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The role of a Gluten-free Diet in the Management of Celiac Disease and Non-Celiac Gluten Sensitivity: A Comparative Review

Weronika Bagińska

Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz,

Ul. Dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland

weronika.baginska@barlicki.pl

https://orcid.org/0009-0002-6325-0915

Jagienka Perzyńska

Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz,

Ul. Dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland

jagienkaperzynska3@gmail.com

https://orcid.org/0009-0006-3723-7708

Urszula Załuska
Masovian Specialist Hospital, 5 J. Aleksandrowicza Street, 26-617 Radom, Poland
urszaluska@gmail.com
https://orcid.org/0009-0008-4666-8790

Kinga Krzyżowska
Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz,
Ul. Dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland
kingakrzyzowska1999@gmail.com
https://orcid.org/0009-0004-7385-9497

Jaśmina Podkościelna
Marszałek Józef Piłsudski Independent Public Healthcare Facility in Płońsk (SPZZOZ Płońsk), ul. Henryka Sienkiewicza 7, 09-100 Płońsk, Poland
jasmina.p@onet.pl
https://orcid.org/0009-0004-6102-6762

Kamila Ryszkowska
Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz,
Dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland
kamilaryszkowska@gmail.com
https://orcid.org/0009-0000-1458-0657

Natalia Pawelec
National Medical Institute of the Ministry of the Interior and Administration,
Ul. Wołoska 137, 02-507 Warsaw, Poland
natalia.pawelec@stud.umed.lodz.pl
https://orcid.org/0009-0003-1234-8450

Natalia Kasterka
Nicolas Copernicus Regional Multispecialist Centre of Oncology and Traumatology of Lodz, Ul. Pabianicka 62, 93-513 Łódź, Poland
kasterkanatalia@gmail.com
https://orcid.org/0009-0004-9903-3415

Aleksandra Purska
National Medical Institute of the Ministry of the Interior and Administration, ul. Wołoska 137, 02-507 Warsaw, Poland
aleksandra.purska@gmail.com
https://orcid.org/0009-0000-2909-7991

Abstract

Celiac disease (CD) and non-celiac gluten sensitivity (NCGS) have been a subject of interest in recent years. The CD is a chronic, gluten-dependent disease characterized by small bowel mucosal inflammation and injury and consequent malabsorption in genetically predisposed individuals. NCGS is characterized by the triggering of intestinal and/or extraintestinal symptoms after the consumption of products made with gluten-containing cereals. Gluten-free diet (GFD) is the only treatment to date of both these conditions.

The aim of this study is to evaluate the role of GFD as a therapeutic intervention in CD and NCGS. An extensive review of the literature was conducted using electronic databases (PubMed, Gastroenterology Journal, The Lancet Gastroenterology and Hepatology), and textbooks.

Although beneficial to many patients, GFD has many limitations, particularly it may lead to nutritional deficiencies and an imbalanced diet. In this review, the scope of these deficiencies was described and possible solutions were proposed.

Introduction. In recent years, a significant increase in scientific and clinical interest has been observed in disorders associated with gluten exposure, including celiac disease and non-celiac gluten sensitivity. Celiac disease (CD) is a common autoimmune disease affecting around 1% of the population.[1] It is a chronic, gluten-dependent disease characterized by small bowel mucosal inflammation and injury and consequent malabsorption in genetically predisposed subjects.[2] The clinical presentation of celiac disease is heterogeneous and may include both gastrointestinal symptoms, such as diarrhea, bloating, and weight loss, as well as extraintestinal manifestations, including anemia, osteoporosis, and neurological disorders. The pathogenesis of celiac disease is based on an abnormal immune response to gluten in genetically predisposed individuals (HLA-DQ2/DQ8), leading to T-cell activation and chronic inflammation of the small intestinal mucosa. Consequently, this results in villous atrophy and impaired nutrient absorption. Standard treatment is a strict gluten-free diet (GFD), which poses significant challenges due to dietary restrictions, cross-contamination and subsequent persistent intestinal inflammation.[3]

Non-celiac gluten sensitivity (NCGS) is a clinical condition characterized by the presence of intestinal and extraintestinal symptoms triggered by gluten ingestion after exclusion of celiac disease and wheat allergy. The first insights of NCGS were published more than 40 years ago. NCGS is characterized by the triggering of intestinal and/or extraintestinal symptoms after the consumption of products made with gluten-containing cereals, but both CD and WA must be properly ruled out as the symptoms overlap among the clinical entities and there is a lack of sensible and specific biomarkers for NCGS diagnosis.[4] The most common gastrointestinal symptoms are bloating, abdominal pain, diarrhea, nausea and reflux. Among extraintestinal symptoms the most common are tiredness, headache, anxiety, muscle or joint pain or depression.[5]

Another gluten-related disorder is wheat allergy (WA), which is an immune-mediated adverse reaction triggered by the consumption of wheat or wheat-based products. It includes three main types: immunoglobulin E (IgE)–mediated, non-IgE-mediated, and mixed-IgE-mediated forms. The latter two types are less common, with their mechanisms yet to be delineated.[6] In the IgE-mediated form of wheat allergy, specific IgE antibodies directed against wheat proteins are produced. Re-exposure to the allergen leads to their binding to receptors on the surface of mast cells and basophils, resulting in the release of inflammatory mediators such as histamine. It affects 0.1% of the population and can have intestinal symptoms similar to CD (diarrhea, abdominal pain and swelling), as well as skin manifestations (dermatitis). Other clinical

features besides food allergy may include respiratory allergy, urticaria and even wheat-dependent exercise-induced anaphylaxis (WDEIA).[7] Clinically, these reactions are characterized by a variety of signs and symptoms that occur within minutes or hours after consumption of the offending food.[8] In non-IgE- mediated WA the symptoms appear later and are more sustained than those in IgE-mediated form, often precluding the ability to discover the link to wheat exposure. Reactions are predominantly from the gastrointestinal tract.[9] However, due to its different pathophysiology, WA is beyond the scope of this review.

Gluten-free diet (GFD) is a form of treatment for the two diseases. Its objective is the complete removal of gluten-containing foods from one's diet, including gluten proteins in wheat (gliadin), barley (hordeins), rye (secalins), oats (avenins), and other closely related grains.[10] There are currently no other treatment options for patients with celiac disease approved by the US Food and Drug Administration (FDA). It is, however, very challenging to avoid gluten-containing products. There is always a risk of cross-contamination of gluten-free foods and up to 20 ppm of gluten is allowed in products labelled 'gluten-free', 'no gluten', 'free of gluten', or 'without gluten', and this small amount can already cause symptoms and histological complications. Gluten can also be found in non-food products such as supplements and cosmetics. Thus, in practice, it is not possible to avoid gluten altogether, not to mention the high costs and social restrictions that contribute to a high treatment burden. There are currently attempts to find a drug that could aid patients on GFD, but it has not been invented yet.[3] Sadly, less than 50% of CD patients achieve long-term adherence to a GFD. It is because dietary regimens are the least appealing medical strategies, contrary to medications.[1] Additionally, strict GFD is necessary to avoid the development of long-term complications, such as anemia, osteoporosis, and malignancy. Also, malabsorption of certain sugars (e.g., lactose, fructose, and sorbitol), intestinal bacterial overgrowth (SIBO), pancreatic exocrine insufficiency (PEI), microscopic colitis, Crohn's disease, or irritable bowel syndrome (IBS) should be investigated as possible causes of symptoms.[11] Thus, understanding the objectives of GFD is of utmost importance for patients' health and well-being.

Aim. The aim of this study is to evaluate the role of gluten-free diet as a therapeutic intervention in celiac disease and non-celiac gluten sensitivity. The study attempts to compare the effectiveness, fundamental mechanisms, and clinical outcomes associated with the implementation of a gluten-free diet across these conditions.

Materials and methods. An extensive review of the literature was conducted using electronic databases (PubMed, Gastroenterology Journal, The Lancet Gastroenterology and Hepatology), and textbooks. The collected information was analyzed, and the findings are presented below.
Keywords: celiac disease, non-celiac gluten sensitivity, wheat allergy, gluten-free diet

The state of knowledge

Gluten-free diet in celiac disease

Impact on symptoms

In the first year of treatment, a strict GFD effectively alleviates classic gastrointestinal symptoms. Decreased abdominal pain and complete relief of bloating are described in weeks or months of treatment. Nonetheless, other clinical signs, like reflux and diarrhea, may persist after prolonged GFD. Although helpful in most cases, GFD is not effective in all celiac patients. Many of them experience persistent digestive symptoms despite long-term adherence to a GFD.[2]

The ineffectiveness of GFD among lifelong GFD-adherent patients may occur because of the struggle to correctly read commercial product labels. Thus, 70–80% of patients adherent to a GFD present gluten contamination in their diet. Their average gluten exposure is around 150 mg/day. It is much higher than the considered safe amount of up to 10 mg/day and higher than the 50 mg/day cutoff that is known to be able to induce mucosal atrophy.[12] Also, more than 15% of adults have persistent or frequent symptoms despite a strict GFD. This state is called "non-responsive celiac disease" (NRCD). Gluten ingestion is the most common cause of NRCD, nonetheless, it is not the only cause of NRCD. Other causes include microscopic colitis, other food intolerances, small intestinal bacterial overgrowth, and irritable bowel syndrome (IBS). Some of the patients (0.04–1.5%) may present refractory celiac disease, defined as persisting symptoms and villous atrophy despite following a GFD. Other conditions may be associated with persisting villous atrophy, such as hidden gluten exposure, small intestinal bacterial overgrowth, autoimmune enteropathy, or common variable immunodeficiency.[13]

Nutrient deficiencies

The GFD is lower in folate, iron, magnesium, selenium, niacin, biotin, riboflavin, pyridoxine, and vitamin D.[11] In general, gluten-free raw food sources have fewer minerals and industrial food processing may reduce the micronutrient content, which might be related to some nutritional deficiencies in CD patients.[11] Physical properties and durability of foods are changed after the removal of gluten. To compensate, the food industry adds high fat and sugar content and decreases healthy supplementation, such as the addition of fiber, iron, folate, and zinc.[12] Studies have shown various nutritional deficiencies associated with following a GFD. The CD population presents a higher risk of insufficient fiber intake in both children and adults.[11] Other reports revealed that children and adolescents with CD have higher intakes of refined sugars and saturated fats. It is due to the nutritional composition of gluten-free rendered products (GFPs) and the limited consumption of grains and unprocessed or unrefined cereal. Consequently, CD patients consume lower fiber.[11] Studies show the risk of excessive consumption of ultra-processed foods. It is associated with inflammatory biomarkers in children with CD. Moreover, higher consumption of gluten-free bread, pastries, and sweet and salty convenience foods in the CD adult population was associated with metabolic dysfunction-associated steatotic liver disease.[11]

Additionally, the CD patient generally has villous abnormalities in the small intestine and intestinal alteration, that lead to malabsorption and multiple nutritional deficiencies. They can provoke a variety of nonspecific signs and symptoms, such as faltering linear growth, short stature, poor weight gain in children, and weight loss in adults.[11]

Iron deficiency anemia (IDA) is one of the most recurrent extraintestinal manifestations in children and adults at diagnosis, occurring in over half of CD patients (including subclinical CD patients), and is more common in adults than children.[11] Thus, celiac patients must be tested for IDA at the diagnosis of CD and during GFD. The absorption of Fe^{2+} primarily occurs in the proximal duodenum, at the brush border of the mucosa cells, through a membrane transport protein called divalent metal transporter (DMT1). Heme-iron is absorbed in the same bowel district, but separately from DMT1 and more efficiently than inorganic iron. This portion of the duodenum represents the most frequently destroyed region in CD, which results in a reduction in iron absorption, and consequently IDA. The achievement of normal hemoglobin levels in

non-celiac patients can generally occur after 2–3 months of oral treatment. It should be further continued for 2–4 months in order to fill the body stores. In some cases of CD, it takes longer to improve intestinal lesions with GFD, so an improvement in IDA can be observed after 24 months. However, some studies showed persistence of anemia after one year of GFD even though histological normalization of the duodenal mucosa was achieved.[14] Studies indicate that CD patients with IDA at diagnosis have more advanced disease, slower dietary response, and worse recovery from mucosal lesions than those without anemia.[11] It was observed that the association of a probiotic such as *Lactobacillus plantarum 299v* and *Bifidobacteriumlactis HN019* could facilitate better iron absorption, though the results are controversial. In a pilot clinical trial, which evaluated the synergistic effect of a prebiotic (oligofructose-enriched inulin) on iron homeostasis in children and adolescents with celiac disease treated with a gluten-free diet, the attained results are promising.[14]

Vitamin B12 deficiency is found in 8–41% of newly diagnosed patients. Its absorption mainly occurs in the distal ileum. The etiology of vitamin B12 deficiency in CD is unknown. Potential causes might be decreased gastric acid, SIBO, autoimmune gastritis, or subtle dysfunction of the distal small intestine.[11]

Calcium and vitamin D absorption takes place in the small intestine, especially in the duodenum. The lack of calcium and vitamin D may result in metabolic bone diseases, such as reduced bone mineral density (BMD) in celiac patients. Approximately 75% of untreated adults with CD suffer from low BMD and bone fracture risks are greater in older people. Calcium deficiency during childhood and adolescence may cause growth problems and impair peak bone mass achievement. Moreover, calcium malabsorption could also result from reduced levels of calcium-binding proteins due to enterocyte loss. The impaired enterocytes can have an effect on the response to calcitriol, which leads to further calcium loss, and leads to secondary hyperparathyroidism, which is common among CD patients.[11]

Zinc and copper are also deficient in celiac patients. Reports have shown that one-third of children at diagnosis and approximately two-thirds of untreated CD patients were zinc-deficient. The deficit is related to an endogenous loss of zinc. Zinc deficiency may lead to reduced protein synthesis, cell-mediated immunity, antioxidant buffer capacity, as well as

diverse skin lesions. Copper deficiency leads to anemia and thrombocytopenia in celiac adults and children as well as to neurological impairment.[11]

The increased incidence of thyroid disease in patients with CD may be due to selenium or iodine deficiency, though the involved mechanisms are not adequately established.[11]

GFD can also reduce bacterial richness while affecting gut microbiota composition, especially in healthy patients, causing a reduction in probiotic species such as Bifidobacteria, in favor of opportunistic pathogens, e.g., Enterobacteriaceae and *Escherichia coli*.[15]

Following a lifelong GFD is the only effective CD treatment nowadays. Considering the deficiencies mentioned above, it should be not only gluten-free, but also balanced, covering total energy and nutritional requirements.[11] Recommendations for an overall healthy GFD should be similar to a regular healthy diet but with a focus on healthy alternatives to grain-based foods. Higher adherence to a Mediterranean diet has been associated with improved bone mineral density in CD children.[11]

Some ingredients can improve the nutritional quality of GFPs. Pseudocereals can be used as substitutes for gluten-containing cereals. Amaranth and quinoa are good vitamin sources; sorghum contains a high level of thiamine, and millet provides carotenoids. These foods increase protein, healthy fats, fiber, and minerals intake on GFD.[11]

In conclusion, routine blood tests at each follow-up visit, including checking for intestinal absorption with a complete blood count, serum calcium, ferritin, vitamin B12, and alkaline phosphate are recommended in order to monitor deficiencies in CD patients. Additionally, thyroid function tests such as TSH and thyroid hormone should be performed to screen for other autoimmune conditions. Lastly, liver function tests, like aspartate aminotransferase and alanine aminotransferase levels should be controlled to monitor for autoimmune liver disease.[10]

Impact on histology

Histological recovery of the small intestinal mucosa begins between 6 months and 3 years after initiating a GFD. However, it is questioned by other studies. Complete remission of histological

lesions was described in 81.4% of children after at least a year of gluten withdrawal, or 97.6–100% in long-term GFD follow-up (≥three years). However, only 10.1% of celiac adults maintained villous atrophy after five years. Further studies indicate that only a third of patients (34%) achieved a mucosal recovery at two years on the GFD, whereas two thirds (66%) achieved it after five years on a GFD, even though a significant amount of them (82%) obtained clinical relief. A lack of intestinal recovery could be responsible for the persistence of one or more digestive signs in adults.[11]

Moreover, some data show incomplete recovery in older patients (between 30 and 60 years) and no statistically significant recovery in the ones older than 60 years. Gluten activation of the immune system causes changes in the intra-epithelial lymphocyte compartment (IEL) and is associated with increased γ/δ IELs. Recent cell sequencing work found high levels of γ/δ IELs in histologically normal-appearing tissue, which may mean that some changes persist following a GFD. Younger individuals tend to show more significant reversal of gastrointestinal symptoms and healing from damage to the gut mucosa.[10]

Other diets, FODMAP

Among patients suffering from persistent digestive disturbances despite following a GFD, some may present with Irritable Bowel Disease (IBS). The treatment of IBS consists of following the Low-FODMAP Diet (LFD). The efficacy of the LFD may extend beyond IBS. Among celiac patients, a higher consumption of vegetables and fruits with high FODMAP contents has been reported, but a clinical impact of a high-FODMAP diet is not proven. Yet, an LFD can decrease gastrointestinal disturbances in CD patients on a GFD and improve their quality of life.[2]

FODMAPs include several dietary components, such as carbohydrates, lactose, and dairy products. Several studies suggest higher frequence of IBS symptoms in celiac patients on a GFD than in the general population. However, the actual prevalence of functional gut disorders in CD patients remains controversial. A study by Barratt et al. showed that IBS is more frequent in CD patients on a GFD.[2]

Taking the above findings into consideration, LFD can be proposed as an additional way of alleviating symptoms in patients who do not fully respond to a GFD.

Impact on psychological health

Both current age and age at diagnosis play a role in CD impact on the patient. Time to diagnosis is also important, as a longer time to diagnosis usually means longer suffering from debilitating symptoms before reaching a diagnosis. Also, the longer the experience of dealing with the GFD, the easier it might be.[11] Adherence to GFD usually leads to an improvement in quality of life (QoL), apart from cases where there are challenging socio-economic factors, or in cases of asymptomatic patients that follow GFD without noticeable benefits. Studies show that depression and anxiety were present in 50% of newly diagnosed patients. Social isolation, fear of being forgotten, and lack of spontaneity which requires constant planification are the main psychological symptoms associated with CD and the GFD.[11] Dining out may be challenging as it is difficult to control gluten contamination, which may subsequently lead to social isolation, anxiety, and impaired QoL.[12] Coping strategies may increase confidence and lower anxiety levels. Social skills, acceptance, and control as well as social support through a psychologist are the most important strategies to mitigate the impact of CD at any age. They also help to develop adequate awareness for optimal long-term adherence to the GFD.[11]

GFD adherence rarely changes over time (<10% of patients) in patients who have an ongoing dietary counselling at a celiac dietary center. It is unlikely for a patient to be initially strictly adherent to a GFD only to later become less adherent. Stricter dietetic input at time of diagnosis and scheduled follow-up consultations throughout the first year after diagnosis can improve GFD adherence.[12]

Gluten-free diet in non-celiac wheat sensitivity

Implementation of GFD

Only CD requires a lifelong, strict GFD and carries the risk for significant health complications, as well as is associated with a risk of disease among relatives. Thus, the differentiation between CD and NCGS is of utmost importance and is based on laboratory and histological results. There is also a method that can differentiate NCWS patients from IBS and functional dyspepsia. The conventional diagnosis protocol for NCGS includes following a regular gluten-containing

diet for at least 6 weeks, followed by a GFD for at least 6 weeks. Then there should be a subsequent gluten challenge, preferably as a cross-over with a placebo challenge.[13] Patients with NCGS often report brain fog, and a gluten-free diet has been observed to improve some of these symptoms after one year of adherence.[6] However, in some studies fructans were associated with significantly higher symptoms scores than gluten in this patient population.[13]

Because of nutritional imbalance or deficiencies, the onset of physical pathologies, such as osteopenia, might occur. A study by Carroccio et al. investigated the prevalence of osteopenia, comparing CD (8 males, 42 females), IBS (10 males, 55 females) and NCGS (12 males, 63 females) patients. NCGS patients were reported to have significantly lower BMD than IBS controls, both at the lumbar spine and at the femoral neck ($p < 0.0001$). CD patients had the lowest BMD. In this study, the correlation of the results with BMI and hemoglobin confirmed the hypothesis of malnutrition, as the dietary calcium intake in NCGWS patients was much lower than the recommended dose of 1000 mg/day. It was probably caused by the presence of multiple food sensitivity (including diary), which implies additional dietary restriction.[15]

In a study by Mansueto et al., the incidence of autoimmune disorders (AD) was higher in NCGS (25%) than IBS patients ($p = 0.05$) and healthy controls ($p = 0.002$). AD was positively associated with female sex, older age at NCGS diagnosis, duodenal lymphocytosis, and eosinophilic infiltration. The researchers hypothesized that the longer the gluten exposure, the stronger the autoimmune reactivity, triggered by a local inflammation (sustained by the mild inflammation—Marsh 1—found in the biopsies). Consequently, it may cause an increased permeability and the development of AD. In this study, 71.4% of NCGWS patients had positivity of serum antinuclear antibodies (ANA).[15]

GFD is the treatment of choice in NCGS cases, although it is not established yet if a life-long and strict GFD is needed in all of them. A study by Carroccio et al. reported that 74% of NCGS patients that were following a wheat-free diet after 8 years of their diagnosis still suffered symptoms triggered by wheat consumption.[4] Alternatively, it has been reported that there is a certain level of tolerance in NCGS patients, and therefore, a controlled reintroduction of gluten might be helpful for improving the QoL in a specific group of patients. This might support the less strict GFD for patients with NCGS and the presence of dietary alternatives (such as ancient wheats with a lower content of gliadin and pesticides) with health, economic, and social

benefits.[16] Some studies suggest that NCGS patients present different gluten tolerance thresholds. It should be determined case by case whether the GFD is necessary. According to some, gluten rechallenge could be implemented after 1–2 years of following a GFD and then determinate the adequate dose of gluten tolerated by the patient.[4]

The determination of GFD necessity is important, because it is associated with an increased intake of macronutrients, such as saturated fats, lipids, and sugar, in addition to calories, and with a decreased intake of micronutrients such as iron, folate, zinc, and others.[4] It has been reported that patients with NCGS had similar rates of overweight (22%), but higher rates of obesity than CD (15% in NCGS and 7% in CD). Moreover, in a single-blind RCT, it has been indicated that GF foods substantially reduce the thermic effect (TE) of a meal by 50% compared with whole foods and by 41% compared with processed foods, even with an isocaloric/macronutrient profile. The subsequent reduction in metabolic rate increases the risk of weight gain and obesity.[17] Additionally, it has been reported that patients with diagnosis of NCGS consume lower amounts of fiber, proteins, carbohydrates and polyunsaturated fatty acids than in healthy controls.[4] Micronutrient deficiencies associated with GFD can be caused by the limited selection of foods, as well as by the lack of fortification of GF products. GF products are typically low in folate and iron. However, unprocessed foods such as fruits, vegetables, meat, and fish provide essential dietary minerals and vitamins, which may help the patients to reach the dietary norms.[17] Thus, gluten-containing foods should not be eliminated unless gluten is proven to be the cause of symptoms, and in that case, diet should contain unprocessed foods. Also, the psychological factors should be taken into account, as the combination of expectancy and actual gluten intake has the largest effect on gastrointestinal symptoms, reflecting a nocebo effect.[18]

Gluten or wheat?

It is still debated whether the component linked to intestinal and extraintestinal symptoms of NCGS is gluten or other components of wheat, such as amylase-trypsin inhibitors (ATIs).[15] Patients with NCGS may be sensitive to another component of wheat besides gluten. These may be the ATIs that trigger a similar immune response to gluten. Wheat germ agglutinin is another plant protein found in wheat, and it has been shown to trigger similar immune

responses. Thus, NCGS patients may be more sensitive to wheat in general instead of specifically gluten, so the term non-celiac wheat sensitivity should be used.[10]

NCGS or IBS?

Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), are short-chain carbohydrates, including fructans and galacto-oligosaccharides (GOS). They are found in various foods, including wheat. After consumption, they are slowly absorbed in the small intestine and later undergo rapid fermentation by gut bacteria, which results in gas production and bloating. They have been implicated in causing symptoms in various gastrointestinal disorders, including NCGS. Biesiekierski JR. observed for the first time the positive effect of a low FODMAP diet in a group of self-reported NCGS.[19]

Thus, patients unresponsive to a GFD should be investigated for other potential causes, such as irritable bowel syndrome (IBS). An overlap between IBS with NCGS is quite common.[15] Typical NCGS symptoms are diarrhea, bloating, and abdominal pain, so IBS with diarrhea can overlap and be clinically similar to NCGS. The difference is that patients with NCGS self-report symptoms when consuming gluten, but IBS patients generally do not report gluten ingestion as a specific trigger for their symptoms.[2]

One component of FODMAPS, fructans, may cause gastrointestinal symptoms in NCGS patients. Studies have shown that LFD, which minimizes fructan consumption, was associated with less severe gastrointestinal symptoms, especially abdominal pain. Dietary intake of FODMAPs was shown to worsen psychological symptoms at baseline.[2] Thus, LFD can reduce the symptom score in NCGS patients. Nonetheless, the implementation of this diet should be carefully considered because of the risk of low intake of natural antioxidants and micronutrients. Of note, FODMAPs have a prebiotic effect on colon bacteria. They stimulate the growth of *Lactobacilli* and *Bifidobacteria*, but limit limiting the colonization of *Bacteroides* spp., *Escherichia coli*, and *Clostridium* spp. Also, FODMAP is associated with an improvement in the lipid metabolism, better absorption of calcium and protective effect against colorectal cancer. Consequently, patients following LFD should supplement prebiotics and vitamins.[4] It has also been reported that FODMAPs improve lipid metabolism, calcium absorption, and have

protective effects against colorectal cancer. Thus, a follow-up 4–6 weeks after starting a low-FODMAP diet is recommended to consider reintroducing high-FODMAP foods into the diet of NCGS patients.[20] All in all, the implementation of a GFD and a low-FODMAP diet in NCGS patients should be considered if there is an improvement of clinical manifestations of the disease. Nonetheless, medical and dietitian advice is recommended to prevent nutritional deficiencies mentioned above.[4]

Impact on histology

The pathogenesis of NCGS is not fully understood. There is, however, some evidence suggesting that the innate immune response plays a primary role in this condition. Toll-like receptors (TLR 2-4) on the epithelial level become activated in response to pathogenic microorganisms. The involvement of the intestinal microbiota has also been described, with an increase in pathogenic *Bacteroidetes* and a decrease in saprophytic bacteria (*Firmicutes*) in patients with NCGS. This is a cause of dysbiosis, that may contribute to the bloating, possibly due to increased fermentation. Also, researchers observed an increase in Claudin-4, an integral component of tight junctions responsible for paracellular permeability. Because of this, the "leaky gut" hypothesis, similar to the one in CD, is proposed for NCGS, suggesting an impaired intestinal barrier.[19]

Nonetheless, from a histological point of view, there are not many differences between NCGS patients and healthy individuals. A normal villous architecture is maintained at the duodenal level of NCGS patients. Normal duodenal histology is defined by a cut-off value of intraepithelial lymphocytes (IELs) ≤25/100 enterocytes, which corresponds to Marsh 0. In NCGS patients, an increased count of duodenal IELs (>25/100 enterocytes) has been shown, corresponding to Marsh I lesions. In a recent multicenter study, the researchers observed that NCGS duodenal mucosa exhibits distinctive changes, consistent with an intestinal response to luminal antigens, even at the Marsh 0 stage of villus architecture. Other studies have also indicated the presence of eosinophils at the lamina propria level in NCGS patients, suggesting a condition that may be closer to a food allergy.[19]

Impact of polyphenols

Polyphenols are defined as plant secondary metabolites derived from the shikimate/phenylpropanoid pathway.[20] Research has shown that polyphenols can exert health-promoting properties by interaction with other macromolecules, like proteins. Preferentially, they bind to proteins rich in proline, such as gluten. The formation of gliadin–polyphenol complexes can be beneficial in protecting against gluten-related disease, as the inflammation persists only until the gluten peptides are free to reach the intestinal mucosa.[20] Polyphenols from different food sources, including olive oil, red grape/wine, fruits, vegetables, cereals, cocoa, coffee, and tea, exert immunomodulatory effects, either stimulatory or inhibitory depending on the context, in both the innate and adaptive immune branches and in particular in monocytes/macrophages, T and B cells, dendritic cells, natural killer (NK) cells, and on T cell differentiation, with associated benefits in immune-related pathologies such as inflammatory bowel disease, autoimmune diseases, atherosclerosis, and cancer.[20]

Polyphenols can exhibit a direct action of capturing gluten, the main trigger of gluten-related diseases such as NCGS, thereby reducing its bioavailability and associated toxic effects. Polyphenols can also dampen the toxic effects of gluten, both at the intestinal and systemic levels, by reducing oxidative stress and inflammation, by regulating the immune response, and by improving the health of the intestinal microbiota and the function of the intestinal barrier.[20]

A number of studies showed that dietary polyphenols exert antioxidant and anti-inflammatory roles and have a protective effect on intestinal epithelium. The presence of polyphenols in the intestinal lumen may favor inflammatory suppression and the tissue repair pathway may be able to prevent the initiation of acute inflammatory responses.[20] Thus, their adoption could contribute to preserving gut health and protecting against the toxicity of gliadin peptides in gluten-sensitive patients.[20]

Thus, polyphenols, through the sequestration of gluten proteins, may present a potentially new therapeutic approach to prevent the onset of gluten-related responses and associated symptoms.[20] Research indicated that polyphenols can improve gut health, even in the framework of gluten-related diseases, by preserving intestinal cells against oxidative aggression and inflammation triggered by gluten proteins.[20]

Discussion

This review was based on the available research on CD and NCGS. Thus, its findings are limited and based on interpretation of previous works. More research should be conducted to assess the role of GFD in these conditions.

Impact of GFD on CD and NCGS symptoms is relevant, making it the only current method of therapy. Many patients benefit from it, as it alleviates GI symptoms as well as other, nonspecific ones, and minimizes the risk of CD complications. However, it is not effective in all patients, because of gluten contamination and NRCD. Also, GFD may lead to nutrient deficiencies, such as iron, vitamin B12, calcium, vitamin D, zinc, copper, selenium and iodine, as well as low fiber intake. Additionally, GFPs are higher in refined sugars and saturated fats. Thus, GFD should be balanced and contain all the nutritious foods tolerated by the patient. Frequent laboratory check-ups should be performed as well.

The impact of GFD on histology depends on adherence to the diet. The epithelial damage can be reversed, and the intestine can work properly again. However, other immunological factors play a part in these changes, and some patients' intestines may appear healthy, although the immune response is still present. Of note, younger patients tend to have better results in the reversal of intestinal damage.

FODMAP may play a role in aiding CD patients to alleviate their GI symptoms. The LFD diet may be proposed to them in addition to GFD. It was shown to improve their QoL.

Impact of GFD on psychological health cannot be understated. CD patients often feel anxiety and loneliness due to their condition. It is important that they seek professional psychological help in time of need. Also, GFD adherence and subsequent cessation of symptoms improve CD patients' QoL.

NCWS may not require a strict, lifelong GFD. Nonetheless, it is often a key to helping patients to alleviate their symptoms. Primarily, CD should be excluded as a diagnosis among these patients.

GFD should be implemented for as short period of time as possible. It may lead to nutritional imbalance and deficiencies, such as BMD, lower intake of fiber, iron, folate, zinc, proteins, and polyunsaturated fatty acids. On the other hand, GFD is largely based on processed foods, which can lead to obesity and related diseases. Also, it has been shown that GI symptoms depend on the gluten intake expected by the patient.

Moreover, gluten may not be the only cause of NCGS. Other components of wheat may be responsible as well, so their content in food must be taken into account too.

NCGS may be also similar to IBS, a condition in which FODMAPs cause GI symptoms. Thus, NCGS patients should be examined and their tolerance to particular foods from FODMAP group should be established. Also, LFD may cause overgrowth of opportunistic bacteria in the gut, so it should not be implemented without diagnosing the patient first.
Polyphenols might be a promising line of treatment among NCGS patients. They minimize the toxic impact of gluten, reduce inflammation, and protect intestinal epithelium. However, more research should be conducted in order to establish their role in NCGS treatment.

Conclusion

In conclusion, GFD is beneficial to both CD and NCGS. It alleviates symptoms and, in case of CD, promotes intestinal recovery and prevents associated diseases. Nonetheless, as every diet in which a dietary component is eliminated, it has many disadvantages, mainly nutritional deficiencies. To prevent them, a well-balanced diet should be implemented, preferably with the help of a registered dietitian.

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Author's contribution

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