small-intestine villi or an antigen-triggering allergic reaction (11, 12). Nevertheless, some groups have reported a greater prevalence of the HLA-DQ2/DQ8 genes known to predispose to CD in NCGS patients than in the general population (12). The epidemiology of IBS and NCGS varies greatly in the Western world (10–15% and 0.6–6%, respectively), with estimations being questionable, as many patients start a GFD without any relevant clinical examination and diagnosis (6–9). The similar presentation patterns recognized so far for IBS and NCGS have led to proposing the term "IBS-like disorders," which also comprises NCGS (13). In general, the onset of symptoms starts after wheat consumption in both NCGS and IBS patients, leading to the assumption that gluten is the culprit. However, 2 other groups of wheat components have been implicated, as follows:

1. The fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs); short-chain fructose oligosaccharides (fructans); galacto-oligosaccharides (GOS; stachyose, raffinose); disaccharides (lactose); monosaccharides (fructose); and polyols (sugar alcohols), which are poorly absorbed in the human small intestine and are partially fermented in the large intestine by gut bacteria (14).
2. The wheat amylase trypsin inhibitors (ATIs), a family of up to 17 proteins with molecular weights of ∼15 kDa and a variable

primary but conserved secondary structure characterized by 5 intrachain disulfide bonds and α-helices and mostly form di- and tetramers.

Both these wheat ingredients induce inflammatory processes and alterations to gut microbiota. Intestinal dysbiosis in NCGS and IBS (15, 16) is known to affect various metabolic and inflammatory processes. The gut microbiota plays a crucial role in intestinal motility regulation and neuroimmune signaling (5). The so-called hidden organ of our body presents contigouos among people with similar genetic background, ethnicity, age, and sex, but remains malleable to noninvasive nutritional interventions (17–19). As such, microbiota manipulations could be of enormous therapeutic potential in inflammatory gastrointestinal diseases, like NCGS and IBS.

This literature review aims to investigate the current knowledge related to whether gluten is the actual culprit for NCGS and IBS disorders or the scapegoat for the benefit of the sales market of GFPs, with other wheat ingredients being responsible, in addition to the putative pathways related to microbiota dysbiosis in those who suffer from these disorders.

Methods

A literature search was performed of relevant published original research and reviews that were pertinent to the aim of this review. This involved searching databases of peer-reviewed published literature (Cochrane Library, EMBASE and CINAHL, MEDLINE, and Google Scholar) of both human and animal studies published from 2000 to 2020 on the involvement of gluten, ATIs, FODMAPs, and gut microbiota in IBS and NCGS.

comparative outline of research findings used is presented in **Table 1**. These in vivo and in vitro studies have published data regarding the distinct and overlapping pathophysiology of NCGS and IBS, which is summarized in **Table 2**. Although the entities remain obscure, the knowledge gained and further discussed can initiate future research for more accurate diagnosis and future therapeutic potentials and stop any unnecessary GFP consumption.

IBS presentation and pathogenesis

In IBS, obvious abnormalities or intestinal mucosal damage are usually absent. According to the Rome IV classification (20), IBS patients suffer from abdominal pain on average at least once a week for >6 mo before the diagnosis (5, 21). Clinical signs vary widely and include alterations in bowel habits, abdominal pain or distension, bloating or flatulence, absence of constitutional symptoms, and absence of alarming features such as weight loss, anorexia, gastrointestinal bleeding, and fever (5). Along with abdominal pain, changes in stool consistency and frequency or pain at defecation, flatulence, and bloating might occur (22). Based on the predominant bowel habit, patients are classified into 4 types: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS.

The outcome of IBS can be influenced by psychosocial stressors, whereas socio-relational status, work ability, and productivity, as well as everyday life activities, can be hindered (23). Emotional and personality patterns can contribute to IBS clinical features, symptomatology, and immune response (21) and can consequently affect treatment (Table 2).

The complexity of IBS pathogenesis is related to the multifactorial impact of symptom exacerbation: diet, sex, antibiotics, regulation of the gut–brain axis, stressful life changes, genetic factors, gut barrier permeability, defective immune responses, gut microflora alterations, and psychosocial factors are all implicated in symptom worsening (24). Notably, IBS is a disease of a gut–brain axis dysregulation, involving altered signaling between immune cells and neurotransmitters. Within the intestinal mucosa, the signaling between immune cells and nerve fibers of the enteric nervous system, such as mast cells and nerves, plays a key role in IBS. The symptom intensity is associated with the activation of immune and neuroendocrine cascades that correlate with changes in the gut microflora, intestinal permeability, and in dysfunctional sensorimotor outputs in the intestine (6).

Possible triggers in IBS

Diet along with stress and menstruation are the most common precipitating or exacerbating factors in IBS (25). Most IBS patients attribute their symptoms to food, with a long list of putative culprits (26). IBS patients' complaints often increase after the consumption of high-carbohydrate meals, resulting in the decision to remove wheat from their diet. Despite the various putative triggers among wheat components, gluten was considered by patients to be the culprit for recurrent gastrointestinal symptoms (23).

A similar presentation of increased colonic motility in IBS-D patients was observed in gliadin-sensitized HLA-DQ8 mice, where gluten stimulated a significant increase in the production of acetylcholine in the myenteric plexus and in high-amplitude propagating contractions, causing an increased colonic motility and a mild inflammation. Gluten removal from the diet eliminated these motor changes, indicating that gluten triggered the gut motor dysfunction (27). Similarly, in a study by Vazquez-Roque et al. (28), the intake of gluten-containing food (mean: 3.10 ± 0.46) in IBS-D patients who were carriers of the HLA-DQ2 and/or -DQ8 haplotypes increased the permeability of the small intestine, which was then accompanied by mild inflammation (Table 2).

Therefore, gluten can be a trigger for IBS patients with CD genetic predisposition. In another double-blind placebo-controlled study [double-blind placebo-controlled food challenge (DBPCFC)] in IBS-D patients without genetic predisposition, a GFD led to a significant improvement in their symptoms such as pain, bloating, stool consistency, and tiredness (29). In addition, Fritscher-Ravens and his group (30) used confocal laser endomicroscopy and reported intestinal leakage and epithelial breaks in half of IBS patients challenged with wheat, while all patients benefited from the GFD in the long term.

TABLE 1 Outline of research findings from the main studies on the role of gluten, ATIs, FODMAPs, and gut microbiota in IBS and NCGS[1]

Study (reference)	Subjects	Number of participants	Methods	Research findings
Human studies				
Biesiekierski et al., 2011 (29)	CD genetically predisposed subjects	34	Double-blind, randomized, controlled study	A GFD in IBS-D patients significantly improved their IBS-like symptoms
Fritscher-Ravens et al., 2014 (30)	IBS patients	36	Confocal laser endomicroscopy	Half of patients presented intestinal leakage and epithelial breaks after wheat challenge
Pedersen et al., 2017 (31)	IBS patients	89	Randomized controlled trial	FODMAP removal from the diet significantly decreased abdominal pain and bloating
Bennet et al., 2018 (32)	IBS patients	67	Randomized controlled trial	Low-FODMAP diet improved IBS symptoms and correlated with reduced *Bifidobacterium* and *Actinobacteria* fecal bacteria and with lactose consumption
Böhn et al., 2015 (33)	IBS patients	75	Multicenter, parallel, single-blind study	Low-FODMAP diet improved IBS symptoms
Frieling et al., 2019 (34)	IBS patients	93	Prospective study	Low-FODMAP diet improved IBS symptoms but patients lost weight and received insufficient nutrients
Staudacher et al., 2017 (15)	IBS patients	104	Randomized, controlled study	Low-FODMAP diet improved IBS symptoms and co-administration with multistrain probiotic increased *Bifidobacterium* fecal bacteria
Hustoft et al., 2017 (35)	IBS patients	20	Double-blind, randomized, controlled study	Low-FODMAP diet improved IBS symptoms and decreased serum IL-6, IL-8, fecal *Actinobacteria*, *Bifidobacterium*, and *Faecalibacterium*, SCFAs, and n-butyric acid
O'Keeffe et al., 2018 (36)	IBS patients	103	Long-term prospective study	Low-FODMAP education can be nutritionally adequate for 18 mo
Klem et al., 2017 (37)	IBS patients	45 studies	Meta-analysis from 1994	IBS onset is due to bacterial, viral, or parasitic infections in the microbiota
Kerckhoffs et al., 2009 (38)	IBS patients	41	FISH and PCR analysis of fecal and duodenal brush samples for microbiota composition	Decreased *Bifidobacteria* levels in IBS
Rajilić-Stojanović et al., 2011 (39)	IBS patients	62	Phylogenic microarray and PCR analysis of microbiota composition	Decreased *Bifidobacterium*, *Faecalibacterium*, and *Bacteroidetes* and increased ratio of *Firmicutes* to *Bacteroidetes*
Parkes et al., 2012 (40)	IBS patients	47	Hybridization of rectal biopsies for microbial quantification	Increased Bacteroides and Clostridia and reduced Bifidobacteria in mucosa-microbiota in IBS
Tana et al., 2010 (41)	IBS patients	26	Liquid chromatography and PCR analysis on fecal samples and abdominal X-ray films for gas quantification	Increased levels of *Veillonella* and *Lactobacillus*, acetic acid, propionic acid, and total organic acids

(*Continued*)

TABLE 1 (*Continued*)

Study (reference)	Subjects	Number of participants	Methods	Research findings
Rigsbee et al., 2012 (42)	IBS-D children	20	Phylogenetic microbiota array, FISH, PCR analysis on fecal samples	Different microbiota taxonomy in IBS with increased *Clostridia* levels
Labus et al., 2017 (43)	IBS patients	29	16S rRNA sequencing on fecal samples and structural brain images	Microbial composition correlated with structural measures of brain regions
Vandeputte et al., 2016 (44)	IBS patients	9	16S rRNA sequencing on fecal samples and lactulose breath testing	Increased levels of *M. smithii* methanogen in IBS-C and correlated with breath methane
Tap et al., 2017 (45)	IBS patients	110	Assessment of 16S rRNA sequencing on fecal samples and mucosal samples for microbiota, exhaled H_2 and CH_4, psychological and gastrointestinal symptoms, and fecal methanogens	IBS symptom severity associated with decreased microbial richness, exhaled CH_4, methanogens, and enterotypes with *Clostridiales* or *Prevotella* species
Silk et al., 2009 (46)	IBS patients	44	Randomized, parallel, crossover, controlled clinical trial	Prebiotics increased fecal bifidobacteria
Hunter et al., 1999 (47)	IBS patients	21	Double-blind crossover study	Oligofructose prebiotics did not improve IBS symptoms
Olesen et al., 2000 (48)	IBS patients	98	Multicenter, prospective, randomized, double-blind, placebo-controlled parallel study	Oligofructose prebiotics did not affect IBS symptoms
Paineau et al., 2008 (49)	IBS patients	105	Comparative, randomized, double-blind study	Oligofructose prebiotics improved significantly the IBS symptoms
Didari et al., 2015 (50)	IBS patients	24 studies	Meta-analysis on the efficacy of probiotics in IBS	Probiotics improve IBS symptoms
Min et al., 2012 (51)	IBS patients	130	Randomized controlled study	Yogurt with acacia fiber and *B. lactis* has significant therapeutic effects in IBS
Tsuchiya et al., 2004 (52)	IBS patients	68	Randomized, blind control study	Administration of symbiotic novel symbiotic Microflorana F (SCM-III) increased *Lactobacilla*, *Eubacteria*, and *Bifidobacteria* and improved IBS symptoms
Chey et al., 2015 (53)	IBS patients	1074	Phase 3, randomized, double-blind, controlled study	Repeated rifaximin treatment was efficacious in IBS-D patients with relapsing symptoms
Dieterich et al., 2019 (22)	NCGS patients	19	Clinical trial	Low-FODMAP diet improved clinical and psychological NCGS symptoms. NCGS patients present a microbiota dysbalance
Zanini et al., 2015 (54)	NCGS patients	35	Randomized, double-blind, clinical study	Symptom recurrence occurred in one-third of the patients after gluten challenge
Dale et al., 2018 (55)	NCGS patients	20	A randomized, double-blind controlled study	NCGS symptoms did not re-appear after gluten challenge in most patients

(*Continued*)

TABLE 1 (*Continued*)

Study (reference)	Subjects	Number of participants	Methods	Research findings
Skodje et al., 2018 (56)	NCGS patients	59	Randomized, double-blind crossover study	Fructans rather than gluten-induced NCGS symptoms in 24 patients
Molina-Infante et al., 2017 (57)	NCGS patients	231	Data analysis from 10 double-blind, controlled study	Heterogeneity and methodology flaws among studies of gluten challenge; the role of gluten in NCGS is questionable
Tovoli et al., 2017 (58)	NCGS patients	44	Questionnaire-based study	About 70% of patients continued to have NCGS symptoms after 1 y of a GFD
Garcia-Mazcorro et al., 2018 (59)	NCGS patients	12	16S rRNA sequencing on fecal and duodenal samples	Significant changes in duodenal *Pseudomonas* levels after 4 wk of a GFD
Animal studies				
Verdu et al., 2007 (27)	CD genetically predisposed subjects	15	Gliadin-sensitized HLA-DQ8 mouse model	Gluten induced IBS-D like symptoms (increased acetylcholine production and colonic motility) that improved upon gluten removal from the diet
Junker et al., 2012 (60)	TLR-4–deficient subjects	12	Mouse model challenged with gliadin and ATIs	Mice with defective TLR-4 or TLR-4 pathways are protected from the intestinal and immune responses when they are challenged with ATIs
Zevallos et al., 2017 (61)	TLR-4–responsive mice	38	TLR-4–sensitized mouse and human cell line model	Gluten-containing cereals have the highest concentrations of ATIs that activate TLR-4
Bellinghausen et al., 2018 (62)	Humanized mice	10	Mice were engrafted with the PBMCs from allergic donors and were challenged	ATIs are strong allergen activators

[1] ATI, α-amylase/trypsin inhibitor; CD, celiac disease; FISH, fluorescent in situ hybridization; FODMAPs, fermentable oligo-, di-, monosaccharide, and polyols; GFD, gluten-free diet; IBS, irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; NCGS, non-celiac gluten sensitivity; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; rRNA, ribosomal RNA; TLR, Toll-like receptor.

TABLE 2 Distinct and overlapping pathophysiology and treatment of NCGS and IBS[1]

	NCGS	IBS
Causative agents	Gluten, wheat FODMAPs, wheat ATIs	High FODMAPs and fat foods, gluten, ATIs
Diagnosis	Exclusion of CD, WA, GA, DBPCFC	Rome IV criteria
Intestinal symptoms	Alterations in bowel habits, abdominal discomfort or pain, bloating, vomiting, constipation, diarrhea	Alterations in bowel habits, abdominal pain or distension, bloating or flatulence, absence of constitutional symptoms, and absence of alarming features such as weight loss, anorexia, gastrointestinal bleeding, and fever
Extra-intestinal symptoms	Muscle, head and body aches, depression, severe fatigue, anxiety, skin manifestations, recurrent oral ulceration	Neuroticism, aggression, reduction in quality of life, physical and sexual relationships, work productivity, general distress in diet, travel, physical appearance, family, education
Sex	Female predominance	Female predominance
Comorbidities	Depression	Psychosocial disturbances such as neuroticism, aggression, anxiety
Microbiome	↓ *Bacteroidetes* ↑*Firmicutes* ↓ *Bifidobacterium* after FODMAPs diet	↑*Enterobacteriaceae*, ↑*Veillonella* or *Ruminococcus* ↑Ratio *Firmicutes* to *Bacteroidetes*↓*Lactobacillus*, *Bifidobacterium*, *Faecalibacterium* ↑Methane production (IBS-C)
Treatment	Strict elimination wheat-free diet for 1–2 y; re-introduction of wheat in the diet in a dose that does not provoke symptoms	Personalized abstinence from foods that trigger symptoms. Nonabsorbable antibiotics: Neomysin, rifaximin
Therapeutic trials with probiotics, prebiotics, symbiotics		Potential beneficial effectPrebiotics: GOS, FOS (↑*Bifidobacterium* levels). Probiotics: *Lactobacillus*, *Bifidobacterium* Symbiotics: - yogurt containing high-dose *Bifidobacterium animalis* subsp. lactis Bb-12 (*B. animalis* subsp. lactis Bb-12) (≥ 1011 cfu/bottle), *Bifidobacterium enhancer*, and acacia dietary fiber

[1]ATI, α-amylase/trypsin inhibitor; CD, celiac disease; DBPCFC, double-blind placebo-controlled food challenge; FODMAPs, fermentable oligo-, di-, monosaccharide, and polyols; FOS, fructo-oligosaccharides; GA, gluten ataxia; GOS, galacto-oligosaccharides; IBS-C, irritable bowel syndrome with predominant constipation; NCGS, non-celiac gluten sensitivity; WA, wheat allergy.

Nevertheless, in ∼70% of IBS patients bloating and pain are induced by FODMAPs (13, 63, 64). As FODMAPS are not absorbed properly in the small intestine, they retain water and are rapidly fermented by the bacteria in the colon, leading to gas and SCFA production, accompanied by luminal distension and abnormal motility (6). In turn, this aggregation of fluids and gases results in visceral hypersensitivity, gut microflora alterations, and changes in intestinal hormones and neurotransmitters that characterize IBS (65). There are ∼15 different types of gastrointestinal endocrine cells releasing different types of hormones depending on the types of sensed nutrients (66). The interactions between FODMAPs and gastrointestinal endocrine cells induce changes in cell densities. Restoring the densities of the gastrointestinal endocrine cells results in IBS symptom improvement. Therefore, the removal of FODMAPs from the diet of the IBS patients is anticipated to result in a remarkable improvement in gastrointestinal and extra-intestinal symptoms in 68–86% of individuals (67, 68, 31, 32). However, it should be stressed that a low-FODMAP diet is very restrictive, resulting occasionally in significant weight loss, but in the majority of the cases in significant nutrient deficiencies (33, 34, 36) and gut dysbiosis due to limited intake of dietary prebiotics; a respectable number of studies reported that a low-FODMAP diet significantly decreased levels of fecal *Bifidobacterium*, *Faecalibacterium*, and *Actinobacteria* populations in the microflora, leading to reduced SCFAs, n-butyric acid, and proinflammatory cytokines IL-6 and IL-8 (15, 32, 35, 43).

Among other triggering agents, wheat ATIs have been shown to elicit inflammatory and immune responses as they have been identified to be strong inducers of innate immune responses (36). ATIs, which represent 2–4% of wheat proteins, are resistant to digestion by the gastric proteases. In a standard Western diet, the daily mean consumption is 10–15 g of gluten/d, containing the co-fractioned with gliadin compounds ATIs in an approximate proportion of 0.375–0.5625 g (69).

In vitro studies revealed that ATIs trigger intestinal inflammation in both celiac and healthy subjects, by activating gut myeloid cells after binding to Toll-like receptor (TLR) 4 (TLR-4), which induces proinflammatory cytokine production (22, 56, 60). ATIs can stimulate the production of intestinal and systemic cytokines and chemokines in mice, including IL-8, TNF-α, and CCL-2, after 2–12 h after they were challenged with ATIs in vivo (60). Mice with defective TLR-4 or TLR-4 pathways are protected from the intestinal and immune responses when they are challenged with ATIs, indicating an important role of TLR-4 signaling (60). Although ATIs exert these immune responses in animal models, human trials are needed to verify these findings.

Microbiota synthesis in IBS

Consistent evidence links bacterial overgrow and dysbiosis patterns in IBS patients' microflora with the disorder's pathophysiology (5, 6, 34), also suggesting that the onset of IBS may be due to bacterial, viral, or parasitic infections in the microbiota (37). Furthermore, data reveal a predominance of bacterial phyla connected with dysbiosis, such as *Enterobacteriaceae*, with an increase in proinflammatory cytokines, decreased concentrations of the tolerogenic dendritic cells, and reduced levels of *Lactobacillus* and *Bifidobacterium* (6, 70, 38–40). The reduced levels of *Bifidobacterium*, *Clostridiales*, *Ruminococcaceae*, and *Erysipelotrichaceae*, which produce SCFAs (6); the reduced levels of *Faecalibacterium* (33); and the impaired *Firmicutes*-to-*Bacteroidetes* ratios, together with an abundance of *Lactobacillus* species (43, 41, 42) and an increase in *Veillonella* and *Ruminococcus*, indicate a perturbation of the bacterial colonization in the gastrointestinal tract (6).

Patients with IBS-D have decreased methane production, whereas it is increased in IBS-C (8, 71). Methane in the gut microbiota is produced exclusively from methanobacteriales. It slows down the intestinal transit and has anti-inflammatory effects (45). Increased methane production in IBS-C patients, however, correlates with microbial overgrowth of the methanobacteriales *Clostridiales* or *Prevotella* species, which further reduces food transition, by an average of 59% in animal models (45, 44, 72).

Potential therapeutic pathways of IBS

Elimination diet.

Due to the lack of reliable biomarkers, the IBS therapeutic milieu is mainly based on subjective estimations of each unique patient of their symptoms' exacerbating agents, among which there is also a long list of implicated foods. Food avoidance of all irritating agents is unavoidable, at least at the initiation of the diet therapy or during symptom eruption. The "IBS Food Pyramid" (73) is an encouraging educational tool for IBS patients to aid in following a healthy diet pattern over the long term. Regular physical activity, adequate fluid intake, and regular eating habits are encouraged. Foods from all food groups can be consumed with appropriate personalized recommendations regarding consumption of gluten-free cereals, low FODMAPs, and lactose-free products. In the case of fat, the anti-inflammatory PUFAs are thought to be beneficial, but further research is needed to confirm this. The avoidance of spicy foods, alcohol, and highly processed foods is recommended. As patients following a low-FODMAP diet are at high risk of developing deficiencies in vitamins B and D, zinc, calcium, iron, folate, and natural antioxidants (56), the strict food avoidance should be reduced and, together with this, the nutrient deficiencies resulting from low fiber intake and extreme dietary choices, like a GFD, could be limited.

Microbiota manipulations.

As IBS symptoms are strongly correlated with microbiota synthesis and methane production, manipulations of the gut microbiota have been investigated for more than a decade, but their beneficial potential is still not confirmed. Probiotic supplements are recommended via the IBS Food Pyramid, to reduce exacerbating symptoms, for a 4-wk period in a dose as recommended by the manufacturer, for the individual patient to evaluate the beneficial effect (73).

Intervention trials in IBS aiming to alter microflora and to improve IBS symptoms are presented in detail in **Table 3**. In short, they were based on the following:

1. Probiotics supplementation, which consist of live bacteria aiming to shift gut microbiota towards abundance of the beneficial bacteria. It is noteworthy that *Lactobacillus* and *Bifidobacterium* species lead to a decrease in pathogens by hampering the intestinal mucosal adhesion and they can reduce mild inflammation by regulating the TLRs, the intestinal permeability, visceral hypersensitivity, intestinal motility, and even neurotransmitter release (50). Data meta-analysis reports suggest that probiotics largely improve IBS symptoms, especially in low doses and short-term administration, and restore the intestinal mucosal barrier, particularly in women (50, 74, 75).
2. Prebiotic supplements confer a health benefit by stimulating the growth of probiotic bacteria, mainly *Bifidobacteria* and *Lactobacilli* (76). Even during early life they are added to infant formulas aiming to resemble breast milk, as they have been found to benefit the gut microbiota of breastfed infants. Prebiotics are predominantly carbohydrate-based, but other substrates, such as polyphenols and PUFAs, might also exert prebiotic effects. In the case of IBS, a prebiotics mixture of fructo-oligosaccharides (FOS) and *trans*-GOS (TGOS) has been suggested as capable of improving symptoms, whereas TGOS are correlated with abundance of *Bifidobacterium* in feces (76, 77, 46, 78, 79, 49). However, the lower prebiotic dose provided the optimum outcome (6), whereas 2 other controlled trials showed no improvement after a similar prebiotic administration (47, 48).
3. Synbiotics contain selected bacteria species in combination with prebiotic components that favor beneficial bacterial growth. Prebiotics that are mainly used include disaccharides, such as lactulose; oligosaccharides, such as FOS, TGOS, and GOS; and polysaccharides, such as fructan, inulin, and cellulose (77). A symbiotic preparation of yogurt supplemented with acacia fibber and *Bifidobacterium lactis,* a combination of *L. acidophilus*, *L. helveticus*, and *Bifidobacterium* in a vitamin-supplemented medium, *Bacillus* coagulans, and FOS improved IBS symptoms (6, 51, 52).

Drug therapy.

Nonabsorbable antibiotics are known to improve symptoms in IBS, probably due to their ability to lower the concentrations and compositions of intestinal bacteria and alter the intestinal permeability and fecal microbiome (5). Neomycin has been found to induce up to 50% improvement in all IBS symptoms, but also led to bacterial resistance (5). Rifaximin, a broad-spectrum nonsystemic antibiotic, has proven to be effective by managing the bacterial overgrowth in the small intestine in IBS patients and to increase bacterial diversity and the *Firmicutes*-to-*Bacteroidetes* ratio (80, 53, 81). Short courses of therapy (2–4 wk) with rifaximin in IBS treatment is recommended; however, bacterial antibiotic resistance should be monitored, especially in patients who require repeat courses of rifaximin and other antibiotics including clarithromycin and metronidazole (80).

NCGS presentation and pathogenesis.

NCGS is characterized by both intestinal, such as alterations in bowel habits, abdominal pain, bloating, and flatulence, and extra-intestinal symptoms, such as body aches, depression, severe fatigue, anxiety, skin manifestations, and oral ulceration (23). In addition, the contribution

TABLE 3 Therapeutic trials in IBS human subjects with probiotic supplements: experimental design, effectiveness, and side effects[1]

Study (reference)	Study design	Subjects	Probiotic's synthesis	Substrate	Effectiveness	Side effects
Koebnick et al., 2003 (82)	Double-blind placebo-controlled randomized trial	35 active; 35 placebo; 18–65 y; males and females	*Lactobacillus casei* Shirota	Beverage (65 mL/d)	Significant improvement in constipation and stool consistency	No side effects
Niv et al., 2005 (83)	Double-blind placebo-controlled randomized trial	54 included/39 completed; 19–70 y; males and females	*Lactobacillus reuteri* ATCC 55,730	Capsule (1×10^8 CFU)	No symptom improvement	Several side effects
Whorwell et al., 2006 (84)	Double-blind placebo-controlled randomized trial; multicenter dose ranging	362 females, 270 active group/92 placebo group; 18–55 y; males and females	*Bifidobacterium infantis* 35,624	Lyophilized capsule (1×10^6, 1×10^8, 1×10^{10} CFU/mL)	*B. infantis* (1×10^8 CFU) improved the symptoms of IBS, such as abdominal pain, bloating, bowel dysfunction, and incomplete emptying	17 (<5%) of the 362 patients reported adverse effects and withdrew from the study
Sinn et al., 2008 (85)	Double-blind placebo-controlled randomized trial	20 active group/20 placebo group; 18–65 y	*Lactobacillus acidophilus*-SDC 2012, 2013	Lyophilized capsules (2×10^9 CFU/mL)	Improvement in abdominal pain and discomfort	No side effects
Guglielmetti et al., 2011 (86)	Double-blind placebo-controlled randomized trial	60 active group/62 placebo group; 18–68 y; males and females	*Bifidobacterium bifidum* MIMBb75	Uncovered capsule (1×10^9 CFU)	GI symptom relief: pain, discomfort, dilation, bloating, digestive disorders, QoL improvements	23/60 patients reported abdominal distension, abdominal pain, diarrhea, nausea, constipation
Ducrotté et al., 2012 (87)	Double-blind placebo-controlled randomized trial	214; 18–70 y; males and females	*Lactobacillus plantarum* 299v (DSM 9843)	Lyophilized capsule (1×10^{10} CFU)	Pain reduction, daily frequency, and bloating in patients	No side effects; only 1 patient mentioned transient vertigo
Niedzielin et al., 2001 (88)	Multicenter double-blind, placebo-controlled study with parallel groups	10^8 active group/10^6 placebo group; males and females	*Lactobacillus plantarum* 299V (LP299V)	Fermented fruit juice with 5% oats	Symptom improvement in 95% of the IBS patients	No side effects
Murakami et al., 2012 (89)	Double-blind cross-matched trial	35 males and females >6 y	*Lactobacillus brevis* KB290	Lyophilized capsule (1×10^{10} CFU)	Improvement in IBS symptoms; increased abundance of *Bifidobacterium* and *Clostridium* in the intestinal microflora	Side effects: abdominal pain and diarrhea

(*Continued*)

TABLE 3 (*Continued*)

Study (reference)	Study design	Subjects	Probiotic's synthesis	Substrate	Effectiveness	Side effects
Stevenson et al., 2014 (90)	Double-blind placebo-controlled randomized trial	54 active group/27 placebo group; 96% females	*Lactobacillus plantarum* 299V (LP299V)	Capsule (5 × 10^9 CFU)	No relief in patients from abdominal pain	Several side effects/not described in detail
Pineton de Chambrun et al., 2015 (91)	Double-blind placebo-controlled randomized trial	86 active group/93 placebo group	*Saccharomyces cerevisiae*	Capsule (8 × 10^9 CFU/g)	Improvement only in abdominal pain and discomfort	Side effects included diarrhea, constipation, headache, abdominal pain, bloating, back pain, gastroesophageal reflux disease, bladder infection, influenza, and hemorrhoidal crisis
Thijssen et al., 2016 (92)	Double-blind placebo-controlled randomized trial	39 active group/41 placebo group; males and females	*Lactobacillus casei* Shirota	Fermented milk with *L. casei* Shirota (6.5 × 109 CFU)	No improvement during intervention; positive effect after completion	No side effects
Spiller et al., 2016 (93)	Double-blind placebo-controlled randomized trial	192 active group/187 placebo group; 18–75 y; males and females	*Saccharomyces cerevisiae* CNCM I-3856	Capsule (500 mg)	No overall benefit in IBS; improvement in abdominal pain, discomfort, bloating	Several side effects/not described in detail
Sadrin et al., 2017 (94)	Double-blind placebo-controlled randomized trial	40 active/40 placebo; 18–65 y	*Lactobacillus acidophilus* NCFM *και* LAFTI L10	Capsule (2,5 × 10^9 CFU)	Reduced abdominal pain; overall improvement of IBS symptoms	Several side effects/not described in detail

[1]ATCC, American Type Culture Collection; GI, gastrointestinal; IBS, irritable bowel syndrome; QoL, quality of life.

of gender has been reported in NCGS, with a female-to-male predominance of 3:1 (12, 95, 96). The basic difference between IBS and NCGS is that patients with the latter assert that their symptoms occur after wheat consumption and blame gluten as the culprit. The main clinical manifestations of NCGS are presented in Table 2.

Even a 3-d challenge with 16 g/d gluten has been related to feelings of depression in NCGS patients (4). This, however, was not associated with cortisol secretion, suggesting the involvement of gluten exorphins, which are opioid peptides that derive from partially digested food proteins (97). Exorphins have been shown to pass through the blood–brain barrier and can therefore directly interfere with pain, emotional pathways, and other hormonal or neurotransmitter systems through the endogenous and exogenous opioid receptors. Orally administered gliadinexorphin A5 was shown to modify learning and anxiety behavior during several laboratory stressors in mice, thus indicating that orally delivered exorphins can influence both the peripheral and central nervous system and suggesting that gluten exorphins possess opioid activity (4).

The onset of symptoms after gluten ingestion appears from hours up to few days and their resolution time also varies and can last up to weeks. Due to the lack of specific serological markers, the diagnosis of NCGS is made after the exclusion of gastrointestinal malignancies and allergic (WA) or autoimmune (CD, dermatitis herpetiformis, and gluten ataxia) reactions (9). Although, for the accurate diagnosis of NCGS, a DBPCFC with 8 g of gluten and at least 0.3 g of the proinflammatory ATIs per day for at least 7 d has been proposed by the Salerno experts in 2015, to date, a proper vehicle to carry out the challenge has not been developed. As trials conducted so far have high heterogeneity, it is difficult to define a diagnostic protocol (4, 69, 98).

Although, and in contrast to CD, there is no evident genetic predisposition identified so far, the activation of innate immunity without any implication of the adaptive immune response has been described (22, 23, 95, 99). Some studies suggest that ATIs or a combination of ATIs and gluten can induce this immune response (61, 62). In NCGS patients, the intestinal permeability and the expression of tight junction proteins claudin-1 and zonulin-1 (ZO-1) appear to be normal, but there is an increased expression of claudin-4 accompanied by the high expression of TLRs (TLR-1, TLR-2, and TLR-4) and a lower number of regulatory T cells (9). TLRs strongly maintain the intestinal epithelial homeostasis by mediating the dynamic host–microbe interactions. The intestinal microbes have been shown to decrease intestinal permeability by upregulating the expression of tight junction proteins. Since the gut microbiota has an essential role in regulating the antigen milieu of enterocytes, it has been suggested that it can activate the immune processes in certain individuals towards CD or NCGS. Moreover, human gastric, pancreatic, and brush-border enzymes cannot completely degrade dietary glutens because of the unusually high proportion of proline residues and T-cell stimulatory gluten peptides up to 33 amino acids in length. Numerous gut micro-organisms, including many sourdough bacteria belonging to *Streptococcaceae*, *Lactobacillaceae*, and *Bifidobacteriaceae*, as well as fungi and yeasts, are able to completely degrade gluten proteins (100). By producing gluten-degrading enzymes, the gut microbiota can convert an immunogenic peptide to a nonimmunogenic peptide, and consequently build up driving function towards an NCGS profile (100).

Possible triggers in NCGS.

Gluten has been considered to be the stimulator of NCGS, forcing patients, similarly those with CD, to a life-long adherence to a GFD. Nevertheless, today we know, via several blinded placebo-controlled studies (4, 22, 54, 55), that ATIs and wheat FODMAPs, apart from gliadin, trigger the innate immune responses (Table 2) (56, 61, 54, 101).

ATIs contribute to symptoms in NCGS by the activation of gut myeloid cells (56, 101). In murine models, dietary ATIs worsened the allergic inflammation in the airways, allergen IgE-dependent colitis, and gut inflammation (62). Since ATIs can trigger and sustain gut inflammation, they should undoubtedly be considered an additional trigger in NCGS pathogenesis.

A meta-analysis reported that only 16% of NCGS patients developed symptoms after challenge with <8 g/d pure gluten, whereas another Double Blind Placebo Challenge (DBPC) demonstrated a significant improvement in gastrointestinal symptoms after a low-FODMAP diet (4, 57). Wheat FODMAPs (fructans) have been blamed for the abdominal pain in NCGS, as they resist digestion in the proximal small bowel and are processed by bacteria in the distal small bowel and colon (102, 103). Many NCGS patients benefit from a low-FODMAP diet, in both their gastrointestinal and psychological symptoms, despite being on a gluten-containing diet (101, 103, 104). In some cases, NCGS patients develop more severe intestinal symptoms after consuming only 2.1 g fructans than when they introduce gluten in their diet (56). Additional evidence comes from a recent study showing that NCGS patients adhering to a GFD have only partial symptom alleviation (2) and FODMAPs were suggested as also being responsible for symptom development in NCGS (2, 22).

Microbiota in NCGS.

As described in Table 2, an abundance of *Firmicutes* with decreased *Bacteroidetes* populations, similar to IBS, has been reported in NCGS patients (5, 6, 98). In a study by Dieterich and Zopf (98), a low-FODMAP diet improved NCGS symptoms and further reduced the levels of *Bifidobacterium* compared with corresponding controls. However, a low-FODMAP diet also eliminates prebiotics and can result in dysbiosis. The gut microbiome in NCGS patients presents high metabolic activity, suggesting that their microflora is more susceptible to dietary changes than in their healthy controls.

In a recent study in Mexico a GFD improved NCGS patients' symptoms and induced a significant increase of an average of 14.8% of *Pseudomonas* in gut microbiota and in duodenal biopsies (59) 4 wk after implementation. Since *Pseudomonas* comprises strains with gluten-degrading capabilities, the authors suggested that some *Pseudomonas* strains could be tested as a probiotic supplement for alleviating symptoms in gluten-related disorders. Nevertheless, research to date is limited and the role of microbiota in NCGS onset and/or development should be further investigated via prospective clinical trials.

Potential therapeutic pathways in NCGS.

The NCGS profile is still obscure in terms of clinical characteristics, diagnostic criteria, and therapy. Although a GFD is generally recommended, there does not need to be lifelong adherence at the level of CD. Usually, patients after a period of 1–2 y of a strict GFD can attempt to reintroduce small and gradually increasing amounts of gluten in their diet, although the decision about the exact tolerated amount should be decided at an individual level, by recording the amount of wheat consumed and the relevant induction of gastrointestinal (Gastrointestinal Symptom Rating Scale) or relevant extra-intestinal symptoms (69).

Conclusions

The literature thus far refers to gluten, FODMAPs, and ATIs as 3 ambiguous villains for symptom exacerbation of IBS and NCGS. These overlapping disorders, in terms of clinical features and some inducing agents, have increasing prevalence. The insufficient knowledge to date, however, and the lack of proper accurate diagnostic criteria make them dependent on subjective report, making self-diagnosis difficult. When wheat products provoke symptoms, a GFD is the diet of choice, which is strict and hard to adhere to in the long term with parallel sufficient macro- and micronutrient intake, unless sufficient personalized dietary guidance is provided by a specialized dietitian. A GFD is low in fiber and high in fat and sugar (105), so patients need to be informed regarding the long-term complications, such as hyperlipidemia, cardiovascular disease, and obesity. Evidence shows that gluten is not the actual cause of NCGS symptoms as patients challenged with pure gluten in a DBPCFC did not present more symptoms than the placebo group (54, 55, 57). In addition, the activation of the innate immune responses and the resulting intestinal inflammation and dysbiosis make the microbiome an open area for intervention.

Opinions on the topic

Taking into consideration that *1*) IBS and NCGS respond in similar ways when wheat is the triggering food; *2*) NCGS symptom deterioration is probably dependent on the total dose of wheat consumed, similar to lactose intolerance (58), therefore a strict elimination might not be obligatory for all patients; *3*) exacerbation of both intestinal and extra-intestinal symptoms after wheat consumption occurs; and *4*) clinical trials with prebiotics in IBS patients induced shifts in healthier microbiota populations, whereas probiotics did not induce changes in the microflora composition but mainly resulted in metabolomic changes in the local bacteria populations, we suggest the following for future research:

1. Standardize the challenge method for NCGS according to the Salerno Experts criteria with a proper challenge vehicle
2. Investigate the microbiome's shifts from a cereal-free diet to a cereal-containing diet in NCGS patients and parallel metabolomic changes
3. Aim for personalized diet therapy in clinical trials with parallel cognitive behavioral therapeutic interventions to minimize anxiety and stress upon interventions and investigate individualized response to diet therapy and psychotherapy (106)
4. Perform clinical trials with symbiotics in NCGS patients, according to results so far from IBS trials, to investigate their actual anti-inflammatory potential in NCGS
5. Enlarge clinical trials including IBS patients sensitive to wheat and NCGS patients and compare the 2 disorders under identical investigation conditions

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