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Review

Practical Review on the Impact of Celiac Disease on the Patient

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Abstract

Celiac disease (CD) is a multisystem immune-mediated disorder resulting in enteropathy of the small intestine with the ingestion of gluten, in genetically susceptible individuals. This condition impact 1% of the population and can result in the development of other conditions such as chronic fatigue, anemia, osteoporosis, aphthous stomatitis, elevated liver enzymes, joint pain, infertility, peripheral neuropathy, and epilepsy. In this review, we outline the clinical presentation of CD, the physiological differences between CD and non-celiac gluten sensitivity, proper management and the need for thorough patient education to increase adherence to a gluten free diet and reduce GI symptoms.

Keywords

Celiac disease; gluten free diet; stigma; patient education

1. Understanding Celiac Disease

Celiac disease (CD) is a multisystem immune-mediated disorder resulting in enteropathy of the small intestine with the ingestion of gluten, in genetically susceptible individuals. Gluten is a storage protein of wheat, rye, and barley that drives villous atrophy, inflammation, and reduction in gastrointestinal (GI) function in CD. The gliadin peptide of gluten triggers innate immune components resulting in intestinal tissue damage [1]. The current treatment for CD is a strict, lifelong gluten-free diet (GFD) [2].

CD impacts about 1% of the population, with a female predominance, and the prevalence is increasing. CD prevalence increased 5-fold in the US from 1975-2000. The exact reason for this rise in CD is unknown [3]. Those with other autoimmune conditions such as thyroid disorders, type 1 diabetes mellitus, Down syndrome, IgA deficiency, and a family history of celiac disease in a first-degree relative are at greater risk for this condition [4-6].

2. Clinical Presentation

The "classic" CD presentation of diarrhea, malabsorption, and failure to thrive is more common in pediatric patients [7]. The adult CD presentation can be variable and may include constipation, gastroesophageal reflux disease, and fatigue. In some cases, individuals with CD are asymptomatic. Although CD primarily affects the gut, it is a complex and diverse disease that often presents different intestinal symptoms [4, 5]. Chronic fatigue, anemia, osteoporosis, aphthous stomatitis, elevated liver enzymes, joint pain, infertility, peripheral neuropathy, and epilepsy are a few known multisystem effects of CD [8].

One retrospective cohort study revealed that 62% of adults experienced extra intestinal manifestations of CD at diagnosis without any gut symptoms in 9% of the cases [8]. Iron deficiency anemia was found to be the most common extra-intestinal symptom in adults, with CD impacting nearly half of the patients. Further, neurological symptoms (e.g., peripheral neuropathy, gluten ataxia, headaches) in untreated CD may occur in as high as 42% and up to 10% in those treated [9, 10]. GI providers must be aware of all potential symptoms that may occur in CD in the absence of GI symptoms to avoid a delay in the diagnosis. An adult cohort study revealed the mean time to CD diagnosis was 2.3 months when a patient presented with intestinal symptoms compared to 42 months for those without GI manifestations [11]. This is concerning as undiagnosed CD is associated with an increased risk of GI, uterine, breast, head, and neck cancer and cardiovascular disease [12].

Nutritional deficiencies can play a role in the clinical profile typical in CD. Untreated CD results in malabsorption and maldigestion, which is associated with bloating and gas, as well as deficiencies in electrolytes, vitamins, and minerals [13]. A prospective study of newly diagnosed CD patients in the Netherlands found deficiencies in almost 90%, notably zinc deficiency, which was present in 66.7% [14]. A small pediatric study assessed micronutrient levels in 25 children with a new CD diagnosis and found low levels in ≥10% of patients for vitamins E (88%), B1 (71%), D (24%), K (21%), A (20%) and B6 (12%), ferritin (79%), and zinc (33%) [15]. This showcases the need for nutritional laboratory testing as part of the initial CD workup to ensure the patient's nutrient deficiencies can be addressed with proper repletion for good health. Furthermore, this data also shows how patients should be encouraged to share any extra-intestinal or GI symptoms with their providers for further assessment as needed. Regular follow-up yearly assessments by a registered dietitian or celiac treatment team to assess nutrient adequacy and/or additional food intolerances that may co-occur

in celiac disease should be encouraged to help manage residual symptoms and reduce the risk of metabolic complications.

3. Diagnostic Measures for CD

The diagnosis of CD is typically achieved by combining clinical symptoms, CD serology tests, and small intestinal mucosal histology during a gluten-containing diet [13]. Small intestinal biopsy remains the diagnostic gold standard, but highly sensitive and specific serology tests, such as tissue transglutaminase, endomysial, and deamidated gliadin peptide antibodies, are often utilized in the diagnostic workup [4]. Serology markers are considered the first-line test for high-risk individuals, followed by duodenal biopsy in the case of positive serology or persistent suspicion of CD due to malabsorption and maldigestion. The intestinal pathology should show histological changes such as an increased number of intraepithelial lymphocytes, elongated crypts, and villous atrophy for a CD diagnosis [16].

In cases with conflicting findings, genetic testing may offer diagnostic insights [17]. Genetic markers may be analyzed to help rule out a CD diagnosis, as a negative test has high reliability for a negative diagnosis [13]. But it should be noted that celiac gene variants, HLA-DQ2/HLA-DQ8 occur in 25-35% of the general population, and only about 3% of these HLA-compatible individuals will go on to develop CD [18].

4. Celiac Disease vs. Non-celiac Gluten or Wheat Sensitivity (NCGS/NCWS)

Beyond CD, there are other gluten or wheat-related disorders such as non-celiac gluten sensitivity or wheat sensitivity (NCGS/NCWS) and wheat allergy [19]. NCGS/NCWS is defined as a non-allergic, non-autoimmune condition characterized by intestinal and/or extra-intestinal symptoms resulting from the consumption of gluten-containing grains that resolve once these grains are removed from the diet [19]. Epidemiologic data on prevalence is lacking for this condition, as there are no biomarkers, yet it is estimated to occur in 3-6% of the general population [20]. NCGS/NCWS is treated with a gluten-free diet, yet it remains unclear if Gluten is the only part of wheat involved in this condition [21]. Wheat contains other components that impact gut physiology, including wheat agglutinin, amylase trypsin inhibitors, fermentable carbohydrates, particularly fructans, a water-soluble fiber found in wheat, barley, and rye [22]. Fructans are a subtype of the low fermentable oligo-di-monosaccharides and polyols (FODMAP) diet [21].

As with CD, NCGS/NCWS may occur with GI and extra-intestinal manifestations. While, unlike CD, in NCGS/NCWS, gluten ingestion does not result in villous atrophy [23]. In patients suspected of NCGS/NCWS CD, wheat allergy and inflammatory bowel disease should be initially ruled out [24]. To confirm a diagnosis of NCGS/NCWS, patients should undergo a GFD, followed by a gluten challenge, ideally with the guidance of a GI expert registered dietitian to confirm the benefit of the diet as well as the onset of symptoms with the reintroduction of gluten [19].

5. Gluten-free Diet: The Details

Gluten is the familiar name for a mixture of water-insoluble prolamin proteins. Gliadin and glutenin, primarily found in wheat, are the most common. Other grains contain prolamins, such as hordeins in barley, secalins in rye, and avenins in oats [25].

Nutritional instruction for an individual new to a CD diagnosis should include a detailed evaluation of the individual's current diet for nutrient adequacy and overall nutrient balance. GFD education should factor in nutrient needs, socio-economic factors such as finances to procure specialized gluten-free food options, as well as cooking abilities, available kitchen equipment, the patient's lifestyle, and food preferences. Practical application of a GFD should include education on menu planning, grocery shopping, label reading tips, dining out recommendations, and instruction on minimizing cross-contact of gluten at home and while dining out [26]. Practitioners should be aware that some patients will experience a grieving process with the newly added complexities of their GFD and its impact on their lifestyle, as well as the loss of some of their favorite foods from their diet [27].

In 2014, the US Food and Drug Administration (FDA) passed a gluten-free labeling rule that defines the legal obligations for labeling a product "gluten-free," "free of gluten," "without gluten," or "no gluten." This labeling helps individuals identify food products that are defined as having <20 ppm of gluten, deemed an appropriate limit for CD [28].

For a general guide on gluten-free and gluten-containing grains, starches, and flours, see Table 1.

Table 1 Gluten-containing grains/starches/flours to allow and avoid.

Gluten-free	**Gluten-containing**
amaranth, arrowroot, buckwheat, corn, flax, legume flours, mesquite flour, millet, nut flours, potato flour, potato starch, quinoa, rice, rice bran, sorghum, soy, sweet potato flour, tapioca, teff.	barley, bulgur, couscous, dinkel, einkorn, emmer, farina, farro, graham flour, hydrolyzed wheat protein or wheat starch, kamut, rye, seitan, wheat, wheat berries, wheat bran, wheat germ, wheat starch

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Given the higher risk of gluten contamination, oats, flaxseed, hempseeds, and legume flours should bear a GF certification on the label when purchasing these foods to ensure they are gluten-free [29]. As gluten can be lurking in additives and ingredient lists, patients should be educated on some common ingredients and foods that may contain hidden gluten, see Table 2 for some examples.

Table 2 Gluten Containing Ingredients + Processed Foods that may contain Gluten.

Gluten-containing ingredients	Processed foods that may contain gluten
Autolyzed yeast extract, wheat dextrin, brewer's yeast, emulsifiers, stabilizers, hydrolyzed wheat protein, texturized vegetable protein, barley malt extract/flavoring, modified wheat starch, and malt vinegar.	Bouillon cubes/soups/broths, breakfast cereals, candy, cold cuts, French fries, gravies + sauces, malted products such as malted milk, matzoh, plant-based "burgers, sausages, chicken"), snack foods (e.g., flavored potato chips, crackers) salad dressings, self-basted poultry, snack bars, soy sauce.

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6. Understanding Cross-contamination/Cross-contact Risks with a Gluten-free Diet

As a minimal amount of gluten can set off intestinal inflammation, patients with CD must be educated on how to limit gluten exposure via cross-contamination/cross-contact. For instance, cross contamination of peanut butter can occur if one uses a knife on gluten-containing bread to spread peanut butter and then re-inserts the same knife back into the peanut butter. To eliminate this type of cross-contact risk, patients are encouraged to buy separate containers of peanut butter, relish, jams, etc., to be used by the individual with GFD needs. Further, squeeze-type bottles for mayonnaise and ketchup may offer lower cross-contact risk as the bottle will have less risk of intermingling with gluten-containing food with this type of application. Other tips to minimize cross-contamination/contact can be found in Table 3.

Table 3 Avoiding cross-contamination/contact with gluten in the kitchen or dining out.

Use squeeze bottles of mayonnaise, ketchup, and relish
Buy separate containers for butter, peanut butter, jam, and label GFD use only
Use a separate toaster for GF bread
Have a GF colander to rinse GF pasta
Avoid buffets and bulk bins where cross-contamination can occur easily
Store gluten-free grains and flours above gluten-containing items in the pantry to limit cross-contact
Only consume fried foods that are cooked in a dedicated gluten-free fryer
Limit oats, legumes, flax, and hemp seeds to certified GF

GF = gluten free GFD = gluten free diet - Case, Shelley (2022) *Gluten Free: The Definitive Resource Guide - Revised Edition* Case Nutrition Consulting; Canada

7. Risks and Obstacles to Gluten-free Living

Diet restrictions can be difficult to manage, especially when gluten was a big part of an individual's former nutritional repertoire. Wheat is a significant food crop worldwide and is consumed commonly in the US diet [30]. A GFD can be complex to follow strictly, impacting adherence. Unfortunately, data reveals that adherence to a GFD may be as low as 36–45% [31-33].

New social situations, romantic relationships, financial constraints, and/or food insecurity may impact compliance with a GFD. A recent survey study evaluating the impact of dating on dietary adherence revealed that dating posed obstacles to compliance with the GFD. The survey results showed that while out on a date, "39.3% of participants were uncomfortable explaining precautions to waiters in front of their date, 28.2% engaged in riskier eating behaviors on a date, and 7.5% intentionally consumed gluten on a date" [34]. Further, gluten-free products from mass-market producers are 139% more expensive than the wheat-based version of the same product, which may impact compliance of those on a limited budget [35].

Food fear and disordered eating are other risks in CD that practitioners should be screening for in their healthcare practice. Avoidance Restrictive Food Intake Disorder (ARFID) is an eating disturbance due to a lack of interest in eating, an avoidance based on sensory characteristics of food, or concern of adverse consequences of eating (such as pain or choking). It is characterized by failure to meet one's nutritional needs. ARFID is considered when the severity of the eating disturbance

exceeds what is routinely associated with the condition [36]. ARFID was found to impact 57% of those with CD in a retrospective study of 137 patients [37]. ARFID was added to the Diagnostic and Statistical Manual, 5th edition, to identify patients at nutritional risk due to patterns characterized by fear of negative consequences from eating. Additionally, maladaptive eating and/or disordered eating patterns are commonly present in CD. One small study of 30 adolescents found disordered eating impacted 53% of this cohort [38].

CD is a complex GI disorder that warrants guidance from a registered dietitian with expertise in CD and the application of a GFD. Given the complexities of a GFD, and that patients are at greater risk for nutritional deficiency, disordered eating, food fears, and dietary non-compliance, access to a knowledgeable GI CD informed healthcare team (dietitian, gastroenterologist, and psychologist) will provide a well-rounded team to provide the complexity of care patients can benefit from living with CD. Further, referring patients to a local celiac support group can provide an additional support network [39].

8. The Need for Accurate Patient Education and Support

CD is a lifelong disorder and requires consistent dietary management. Recent data suggest that patients with a diagnosis of CD have a more significant disease burden and find their condition quite stigmatized due to the restriction of diet and its impact on their quality of life [40]. It remains the duty of providers, both physicians and dietitians, to provide accurate and evidence-based education in a manner that reduces the stigma felt by patients and empowers the patient to feel more in control of their CD management [41].

Education for patients might vary depending upon the stage of their diagnosis and management. Some newly diagnosed patients may have undergone recent but extensive diagnostic testing leading them to a CD diagnosis without any real education about what this new diagnosis means for them long-term, while others might have had severe disease symptoms for many years and fully understand the management necessary to manage their illness. For newly diagnosed patients, a diagnosis of CD can provide relief and validation of previously unexplained symptoms. However, for others, a diagnosis of a life-long condition can bring a sense of disbelief and grief. Providers should recognize that every patient will respond differently and bring different levels of understanding about what this means for them long term [40].

A 2015 Finnish study showed that many patients with CD were dissatisfied with the amount and quality of education their health care providers provided. Most patients reported being told to find more about their management online and were left to research the pathology of CD and its long-term management [40]. In a study by A. Buseck et al in 2021, the quality of patient education widely available to patients online was evaluated based on relevant clinical information, and found that while national health organizations provided quality patient education on CD, the majority of the information available to patients from commercial or private entities lacked evidence-based information and made claims about management that were untrue and even harmful [42]. Patients must not be left to find inaccurate information independently but be given education in the clinical encounter. Buseck also showed that education that was of low quality or infrequently provided correlated strongly with a patient's negative attitude toward the diagnosis of CD in general and contributed to higher levels of stigma [42].

Strict adherence to a GFD remains the only treatment for CD [43]. Data on adherence to GFD among patients is limited; however, this limited data does support the belief that adherence to a GFD is strongly correlated with the patient's knowledge and understanding of the disease [3]. Other factors that may influence dietary adherence may be influenced by depression, symptoms upon ingestion of gluten, nutritional counseling, knowledge of GF foods and GF food labels, cost and availability of GF foods, as well as a membership in a celiac society [44].

For many patients, family involvement is critical in their management of CD. It is common in chronic diseases for family members to participate in the responsibility for dietary adherence, even in adult patient populations [45]. Parental and familial involvement in diet and adherence is even more critical among pediatric patients with CD [46]. The family's participation in the dietary management of CD can help reduce the stigma felt by the patient and provide support in adhering to the diet while positively influencing the psychological impacts that the diagnosis might have. While this might benefit the patient, there are considerations for the accompanying family members who might have all the same social restrictions of a GFD suddenly placed on them as well, leading to negative impacts on the family dynamic as a whole [45]. Providers should screen families for negative psychological implications of a CD diagnosis on the patient and accompanying family members and refer patients and their families to GI behavior health support if needed [41].

Finally, physicians and dietitians should recognize the stigma patients, particularly pediatric patients, might feel with a CD diagnosis [47]. Data from a Swiss study published by C. Olsson et al, in 2009 showed that adolescents with CD reported feelings of stigma and feeling singled out among peers due to their meal appearance and the difficulty in availability of gluten-free food. The study showed that eating in public had a higher stigmatization effect due to making a previously invisible condition known to peers and leading to higher levels of internalized or enacted stigma [47, 48]. For most patients, maintaining the invisibility of their illness allowed them to avoid the negative consequences of stigma [49]. Providers should understand this feeling among patients and recognize that these feelings can lead to lower adherence to dietary management, especially among pediatric patients when peer influence is the greatest [50].

9. Clinical Takeaways

- Celiac disease (CD) is a multisystem immune-mediated disorder resulting in enteropathy of the small intestine with the ingestion of gluten, in genetically susceptible individuals.
- The "classic" CD presentation of diarrhea, malabsorption, and failure to thrive is more common in pediatric patients.
- The adult CD presentation can be variable and may include constipation, gastroesophageal reflux disease, and fatigue. In some cases, individuals with CD are asymptomatic.
- Although CD primarily affects the gut, it is a complex and diverse disease that often presents with extra-intestinal symptoms.
- CD is a complex GI disorder that warrants guidance from a registered dietitian with expertise in CD and the application of a GFD.
- Nutritional instruction for an individual new to a CD diagnosis should include a detailed evaluation of the individual's current diet for nutrient adequacy and overall nutrient balance.

- GFD education should factor in nutrient needs, socio-economic factors such as finances to procure specialized gluten-free food options, as well as cooking abilities, available kitchen equipment, the patient's lifestyle, and food preferences.
- New social situations, romantic relationships, financial constraints, and/or food insecurity may impact compliance with a GFD.
- It remains the duty of providers, physicians, and dietitians, to provide accurate and evidence-based education that reduces the stigma patients feel and empowers them to feel more in control of their CD management.
- Providers should understand feelings of stigma among patients with CD and recognize that these feelings can lead to lower adherence to dietary management, especially among pediatric patients when peer influence is the greatest.

Author Contributions

Each author contributed to this work equally. KS provided the clinical portions with expertise as a registered dietitian, JR provided the psychosocial and patient education portions with expertise in psychological aspects such as stigma.

Competing Interests

The authors have declared that no competing interests exist.

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