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REVIEW

Gluten-free diet in non-celiac patients: beliefs, truths, advantages and disadvantages

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ABSTRACT

A gluten-free diet is the safest treatment for the treatment of patient with celiac disease (CD) and other gluten-related disorders. However, in the last years, gluten-free diet is one of the most popular diet followed by the general population and by patients affected from others clinical conditions, such as non-celiac gluten sensitivity (NCGS), irritable bowel syndrome (IBS), autism, neurological, psychiatric and rheumatologic diseases and for improving sports practice. This review highlights some questions about the appropriateness of following this trend answering to some questions such as how safe are the current gluten-free products, what are the benefits and side effects of gluten-free diet and what are clinical conditions that might benefit from gluten avoidance.

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Gluten is a glycoprotein composed by two components: gliadin and glutenin. The glutenins occur in two forms, the high- and low-molecular-weight fractions, while the gliadins exist as three structural forms, α-, ω-, and γ-gliadins.[1, 2] Glutenins and gliadins undergo partial digestion in the upper gastrointestinal tract, resulting in the formation of various peptides resistant to digestion by gastrointestinal proteases.[3]

Gluten is a food source of the regular diet in the majority of western countries, found in wheat, barley, rye and, in a lower proportion, in oats. In addition, gluten has been added to processed food to improve texture and increase volume.[4] Wheat became much-demanded relative to other cereals mainly due to the flour with gluten properties of produce an elastic network resulting in a light and optimally chewy bread.[5] In addition, wheat and wheat-based products make substantial contributions to the dietary intake of protein, dietary fiber, minerals (especially iron, zinc, and selenium), vitamins, phytochemicals, and energy.[6]

Nevertheless, in the last decade, gluten was popularly stigmatized and, as a result, gluten-free diets have become increasingly prevalent in patients without a diagnosis of gluten allergy (an Ig mediated condition with risk of anaphylactic reaction that you search with RAST and prick tests) or celiac disease (CD) (an intolerance to

the gluten), especially in North America, where in 2013, 30 percent of USA adults reported reducing or eliminating gluten in their diets.[7] Specifically, gluten-free followers with self-made diagnosis that also make diagnosis of gluten-related diseases increased (especially by individuals reporting negative experiences with doctors).[7] Anyway, in some cases, there are also benefits of gluten-free diet in patients affected by irritable bowel syndrome (IBS), non-celiac gluten sensitivity (NCGS)[8] and some neurological manifestations[9] but there is no strong evidence for a strict indication to a gluten-free diet in endocrinological, psychiatric, and rheumatologic diseases, or to improve performance in elite sports.[10]

To address these gaps, we produced a review about the appropriateness of gluten-free diet, describing which category of non-celiac patients might benefits, disclosing myths, realities, and healthy and nutritional characteristics of the most current followed diet.

Literature search

We searched Pubmed/Medline using the terms "gluten-free diet in non-celiac patients," "gluten-free diet in non-celiac disease," "gluten-related disorders," and "gluten-free diet followers." Selected papers from 1980 to 2018 available were chosen based on their content (evidence-based quality and reliability) and in relation to the manuscript topic. Clinical and experimental articles, original articles, systematic review, and reports were included.

Gluten-free diet in NCGS

NCGS is a clinical condition characterized by gastroesophageal reflux disease (*i.e.*, retrosternal pyrosis and regurgitation) and IBS-like symptoms (*i.e.*, abdominal pain, bloating, diarrhoea, constipation and alternating bowel) along with extra-intestinal manifestations ("foggy mind," headache, fatigue, joint and muscle pain, leg/arm numbness, eczema/rash, depression/anxiety and anemia) that occur soon after gluten ingestion, rapidly improving after gluten withdrawal and relapsing in a few hours or days after gluten challenge.[11] NCGS is thought to be more frequent than CD, although its actual prevalence is still poorly defined[12, 13] and affected patients are negative for antiendomysial (EmA), antigliadin antibodies (AGA) and anti-tissue transglutaminase antibodies (tTGA),[14] in spite of celiac patients. In some cases they might be positive to AGA of the IgG class and a gluten-free diet produces a reduction of this marker in positive non-celiac patients.[15] In fact, gluten-free diet modulates innate immunity that has been thought to be activated by gluten proteins in NCGS and improve significantly gastrointestinal and extra-intestinal symptoms.[15] Specifically, the study conducted by Caio G *et al.* showed the disappearance of antigliadin antibodies of IgG class after 6 months of gluten-free diet; in contrast, 16/40 (40%) of celiac patients displayed the persistence of these antibodies after gluten withdrawal. In non-celiac gluten sensitivity patients, antigliadin antibodies IgG persistence after gluten withdrawal was significantly correlated with the low compliance to gluten-free diet and a mild clinical response. A possible link between gluten and symptoms has been suggested in NCGS patients,[16] although other components, mainly contained in the wheat (*i.e.* proteins), may trigger symptoms in NCGS. For example, wheat amylase and trypsin-inhibitors, a complex of proteins triggering innate immunity, could contribute to symptom generation in NCGS.[17] Similarly to IBS, it is likely that fermentable oligo-, di-, mono-saccharides and polyols (FODMAPs) may also play a role in evoking gastrointestinal (as well as extra-intestinal) symptoms in patients with NCGS.[18, 19] In this line, recent evidence by Bisierkieski *et al.* showed that a diet low in FODMAPs resulted in an improvement of the clinical picture of NCGS in IBS patients, thus supporting a major role of these dietary factors, rather than gluten.[20] The fluctuation of AGA with dietary changes (*i.e.* gluten withdrawal and re-challenge) in NCGS patients remains another very interesting aspect. In a recent double blind, placebo controlled study, Biesiekierski *et al.* have shown that NCGS patients in gluten-withdrawal for 6 weeks and re-challenged with high dose of gluten (16 g/day for one week) had an increase of AGA IgG and IgA in 8% and 21% of cases, respectively.[20]

Gluten-free diet in IBS

As mentioned above, there is overlap in the symptoms of IBS, NCGS and CD. Since the diagnosis of IBS is based mainly on symptom assessment using symptom criteria such as the Rome III criteria, there is a risk of CD patients being misdiagnosed as having IBS.[21] The situation is complicated even further by the fact that the ingestion of wheat products triggered abdominal symptoms. However, whereas this is caused by gluten allergy in CD patients, it is attributed in IBS patients to the long-sugar-polymer fructans in wheat.[22] One could speculate that mucosal damage and failure of the mucosal barrier caused by acute or chronic alcohol consumption,[23] or by a bout of gastroenteritis, would allow the immunogenic peptides resulting from the partial digestion of glutamines and gliadins to enter the lamina propria, where they could interact with immune cells, resulting in the production of AGA in both the healthy subjects and IBS patients. A study of eight adult females with abdominal pain, diarrhea, and small-intestine biopsy findings with no significant changes published in 1980 found that symptoms were relieved when the patients adhered to a gluten-free diet and returned after a gluten challenge.[24] Similar results have been reported in patients with non-celiac IBS-like symptoms.[25-27] In addition, the withdrawal of wheat products was found to improve these symptoms in double-blind randomized, placebo-controlled studies involving patients with IBS-like symptoms.[16, 28] Whereas some studies involving experimental animals and humans revealed that exposure to gluten induces intestinal low-grade inflammation, proliferation of peripheral blood monocytes, and enhancement of cytokine production,[26, 29-31] others were unable to find any gluten-induced inflammation in non-celiac patients with IBS.[32] Similar discrepancies have been reported regarding small-intestine permeability.[16, 26, 33] Anyway, it is possible that the frequency of IgG/IgA AGA is higher and the association with human leukocyte antigens (HLA) DQ2 and DQ8 is stronger in these patients.[28] However, confirmation of AGA positivity is not a specific test, since a considerable number of healthy individuals are positive for this antibody and HLA DQ2 and DQ8 are common in healthy population. The fructan contents in gluten-free bread (mostly made of rice/corn), bread made from white wheat flour, and bread made from spelt flour are 0.19 g/100 g, 0.68 g/100 g, and 0.14 g/100 g, respectively.[34] In addition, spelt flour contains 16% less protein (mostly gluten) compared to wheat.[35] Given the likelihood that it is the carbohydrate components of wheat that trigger symptoms in IBS, spelt products would be a better alternative to wheat than a gluten-free diet, which is widely used by IBS patients.[36, 37]

Gluten-free diet in ataxia and other neurologic manifestations

The term gluten ataxia was first proposed by Hadjivassiliou *et al.*[38] in 1998 in patients with progressive, idiopathic ataxia (a lack of coordination of muscle movements) and elevated AGAs. All of these patients had gait ataxia, some had limb ataxia, and more than half had peripheral neuropathy. The mechanisms by which gluten interacts with the nervous system have yet to be fully elucidated. In human and rat cerebellum, there is antibody cross-reactivity between gluten peptides and the Purkinje cells in the cerebellar cortex.[39] In addition, in the serum of patients with gluten ataxia, there is evidence for antibodies targeting Purkinje cell epitopes.[39] In addition, TTG IgA deposits have been reported in both jejuna tissue and around the blood vessels of the brain (cerebellum, pons, and medulla) in these patients.[40-42] Gluten-free diet is the mainstay of treatment for gluten ataxia, although one uncontrolled trial reported improvement in 4 patients after intravenous immunoglobulin.[43]

Other neurologic manifestations that might benefits from a gluten-free diet include inflammatory myopathy[44] and sensory ganglioneuropathy.[45] It is controversial whether multiple sclerosis, although reported to be associated with elevated AGAs, it truly part of the gluten sensitivity spectrum.[46, 47]

Others neuro-psychiatric disorders, such as autism, schizophrenia and depression has been related to NCGS.[48] Lionetti E *et al.*[48] report a pediatric case of a psychotic disorder clearly related to NCGS and investigate the causes by

a review of literature. Results showed that the pathogenesis of neuro-psychiatric manifestations of NCGS is unclear. It has been hypothesized that: 1) a "leaky gut" allows some gluten peptides to cross the intestinal membrane and the blood brain barrier, affecting the endogenous opiate system and neurotransmission; or 2) gluten peptides may set up an innate immune response in the brain similar to that described in the gut mucosa, causing exposure from neuronal cells of a transglutaminase primarily expressed in the brain. Well-designed prospective studies are needed to establish the real role of gluten as a triggering factor in neuro-psychiatric disorders.

The opioid hypothesis states that autism results from excessive brain opioid activity during the neonatal period. This leads to an inhibition of social motivation, yielding aloofness and autistic isolation. This hypothesis is supported by the arguments that animals exhibit similar behavior after injections of exogenous opioids (decreased vocalization and increased aloofness), direct biochemical evidence of abnormal peripheral endogenous opioids in autistic patients, and case reports of the therapeutic effects of naltrexone (a long-lasting opioid receptor blocking agent) in patients.[49, 50] In 1991, Reichelt[51] theorized that gluten (in addition to casein) peptides, which have similar chemical structures, play a role in the pathogenesis of autism. He forwards that the inability to adequately process gluten is proposed to result in, or exacerbate, a variety of disorders, including autism, schizophrenia, and postpartum psychosis. Specifically, he imagined that inadequately metabolized gluten proteins break down into peptides that are absorbed across the gut barrier. These peptides, names "gliadorphin" bind with endogenous opioid receptors, and high levels of peptides can be measured in the urine. A small proportion of these peptides cross the blood-brain barrier, causing "interference of signal transmission." In addition, Knivsberg *et al.*[52] argued that these peptides have a negative pharmacological effect on attention, brain maturation, social interaction, and learning. There are high rates of using complementary and alternative medicine (CAM) by the parents of children with autism spectrum disorders and among these also the adhesion to a gluten-free diet.[9] Two Cochrane reviews published in 2004 and 2008 investigates if autism might benefits from this nutritional approach. The participants included children, adolescents, and adults clinically diagnosed with autism spectrum disorder and the types of interventions studied were a gluten-free diet *vs.* placebo/no treatment, casein-free diet *vs.* placebo/no treatment, and gluten-free diet *vs.* casein-free diet. The outcomes measured included urine peptide concentrations, standardized autistic behavioral assessments, communication/linguistic ability, cognitive functioning, motor ability, and "disbenefits" (harms, costs, and impact on quality of life).[53] From 1965 to 2007, 61 studies were identified, of which only 3 were considered to be of high enough quality to be included in the analysis.[52, 54, 55] The other 58 studies were thought to have either significant bias or were not randomized or blinded (mostly case reports). These 3 studies comprised 2 small trials: the first with 10 participants in each arm and the second with 15 participants. In the first study, gluten-free diet was reported to reduce the autistic traits of "social isolation" and "bizarre behavior" at 12 months. In the second study, there was no significant difference in outcome measures between the diet group and the control group with regard to cognitive skills at 12 months, motor ability at 12 months, communication and language sampling at week 6, or Childhood Autism Rating Scale at week 6. There were no reported adverse outcomes or potential disbenefits. These meta-analyses concluded that "this is an important area of investigation and large scale, good quality randomized control trials are needed."[53] However, the underlying mechanism of benefit for such diets remains unclear.

Epigenetic programming, including CpG methylation and histone modifications, occurring during early postnatal development can influence the risk of disease in later life, and such programming may be modulated by nutritional factors such as milk and wheat, especially during the transition from a solely milk-based diet to one that includes other forms of nutrition.[56] In this context, the hydrolytic digestion of gliadin releases peptides with opioid activity that modulate cysteine uptake in cultured human neuronal and gastrointestinal epithelial cells via activation of opioid receptors. Decreases in cysteine uptake

were associated with changes in the intracellular antioxidant glutathione and the methyl donor S-adenosyl-methionine. Bovine and human wheat-derived opioid peptides increased genome-wide DNA methylation in the transcription start site region with a potency order similar to their inhibition of cysteine uptake. Altered expression of genes involved in redox and methylation homeostasis was observed, suggesting that wheat-derived peptides exert antioxidant and epigenetic changes, which may be particularly important during the postnatal transition from placental to gastrointestinal nutrition. Then, restricted antioxidant capacity, caused by wheat -derived opioid peptides, may predispose susceptible individuals to inflammation and systemic oxidation, partly explaining the benefits of gluten-free diets.

Gluten-free diet in rheumatoid arthritis

Patients with rheumatoid arthritis are at increased risk of cardiovascular disease[57-59] and atherosclerosis.[60] They also have a dyslipidemia that is characterized by normal or increased low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, and high triglycerides (TG) in a manner that is comparable to inflammatory and infectious diseases[61] and that is associated with disease activity.[62] Phosphorylcholine (PC) is immunogenic when exposed to the immune system and is involved in the development of atherosclerosis.[63, 64] Although treatment with antirheumatic drugs has been shown to improve the lipid profile in treatment responders,[60] dietary intervention is another modality that might affect the dyslipidemia in this disease. Specifically, a gluten-free vegan diet decreases total cholesterol, LDL, and the LDL: HDL ratio and increases levels of natural antibodies of IgA and IgM subclasses to PC. Because LDL is atherogenic and anti-PC levels are negatively associated with the development of atherosclerosis, this diet is likely to be antiatherogenic with an ameliorating effect.[65] However, the actual role gluten itself plays is not known; what has been demonstrated so far is that a gluten-free vegan diet for 1 year significantly reduced disease activity and levels of antibodies to β-lactoglobulin and gliadin in patients with rheumatoid arthritis.[66]

Gluten-free diet in athletic performances

The concept of performance extends beyond the actual physical wins or losses in sport. It also encompasses aspects of individual well-being performance that are influenced by dietary intakes and beliefs that ultimately may provide a competitive edge.[67] Non-celiac athletes have rapidly become a prevalent group adopting a gluten-free diet as a means to optimize health and gain a performance edge.[67] This belief is also incentivized by commercial claims equating gluten-free diets with enhanced health, as well as some high profile athletes touting this diet as the secret to their athletic success.[67] A survey reports that about 41% of athletes report adhering to a gluten-free diet, which is four-fold higher than the population-based clinical requirements.[67] Many non-celiac athletes believe that gluten avoidance improves gastrointestinal well-being, reduces inflammation, and provides an ergogenic edge, despite the fact that limited data yet exist to support any of these benefits. There are several plausible associations between endurance-based exercise and gastrointestinal permeability whereby a gluten-free diet may be beneficial. In addition, athletes eliminate gluten to promote weight loss or improve body composition for sport,[68] although evidence to support this is lacking,[69] and controversially in CD following a gluten-free diet there is an increased risk of obesity suggested to be linked to increased nutrient absorption and intakes of high-fat/sugar gluten-free products.[70] The survey also reports that 70% of interviewed are recreationally competitive endurance athletes with the conviction that it is healthier, improves conscientiousness of food choices, and promotes overall more balanced eating.[68] It is debatable whether a gluten-free diet equates to dietary changes resulting in a healthier or less healthy diet, or if other dietary habits are subsequently modified resulting in improved or worsened eating behaviors. Hype about this diet brings in the question of dietary and nutritional adequacy and the issue of suboptimal fueling risk as described in other elimination type diets.[71]

Non-celiac athletes adhering to a gluten-free diet do so in varying degrees, ranging from periodic gluten elimination, elimination 1 to 2 weeks before competition, or up to 100% of the

time.[68] Although adherence rates vary, enhanced dietary mindfulness is suggested as an outcome to avoidance of gluten containing products.[68, 72] Converting to a gluten-free diet plausibly results in some athletes increasing their conscientiousness of healthy balanced eating, increasing fruit and vegetable and whole grain intake and decreasing processed food selections.[72] The proliferation of the gluten-free food products market results in both an increase of unhealthy gluten-free products as well as the production of more nutrient-rich pseudocereals, such as amaranth, buckwheat, and quinoa, replacing corn and rice flour.[73] These substitutions could potentially reduce the risk of omitted dietary sources of B vitamins and iron that are critical for metabolism and athletic adaptations. Analysis of the capacity of a gluten-free diet to support athletic energy demands has not been conducted so it is unknown if the dietary restriction associated with this diet compromises energy availability. However, the implications of confounding factors, including the risks of unnecessary dietary restriction, financial burden, food availability and psychosocial implications emphasize the need for further evaluation.

Safety, nutritional and health profile of gluten-free diet in general population

Gluten-free diet is essential in nutrition of patients affected by CD, but as mentioned above, there is a substantial proportion of the population may benefit from reducing gluten in their diet.[74] However, clinical evidence for the existence of such conditions and other purported adverse health effects of gluten remain inconsistent.[75] Nevertheless, there is growing popular perception that gluten-free foods are healthier, and in recent years, there has been a dramatic increase in demand and consumption of gluten-free foods in many Western countries. Despite the tremendous rise in popularity and consumption of gluten-free foods, there is a lack of evaluation of their nutritional profile and how they compare with non-gluten-free foods. Such an assessment is important for several reasons. Gluten-containing grains such as wheat, rye and barley are important sources of nutrients. Staple foods that traditionally contain these grains are core to the diet of many countries, and consumed by large proportions of the population.[76] There are concerns that removal or substitution of these grains from gluten-free products with other ingredients could adversely affect nutrient intake in those consuming a gluten-free diet.[77, 78] Furthermore, consumers may perceive gluten-free products as healthier than non-gluten-free foods and food companies may market them as such and charge a premium price.[79, 80] This may occur even when the foods concerned are energy-rich, nutrient-poor discretionary products such as cakes and biscuits.[79-81] For most food categories, it is unclear whether gluten-free products contain comparable, higher or lower levels of sugar, salt and saturated fat relative to non-gluten-free products. A review evaluated the nutritional quality of gluten-free and non-gluten-free foods in core food groups, and a wide range of discretionary products in supermarkets.[76] Nutritional information on the Nutrition Information Panel was systematically obtained from all packaged foods at four large supermarkets in 2013. Food products were classified as gluten-free if a gluten-free declaration appeared anywhere on the product packaging, or non-gluten-free if they contained gluten, wheat, rye, triticale, barley, oats or spelt. The primary outcome was the 'Health Star Rating' (HSR: lowest score 0.5; optimal score 5), a nutrient profiling scheme endorsed by the local Government. Differences in the content of individual nutrients were explored in secondary analyses. 3213 food products across ten food categories were included. On average, gluten-free plain dry pasta scored nearly 0.5 stars less ($P<0.001$) compared with non-gluten-free products; however, there were no significant differences in the mean HSR for breads or ready-to-eat breakfast cereals ($P\geq0.42$ for both). Relative to non-gluten-free foods, gluten-free products had consistently lower average protein content across all the three-core food groups, in particular for pasta and breads (52 and 32% less, $P<0.001$ for both). A substantial proportion of foods in discretionary categories carried gluten-free labels (*e.g.* 87% of processed meats), and the average HSR of gluten-free discretionary foods were not systematically superior to those of non-gluten-

free products. These results suggest that the consumption of gluten-free products is unlikely to confer health benefits, unless there is clear evidence of gluten allergy or intolerance.

In addition, two additional studies have shown that many gluten-free foods are not enriched and may be deficient in several nutrients, including dietary fiber, folate, iron, niacin, riboflavin, and thiamine,[82, 83] zinc, magnesium, calcium[84] and polyunsaturated fatty acids.[85] Another study pointed out differences also in calories, macronutrient, fiber, sodium, salt and cholesterol content between gluten free rendered and gluten-containing foodstuffs.[86] Thus, calorie and nutrient intake in a gluten-free diet is different when compared to its equivalent diet with gluten. Following a diet based on gluten-free products could suppose a nutritional imbalance for celiac patients as well as for non-celiacs who follow a diet that includes many gluten-free rendered foodstuffs.

A National Health and Nutrition Examination Survey conducted from 2009 to 2014 in the USA investigated obesity, metabolic syndrome, and cardiovascular risk in gluten-free followers without CD.[87] 13,523 persons without CD who had gluten-free diet information were included and gluten-free followers without CD and the general population were compared by selective metabolic and cardiovascular disease risk profiles using survey-weighted generalized logistic regression. Results showed that there were 155 gluten-free followers without CD and cardiovascular disease, corresponding to a weighted prevalence of 1.3% (3.2 million Americans). Gluten-free followers tended to be women and have a smaller waist circumference and higher HDL cholesterol. They also had a lower BMI with a borderline p value (0.053) and significant self-reported weight loss (-1.33 kg) over one year. Moreover, gluten-free followers were more likely to consider their weight appropriate. There was no statistical difference by age, smoking, hypertension, total cholesterol, triglyceride cholesterol, HbA1c, or fasting glucose. Despite a lower probability of having metabolic syndrome (33.0 *vs.* 38.5%) and lower 10-year cardiovascular disease risk score (4.52 *vs.* 5.70%) in gluten-free followers, there was no statistical difference. These results suggest that although being on a gluten-free diet may be beneficial in weight management, there was no significant difference in terms of prevalence of metabolic syndrome and cardiovascular disease risk score in gluten-free followers without CD.

In addition, gluten-free foods were substantially higher in cost, ranging from +205% (cereals) to +267% (bread and bakery products) compared to similar gluten-containing products without providing additional health benefits from a nutritional perspective.[88]

Conclusions

In conclusion, the gluten-free diet has become one of the most popular diets in modern history. The consumption of gluten-free products is unlikely to confer health benefits, unless there is clear evidence of CD. There is a moderate likelihood that gluten-free labelling is being used to infer healthiness for discretionary items, which is unwarranted. The gluten-free diet although safe and effective, is currently only indicated for specific medical conditions such as CD, NCGS and IBS. Widespread media validation continues to drive the popularity of gluten-free diet forward, yet this diet has not been shown to affect either positive or negative competitive performance or symptoms of gastro-intestinal health and inflammation and/or nutritional status not only in non-celiac athletes but also in general population. Gluten-free diet was found to be poor in alimentary fiber due in particular to the necessary avoidance of several kinds of foods naturally rich in fiber (*i.e.* grain) and the low content of fiber of gluten-free product that are usually made with starches and/or refined flours. Micronutrients are also found to be poor, in particular vitamin D, vitamin B12 and folate, in addition to some minerals such as iron, zinc, magnesium and calcium, although gluten-free foods were substantially higher in cost.

It is mandatory to consider potential risks associated with unnecessary food restrictions, psychosocial implications, and cost. Given the adverse health effects caused by poor diets, institutional initiatives should target increased consumption of core foods such as whole grains, fruit and vegetables and reduced consumption

of discretionary foods (gluten-free or otherwise) as a public health priority. In addition, because of the main motivations for following a gluten-free diet were weight control and the perception that a gluten-free diet is healthier, trustable scientific information about the benefits and potential consequences of following a gluten-free diet should be given to the general population in the absence of a proper diagnosis of gluten-related disorders.

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