Curr Treat Options Gastro (2019) 17:554–563
DOI 10.1007/s11938-019-00255-0

Obesity and Nutrition (O Pickett-Blakely, Section Editor)

# The Gluten-Free Diet: Use in Digestive Disease Management

*Carolyn Newberry, MD*

**Address**
Division of Gastroenterology, Weill Cornell Medical Center, 1305 York Avenue, 4th Floor, New York, NY, 10021, USA
Email: can9054@med.cornell.edu

Published online: 9 November 2019


This article is part of the Topical Collection on *Obesity and Nutrition*

**Keywords** Gluten · Gluten-related disorders · Diet · Nutrition

## Abstract

*Purpose of Review* Gluten is a commonly ingested polymeric protein found in wheat, barley, and rye that has gained recent notoriety because of its relationship to disease and health. Avoidance of gluten is appropriate in patients with a diagnosed gluten–related disorder and may have treatment implications in other diseases of the digestive tract. This review highlights current knowledge of gluten related disorders and the use of a gluten-free diet in gastrointestinal disease management.

*Recent Findings* Gluten-free diets should be used in patients with a diagnosed gluten–related disorder including celiac disease, non-celiac gluten sensitivity, and wheat-sensitive eosinophilic esophagitis. Use of this diet in management of other digestive conditions including gastroesophageal reflux disease, irritable bowel syndrome, and inflammatory bowel disease is controversial and not currently supported by the literature.

*Summary* This review provides a framework for classifying gluten-related disorders in terms of pathogenesis, understanding the literature that supports dietary avoidance in modulation of gastrointestinal disease, and identifies limitations of dietary restriction in patients.

## Introduction

Gluten is a polymeric protein found in foods containing wheat, barley, and rye [1]. It has risen in notoriety over the last decade due to proposed associations with disease, health, and wellness. Although true gluten-related disorders (GRD) are uncommon, increasing percentages of the population are following a gluten-free diet (GFD) [2]. This is despite lack of evidence confirming proposed health benefits of dietary avoidance in patients without a medical diagnosis. The following is a general overview of the indications for a GFD including emerging use as a treatment for gastrointestinal diseases (Table 1).

## Gluten: Composition, Chemical Structure, and Immunogenicity

Gluten is a complex protein comprised of a monomeric component, called prolamin, and polymeric component, called glutelin. Prolamins are responsible for the viscous properties of gluten whereas glutenin provides elasticity. These unique attributes impart the characteristic consistency of pasta and bread products and provide a challenge in texture recreation in gluten free foods [3]. Prolamins comprise the major storage protein in gluten and vary based on type of grain: wheat (gliadin), barley (hordein), and rye (secalin) [4]. Oats also contain small amounts of prolamin in the form of avenin but are not usually classified as a gluten protein [5]. The most abundant form of gluten in the western diet is wheat, which is composed of gliadin and a glutelin protein known as glutenin [6]. Gliadins are subdivided by inherent properties during electrophoresis, which characterizes them by shape and size into α, γ, and ω subfractions. Glutenin is categorized by molecular weight into low weight and high weight subtypes of which multiple types can be contained in a single grain. Prolamins as a whole contain long sequences of the amino acids proline and glutamine, which are resistant to degradation by intestinal proteases. This enhances the immunogenic properties of gluten proteins as they remain largely intact when interacting with lymphoid-dense small bowel mucosa [3]. This is the proposed mechanism of immune-mediated gluten–related disorders like celiac disease, where antigenic presentation of gluten leads to stimulation of the innate immune system and subsequent inflammatory cascades [7]. Patients who develop celiac disease have either a DQ2 or DQ8 haplotype, as these antigen-presenting cell surface molecules govern T cell–mediated inflammation and are necessary for development of disease (Fig. 1) [1]. These haplotypes may also be implicated in the pathogenesis of non-celiac gluten sensitivity; however, the importance of their presence is still unknown [8].

**Table 1. Use of the gluten-free diet (gfd) for digestive disease management**

| Digestive disorder | Disease pathogenesis secondary to gluten exposure | Use of the GFD in management |
|---|---|---|
| Eosinophilic esophagitis | Non-IgE mediated allergic response to gluten subtype (wheat) | 6 food elimination diet is one of the first line therapies (includes wheat), limited data to support broader GFD |
| Gastroesophageal reflux disease | No correlation, fiber may be protective against disease by unknown mechanism | Not indicated |
| Celiac disease | Autoimmune reaction in response to gluten ingestion | GFD is first line therapy and represents the only treatment option |
| Non-celiac gluten sensitivity | Still unknown, possibly innate immune system activation secondary to gluten exposure | GFD thought to mitigate symptoms, though may have overlap with FODMAP ingestion |
| Inflammatory bowel disease | No correlation, though ingestion of specific carbohydrates may worsen symptoms | Not indicated |

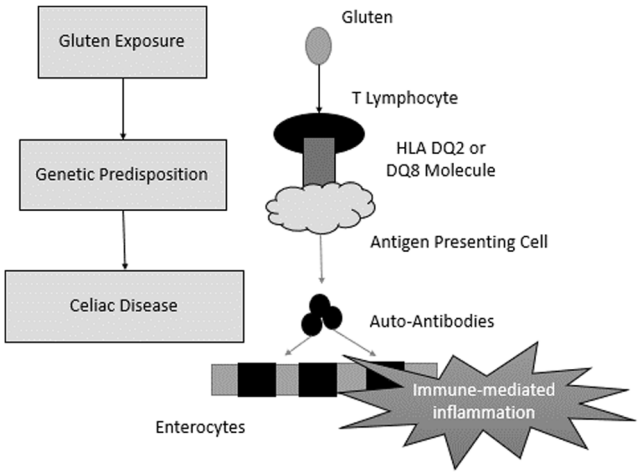


**Fig. 1.** Pathogenesis of celiac disease. Genetically predisposed individuals (those who possess specific HLA haplotypes) develop T lymphocyte mediated inflammation in the setting of gluten exposure

# Gluten-Related Disorders

Gluten-related disorders represent a spectrum of medical diseases related to gluten exposure. They are classified based on pathogenesis and divided into three types: allergic responses, autoimmune diseases, and diseases of unknown mechanism [9••].

## Allergic Responses

Wheat, a subtype of gluten, is implicated in both IgE and non-IgE-mediated allergic reactions. In IgE-mediated disease, ingestion or inhalation of wheat leads to enhanced T helper type 2 (Th2) and B cell activity and development of IgE antibodies. These cellular changes cause mast cell destabilization, activation of basophils, and release of histamine, leukotrienes, and platelet activation factors [10]. Patients subsequently develop classic allergic symptoms including urticaria, generalized pruritus, nausea, emesis, and/or respiratory difficulties [8]. Prevention of symptoms relies on strict avoidance of wheat. Treatment options after exposure include antihistamines, corticosteroids, and epinephrine injections. Wheat allergy affects approximately 3–5% of children, but less than 1% of adults.

Wheat-induced allergic disease can also be non-IgE-mediated and mechanistically is less clearly understood. Proposed pathogenesis includes enhanced activation of Th2 cells without the involvement of IgE and manifests as eosinophilic infiltration of gastrointestinal mucosa, most commonly in the esophagus. Eosinophil-predominant inflammation leads to swallowing dysfunction, abdominal pain, and nausea with emesis after wheat exposure [10]. Management of non-IgE mediated wheat allergy also responds to avoidance of culprit foods, though may require additive therapies including swallowed steroids. Prevalence in the general population is increasing and is now estimated to affect about 50/100,000 patients [11].

### Autoimmune Disorders

The most common autoimmune disorder associated with gluten exposure is celiac disease. This is defined as an immune-mediated disorder of the small bowel that occurs after gluten exposure. Proposed mechanisms of disease include miscategorization of gluten molecules as pathogens with release of inflammatory cytokine cascades after exposure [12]. Although all individuals exposed to gluten may have changes in intestinal permeability after ingestion, molecular mimicry inducing antibody response only occurs in patients with certain genetic predisposition (i.e., those with HLA DQ2 and DQ8 haplotypes) [13]. Notably, not all patients with these genetic markers develop the disease indicating additional epigenetic factors contribute to pathogenesis. With exposure in genetically primed individuals, inflammation in the small bowel leads to cellular changes, malabsorption of nutrients with weight loss, and gastrointestinal distress including bloating, pain, and diarrhea. Additionally, patients may develop a characteristic vesicular rash known as dermatitis herpetiformis [14]. The disease is estimated to affect up to 1% of the population and may be underdiagnosed [15].

Gluten ataxia is the other form of autoimmune disease associated with gluten ingestion. This is defined as the development of neurological dysfunction including abnormal gait patterns in the setting of exposure to gluten. Pathogenesis is related to auto-antibody development to cerebellar Purkinje cells, which are molecularly similar to gluten protein molecules [16]. Symptoms respond to a strict gluten free diet. The condition is thought to be more common than previously thought, accounting for up to 40% of cases of idiopathic ataxia [17]. Although the condition may present concomitantly with gluten-associated enteropathies, the conditions are distinct entities [16].

### Mechanism Unknown

Growing literature supports a link between gluten exposure and development of gastrointestinal symptoms in the absence of classic serological testing or distortion of villous architecture. Initially known as "gluten-sensitive diarrhea", this condition has now been classified as non-celiac gluten sensitivity (NCGS) [18]. A significant overlap exists between patients with self-reported NCGS and those who meet criteria for irritable bowel syndrome [19]. This may be most prevalent in those who carry the genes associated with celiac disease but do not display classic manifestations of the condition [20]. Proposed mechanisms of disease include alterations in intestinal permeability and activation of the innate immune system, though definitive markers have not been established. The prevalence of the condition is unknown due its diagnostic uncertainty [21].

## Use of the Gluten-Free Diet in Digestive Disease Management

Considering the unique chemical structure and enhanced immunogenic properties of gluten, its use as a therapy for digestive diseases is becoming increasingly common. The benefit of such restriction varies among disease state and is most supported by the literature in known GRDs.

## Celiac Disease

The only effective treatment for celiac disease is a strict GFD, as there are no approved medications [15]. The GFD resolves characteristic small bowel inflammation in nearly all patients and is associated with reduction in complications of disease including malignancy, micronutrient deficiencies, and alterations in bone mineral density and lean muscle mass [22]. Patients with celiac disease are instructed to avoid any food with wheat, barley, and rye and need to be aware of cross-contamination and hidden sources of environmental gluten including cosmetics [23]. After gluten withdrawal, serological markers of disease normalize within a few months and can be monitored over time [24]. Only a small percentage of patients (1–2%) do not fully respond to the GFD and are known as having "refractory" disease. This is defined by lack of serological and pathological resolution after a strict GFD for at least 6 months. These patients can develop more severe complications of disease including ulcerative jejunitis and enteropathy-associated T cell lymphoma [12]. Treatment options include high dose topical steroids in addition to gluten restriction [25].

## Non-Celiac Gluten Sensitivity/Functional Bowel Disorders

Gluten restriction as treatment for functional bowel disorders is common, though the efficacy of this approach is still unclear. The subset of patients who note gastrointestinal complaints with gluten exposure in the absence of serological or biopsy abnormalities (i.e., NCGS) are a heterogeneous group and identification is difficult. There is no test for NCGS, although recent studies indicate these patients are more likely to have positive nonspecific celiac markers like deamidated gliadin antibodies [26]. Additional considerations include the overlap between foods containing gluten and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FOMAPs), which have also been implicated in functional disease. This was exemplified by a study of thirty-seven patients with reported NCGS, of which only 8% complained of gluten-specific symptoms with control of FODMAP intake [27••].

## Eosinophilic Esophagitis

Treatment options in eosinophilic esophagitis (EoE) include pharmacotherapy (acid suppressive agents and swallowed steroids) and dietary manipulation (elemental and elimination diets). The latter remains popular to avoid medications and is considered a first line therapy in both adult and pediatric populations [28]. Dietary therapy options include elemental diets, empiric elimination diets, and targeted elimination diets. Of these options, elemental diets are the most effective, although empiric elimination diets are an acceptable alternative and usually better tolerated [29]. This approach includes eliminating the six most common food allergens including soy, dairy, eggs, nuts, fish/shellfish, and wheat with sequential reintroduction [30]. Newer research indicates four food elimination diets (soy, dairy, eggs, and wheat) may also induce remission in up to half of patients [31]. In terms of wheat's association with EoE, recent studies report a substantial number of patients (26–60%) can achieve mucosal response with wheat avoidance alone [32, 33]. Gluten's role in disease pathogenesis is less clear. Wheat may cross-contaminate other closely related grains like barley and rye during processing which could induce

response in primed individuals [34]. This is further supported by the high presence of hypersensitivity to other related gluten-containing grains in patients with wheat allergies [35]. However, gluten's role in pathogenesis of EoE specifically has not been defined and future research is needed to guide therapy.

## Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is characterized by troublesome symptoms that develop in response to increased esophageal exposure to gastric acid [36]. It is usually treated with acid suppressive medications; however, lifestyle factors including diet are becoming increasingly common means of controlling symptoms [37]. The relationship between gluten ingestion and GERD is not well defined; however, studies examining the effect of generalized diet on pathophysiology of disease continue to emerge. For instance, growing evidence supports alterations in carbohydrate ingestion as a means of treating GERD symptoms. Carbohydrates can take several forms including simple sugars (which are composed of only one or two glucose molecules) and complex carbohydrates (which are composed of many). Complex carbohydrates can be either starches or fiber, depending on chemical bonds. Starch can be broken down by the body, while fiber cannot [38]. Alterations in complex carbohydrate ingestion may be associated with increased GERD, favoring reduction in dietary starch and increased fiber intake. In terms of mechanism, starch has been linked to reductions in lower esophageal sphincter pressures via colonic fermentation [39] whereas the protective effects of fiber are unknown, though frequently reported [40, 41]. Most starch in the western diet comes from refined grains, which are usually gluten-based. However whole grain products (which are also gluten-based) have high fiber content, so it could be inferred grain processing would be more important to disease pathogenesis than inherent properties of gluten. The effect of gluten on GERD symptoms has been studied in a small group of patients with celiac disease with noted reduction in symptoms after acid suppression withdrawal when compared with controls not on a GFD [42]. However, this dietary approach is not commonly employed in those without a GRD and would be of unclear benefit considering current understanding of GERD and diet.

## Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by chronic relapsing inflammation in the digestive tract. Numerous factors are thought to play a role in pathogenesis, one of which may be diet [43]. On meta-analysis, diets implicated in disease include those high in fat, simple carbohydrates (mono- and disaccharides), and meat intake. Negative associations have been identified with fruit, vegetable, and overall fiber intake [44]. A recent Cochrane Review confirmed these findings, noting enhanced remission rates with low refined carbohydrate diets; however, studies included were small and poorly designed limiting conclusive recommendations [45]. Analysis of gluten's effect on development of disease has not been studied. Several studies have investigated the relationship between the GFD and IBD in terms of symptoms. For instance, a large survey of patients diagnosed with IBD noted 19% had tried a GFD in the past with two-thirds of these patients noting GI symptom improvement with dietary restriction [46]. Another smaller survey–based study noted the

prevalence of self-reported gluten sensitivity was high (23% in Crohn's, 27% in ulcerative colitis) and associated with presence of recent flare indicating a bidirectional relationship [47]. Again, study design and size limit generalizability and research is warranted to understand this relationship. Additionally, overlap between gluten and FODMAP ingestion may be difficult to ascertain in this type of study design and needs to be considered.

# Limitations of the Gluten-Free Diet

The GFD is appropriate for patients with diagnosed GRDs and may benefit patients with other digestive diseases as outlined. However, limitations to the diet need to be considered, and patients should be counseled on these factors prior to gluten restriction.

## Cost, Accessibility, and Palatability

Although the increased popularity of the GFD has also led to an increase of available gluten free products, limitations exist in terms of cost, accessibility, and palatability. Gluten-free products have been found to be more expensive than their gluten-containing counterparts [48]. Additionally, availability of these foods may be limited in certain areas [49]. If products are affordable and accessible, alterations in taste may reduce dietary compliance as recreation of the texture, and consistency of gluten remains challenging [3].

## Nutritional Deficiencies

Because the GFD is restrictive, certain nutritional intakes may be altered. For instance, total carbohydrate intake has been found to be lower in patients on a GFD with an increase in sugar in favor of fiber. Additionally, overall fat intake in the GFD is elevated as gluten-free products may contain higher levels of fat and dietary staples like wheat are restricted [50, 51]. Micronutrient intake is also of concern, with reduction in overall intake of calcium, iron, and B vitamins including thiamine, riboflavin, niacin, and folate reported in patients on GFDs [52, 53]. Introduction of alternative grains and consultation with a dietician may mediate these effects and should be considered [54].

# Conclusion

Gluten is a commonly ingested protein found in wheat, barley, and rye. Its unique chemical composition is associated with increased immunogenicity. Its ingestion is implicated in several disorders collectively known as GRDs, most of which are associated with digestive diseases. Gastroenterologists should understand the indications and limitations of the diet as well as how to use it in clinical practice. Currently, the GFD is recommended for management of celiac disease and non-celiac gluten sensitivity whereas wheat avoidance can be used to manage wheat sensitive EoE. The GFD is currently not recommended for patients with GERD or IBD due to lack of data supporting its efficacy.

## Author Contributions

Carolyn Newberry, MD was involved in the manuscript research, preparation, and final approval of the manuscript.

## Compliance with Ethical Standards

**Conflict of Interest**
Carolyn Newberry declares the she has no conflict of interest.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


1. Guandalini S, Gokhale R. Update on immunologic basis of celiac disease. Curr Opin Gastroenterol. 2002;18(1):95–100 Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00001574-200201000-00017.
2. Kim H, Patel KG, Orosz E, et al. Time trends in the prevalence of celiac disease and gluten-free diet in the US population: results from the national health and nutrition examination surveys 2009-2014. JAMA Int Med. 2016;176(11):1716–7. Available from. https://doi.org/10.1001/jamainternmed.2016.5254.
3. Stamnaes J, Sollid LM. Celiac disease: autoimmunity in response to food antigen. Semin Immunol. 2015;27(5):343–52 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S104453231500072X.
4. Cebolla Á, Moreno ML, Coto L, Sousa C. Gluten immunogenic peptides as standard for the evaluation of potential harmful prolamin content in food and human specimen. Nutrients. 2018;10(12):1927 Available from: https://www.ncbi.nlm.nih.gov/pubmed/30563126.
5. Real A, Comino I, de Lorenzo L, et al. Molecular and immunological characterization of gluten proteins isolated from oat cultivars that differ in toxicity for celiac disease. PLoS One. 2012;7(12):e48365 Available from: https://www.ncbi.nlm.nih.gov/pubmed/23284616.
6. Graveland A, Bosveld P, Lichtendonk WJ, et al. A model for the molecular structure of the glutenins from wheat flour. J Cereal Sci. 1985;3(1):1–16 Available from: https://www.sciencedirect.com/science/article/pii/S0733521085800291.
7. Kagnoff MF. Celiac Disease Pathogenesis of a model immunogenetic disease. J Clin Invest. 2007;117(1):41–9 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1716218/.
8. Pietzak M. Celiac disease, wheat allergy, and gluten sensitivity. J Parenter Enteral Nutr. 2012;36(1_suppl):75S Available from: https://journals.sagepub.com/doi/full/10.1177/0148607111426276.
9. •• Sapone A, Bai J, Ciacci C, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Medicine. 2012;10:13 Available from: https://search.datacite.org/works/10.7916/D8PR7TBW.

This consensus statement defines current classification of gluten related disorders based on pathogenesis of disease.

10. Cianferoni A. Wheat allergy: diagnosis and management. J Asthma Allergy. 2016;9:13–25 Available from: https://www.ncbi.nlm.nih.gov/pubmed/26889090.
11. Reed CC, Dellon ES. Eosinophilic esophagitis. Med Clin of N Amer. 2019;103(1):29–42 Available from: https://www.sciencedirect.com/science/article/pii/S0025712518301007.
12. Leonard MM, Sapone A, Catassi C, et al. Celiac disease and nonceliac gluten sensitivity: A review. JAMA. 2017;318(7):647–56. Available from. https://doi.org/10.1001/jama.2017.9730.
13. Kim SM, Mayassi T, Jabri B. Innate immunity: actuating the gears of celiac disease pathogenesis. Best Prac Res:

Clin Gastroenterol. 2015;29(3):425–35 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S1521691815000554.
14. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. J Am Acad Dermatol. 2010;64(6):1017–24 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S0190962210021225.
15. Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Amer J Gastroenterol. 2013;108(5):656–76 Available from: https://www.ncbi.nlm.nih.gov/pubmed/23609613.
16. Hadjivassiliou M, Boscolo S, Davies-Jones GAB, et al. The humoral response in the pathogenesis of gluten ataxia. Neurology. 2002;58(8):1221–6 Available from: https://www.ncbi.nlm.nih.gov/pubmed/11971090.
17. Hadjivassiliou M, Davies-Jones GAB, Sanders DS, et al. Dietary treatment of gluten ataxia. J Neurol, Neurosurg & Psych. 2003;74(9):1221–4. Available from. https://doi.org/10.1136/jnnp.74.9.1221.
18. Hollon J, Puppa EL, Greenwald B, et al. Effect of gliadin on permeability of intestinal biopsy explants from celiac disease patients and patients with non-celiac gluten sensitivity. Nutrients. 2015;7(3):1565–76 Available from: https://www.ncbi.nlm.nih.gov/pubmed/25734566.
19. Matuchansky C. Gluten-free diet and irritable bowel syndrome–diarrhea. Gastroenterol. 2013;145(3):692–3 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S0016508513009992.
20. Roque V, Camilleri MI, Smyrk M, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. Gastroenterol. 2013;144(5):911.e3 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S0016508513001352.
21. Lebwohl B, Ludvigsson J, Green PH. Celiac disease and non-celiac gluten sensitivity. BMJ. 2015;351:h4347 Available from: https://www.bmj.com/content/351/bmj.h4347.
22. Bardella MT, Fredella C, Prampolini L. Body composition and dietary intakes in adult celiac disease patients consuming a strict gluten-free diet. Amer J Clini Nutr. 2000;72(4):937–9 Available from: https://www.ncbi.nlm.nih.gov/pubmed/11010934.
23. Kupper C. Dietary guidelines and implementation for celiac disease. Gastroenterol. 2005;128(4):S127 Available from: https://www.sciencedirect.com/science/article/pii/S0016508505001939.
24. Nachman F, Sugai E, Vázquez H, et al. Serological tests for celiac disease as indicators of long-term compliance with the gluten-free diet. Eur J Gastroenterol Hepatol. 2011;23(6):473–80 Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00042737-201106000-00005.
25. Malamut G, Murray J, Cellier C. Refractory celiac disease. Gastrointest Endosc Clin N Am. 2012;22(4):759–72 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S1052515712000992.
26. Cash BD, Rubenstein JH, Young PE, et al. The prevalence of celiac disease among patients with non-constipated irritable bowel syndrome is similar to controls. Gastroenterology. 2011;141(4):1187–93 Available from: https://www.ncbi.nlm.nih.gov/pubmed/21762658.
27.•• Biesiekierski JR, Peters SL, Newnham ED, et al. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterol. 2013;145(2):328.e3 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S0016508513007026.
This article discusses the potential overlap between symptoms induced by gluten and FODMAP ingestion by double blind crossover trial.
28. Dellon ES, Gonsalves N, Hirano I. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Amer J Gastroenterol. 2013;108(5):679–92 Available from: https://www.ncbi.nlm.nih.gov/pubmed/23567357.
29. Warners MJ, Vlieg-Boerstra BJ, Bredenoord AJ. Elimination and elemental diet therapy in eosinophilic oesophagitis. Best Prac Res: Clin Gastroenterol. 2015;29(5):793–803 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S1521691815000980.
30. Kagalwalla AF, Sentongo TA, Ritz S. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006;4(9):1097–102 Available from:.
31. Molina-Infante J, Lucendo AJ. Dietary therapy for eosinophilic esophagitis. J Allergy Clin Immunol. 2018;142(1):41–7 Available from: https://www.sciencedirect.com/science/article/pii/S0091674918303208.
32. Gonsalves N, Yang G-Y, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterol. 2012;142(7):1459.e1 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S0016508512003095.
33. Kagalwalla A, Shah A, Li B, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. J Ped Gastroenterol Nut. 2011;53(2):145–9 Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00005176-201108000-00006.
34. Doerfler B, Bryce P, Hirano I, et al. Practical approach to implementing dietary therapy in adults with eosinophilic esophagitis: the chicago experience. Dis Esophagus. 2015;28(1):42–58 Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/dote.12175.
35. Kliewer K, Venter C, Cassin A, et al. Should wheat, barley, rye, and/or gluten be avoided in a 6-food elimination diet? J Allergy Clin Immunol.

2015;137(4):1011–4 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S0091674915017261.
36. Vakil N, van Zanten Sander V, Kahrilas P, et al. The montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Amer J Gastroenterol. 2006;101(8):1900–20. Available from. https://doi.org/10.1111/j.1572-0241.2006.00630.x.
37. Ness-Jensen E, Hveem K, El-Serag H, et al. Lifestyle intervention in gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2016;14(2):175 Available from: http://kipublications.ki.se/Default.aspx?queryparsed=id:132991735.
38. MacFarlane NG. Digestion and absorption. Anesth Int Care Med. 2018;19(3):125–7 Available from: https://www.sciencedirect.com/science/article/pii/S1472029918300018.
39. Piche T, des Varannes SB, Sacher-Huvelin S, Holst JJ, et al. Colonic fermentation influences lower esophageal sphincter function in gastroesophageal reflux disease. Gastroenterol. 2003;124(4):894–902 Available from: https://www.sciencedirect.com/science/article/pii/S0016508503000738.
40. Morozov S, Isakov V, Konovalova M. Fiber-enriched diet helps to control symptoms and improves esophageal motility in patients with non-erosive gastroesophageal reflux disease. World J Gastroenterol. 2018;24(21):2291–9 Available from: https://www.ncbi.nlm.nih.gov/pubmed/29881238.
41. DiSilvestro RA, Verbruggen MA, Offutt EJ. Anti-heartburn effects of a fenugreek fiber product. Phytotherapy Res. 2011;25(1):88–91 Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ptr.3229.
42. Usai P, Manca R, Cuomo R, et al. Effect of gluten-free diet on preventing recurrence of gastroesophageal reflux disease–related symptoms in adult celiac patients with nonerosive reflux disease. J Gastroenterol Hepatol. 2008;23(9):1368–72 Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1440-1746.2008.05507.x.
43. Zhang Y-Z, Li Y-Y. Inflammatory bowel disease: pathogenesis. World J Gastroenterol. 2014;20(1):91–9 Available from: https://www.wjgnet.com/1007-9327/full/v20/i1/91.htm.
44. Hou JK, Bincy AB, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. Am J Gastroenterol. 2011;106(4):563–73 Available from: https://www.ncbi.nlm.nih.gov/pubmed/21468064.
45. Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. Cochrane Database Syst Rev. 2019;2:CD012839 Available from: https://www.ncbi.nlm.nih.gov/pubmed/30736095.
46. Herfarth HH, Martin CF, Sandler RS, et al. Prevalence of a gluten-free diet and improvement of clinical symptoms in patients with inflammatory bowel diseases. Inflamm Bowel Dis. 2014;20(7):1994–7 Available from: https://www.ncbi.nlm.nih.gov/pubmed/24865778.
47. Limketkai BN, Sepulveda R, Hing T, et al. Prevalence and factors associated with gluten sensitivity in inflammatory bowel disease. Scand J Gastroenterol. 2018;53(2):147–51 Available from: http://www.tandfonline.com/doi/abs/10.1080/00365521.2017.1409364.
48. Singh J, Whelan K. Limited availability and higher cost of gluten-free foods. J Human Nutr Diet. 2011;24(5):479–86 Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-277X.2011.01160.x.
49. Allen B, Orfila C. The availability and nutritional adequacy of gluten-free bread and pasta. Nutrients. 2018;10(10):1370 Available from: https://www.ncbi.nlm.nih.gov/pubmed/30257431.
50. Shepherd SJ, Gibson PR. Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease. J Hum Nutr Diet. 2013;26(4):349–58 Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jhn.12018.
51. Vici G, Belli L, Biondi M, et al. Gluten free diet and nutrient deficiencies: a review. Clin Nutr. 2016;35(6):1236–41 Available from: https://www.clinicalkey.es/playcontent/1-s2.0-S0261561416300887.
52. Thompson T. Folate, Iron and dietary fiber contents of the GFD. J Amer Diet Assoc. 2000;100(11):1389–96 Available from: https://www.researchgate.net/publication/12223715_Folate_Iron_and_Dietary_Fiber_Contents_of_the_Gluten-free_Diet.
53. Thompson T. Thiamine, riboflavin, and niacin contents of the GFD. J Am Diet Assoc. 1999;99(7):858–62 Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002822399002059.
54. Newberry C, McKnight L, Sarav M, et al. Going gluten free: the history and nutritional implications of today's most popular diet. Curr Gastroenterol Rep. 2017;19(11):1–8 Available from: https://www.ncbi.nlm.nih.gov/pubmed/28948465.

## Publisher's Note