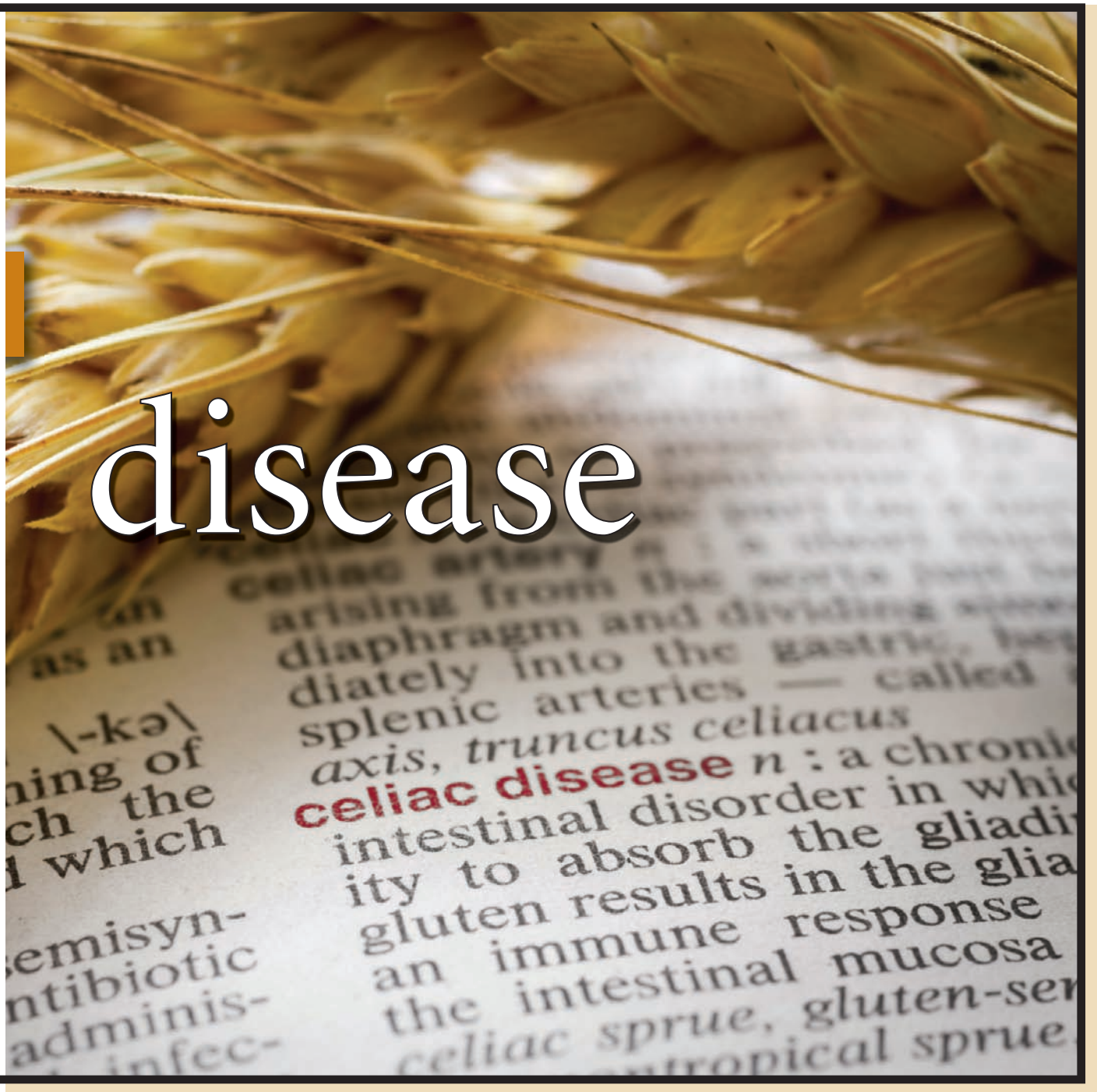
CE 2.0 CONTACT HOURS

Primary care management of celiac

Abstract: Celiac disease is an autoimmune disorder with genetic predisposition that affects as many as 1 in 100 individuals. Treatment is a lifelong, strict adherence to a gluten-free diet. Management by a primary care provider may lead to increased adherence and can minimize effects of nonadherence to the diet.

YoungVet / Andrew Shka / iStock ©

By Brittani Ledford Robinson, MS, RN, FNP-BC;
Stephanie C. Davis, PhD, RN, FNP-BC;
Joy Vess, DNP, RN, FNP-BC; and Joseph Lebel, MD



disease

Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is an autoimmune disorder in genetically susceptible individuals who have a permanent intolerance to gluten, a protein found in wheat, barley, and rye.[1] Pure oats that have not been contaminated with gluten-containing grains are safe for those with celiac disease to consume. It should be noted, however, that commercial oats are likely to be contaminated with gluten, and there should be close monitoring for signs of relapse.[1] Persons with celiac disease almost always carry either HLA-DQ2 or HLA-DQ8 heterodimers.[1] Common complaints in patients with celiac disease are generalized abdominal pain, bloating, diarrhea, fatigue, and joint or muscle pains. Complications of celiac disease can include reduced bone mineral density, complications related to malabsorption, ischemic heart disease, increased risk of additional autoimmune diseases, higher risk for non-Hodgkin lymphoma and small bowel cancer, depression, and dermatitis herpetiformis.[2-7]

In addition to the potential health complications of celiac disease, there is also a significant impact to the personal lives of those affected, society, and the healthcare system. Celiac disease is often diagnosed by a gastroenterologist, but many patients have complications or adverse reactions that can effectively be managed by nurse practitioners (NPs). The purpose of this article is to examine the prevalence, presentation, risks, and complications of celiac disease. Treatment options and adherence to treatment will also be examined.

Keywords: autoimmune, celiac disease, gluten, gluten-sensitive enteropathy

Implications for nursing practice, education, and research will be provided.

Impact

Celiac disease has an impact on patients' personal lives, their families, society, and the healthcare system. In addition to the physical complications, there is a significant psychosocial impact on those with celiac disease as evidenced by the number of those affected by decreased quality of life scores, anxiety, and depression.[6,8-10] One study examining healthcare costs associated with celiac disease in Italy and the United States found that the cost in the 3 years prior to a diagnosis of celiac disease in the United States was an estimated $8,748.[11] The true healthcare costs are likely much higher than this due to the 10-year average spent before an accurate diagnosis of celiac disease. Interestingly, the projected cost required to diagnose celiac disease was only $2,707.[11] The total costs were likely elevated by repetition of studies, poor application of diagnostic studies, and testing while on a gluten-free diet. Screening patients as appropriate and increasing provider awareness about celiac disease could improve healthcare-associated costs.[11] In addition to impact of healthcare costs on society, there has been a recent gluten-free diet trend. Although the gluten-free diet is not recommended for everyone, the increased attention has raised awareness of the gluten-free diet and led to improved quality and cost for those with celiac disease.[12,13]

Celiac disease has an impact on the patients' personal lives, their families, society, and the healthcare system.

Presentation

Celiac disease can have many different presentations, likely a factor in a delayed diagnosis. Celiac disease has been described as early as the late 1800s, but it was not until the 1950s that the disease was found to be caused by gluten or histological evidence was able to support a physiologic difference in persons with celiac disease.[14] Before the 1950s, celiac disease was diagnosed based on severe symptomatology, such as weight loss, diarrhea, anemia, osteomalacia, and tetany.[15] In 1888, the symptoms were often so severe that Samuel Gee said, "Death is a common end."[16] Currently, the "classic" presentation of celiac disease consists of diarrhea, abdominal pain and distension, with failure to thrive noted in children.[3] Due to the advances in immunology, more precise screening techniques are available with the antitissue transglutaminase antibody tests.[14] Now that screening of certain high-risk populations is increasingly becoming standard, differing presentations are becoming more common. These other presentations include anemia, osteoporosis, vague abdominal complaints, ataxia, neuropathy, alopecia areata, psoriasis, and multiple other extra-intestinal manifestations.[3]

A potential presentation of a patient with celiac disease is a rare condition known as dermatitis herpetiformis (an autoimmune disorder associated with gluten-sensitive enteropathy), which is the cutaneous expression of celiac disease. The lesion begins as pruritic symmetrical, erythematous blisters and evolves into excoriations and hyperpigmentation. Lesions are most often noted to extensor aspect of elbows and knees, but shoulders, buttocks, sacrum, and the face can also be involved. The gluten-free diet is the most effective treatment for patients with dermatitis herpetiformis, although dapsone, topical corticosteroids, and some oral antihistamines are options to minimize symptoms until the gluten-free diet is effective.[7] Primary care providers should be aware of this skin condition, as they are more likely than a gastroenterologist to be confronted with this type of presentation.

Clinical decision making

According to the 2013 guidelines from the American Journal of Gastroenterology, persons with the following should be screened for celiac disease: those with signs of malabsorption, chronic diarrhea, weight loss, postprandial abdominal pain, and/or bloating.[1] Additionally, first-degree family members of persons with confirmed celiac disease who have signs or symptoms suggestive of the disease, persons with unexplained elevated transaminases, and those with type 1 diabetes with digestive complaints should be screened.[1] Celiac disease has been found in as many as 27% of those with lymphocytic colitis. For this reason, those found to have lymphocytic colitis should also be screened for celiac disease, especially when symptoms are refractory to treatment for colitis. If no improvement with gluten-free diet is seen, poor dietary adherence should be assessed for, which can be done with repeat serology, as antibodies should revert to normal in those on a gluten-free diet within 1 year, and other causes or coexisting conditions, such as: irritable bowel syndrome, primary lactase deficiency, microscopic colitis, small intestinal bacterial overgrowth, lymphoma, or refractory sprue.[17]

Diagnosis

The first step for the diagnosis of celiac disease is serologic studies while on a gluten-containing diet, starting with

immunoglobulin A (IgA) anti-tissue transglutaminase (tTG), which has a sensitivity estimated as high as 95%.[1,17] There is a high prevalence of selected IgA deficiency in celiac disease compared to the general population, and for this reason, a total IgA level should be obtained for negative IgA tTG results when there is a high level of suspicion. Further testing with IgG tTG and IgG-deamidated gliadin peptides should be performed if selective IgA deficiency is identified.[1,17] If celiac disease is strongly suspected, endoscopy with intestinal biopsies should still be pursued, even if serologic studies are negative. Genetic testing for celiac disease should be reserved for patients with atypical symptomatology or when there are discrepancies between serologic and histological findings.[1,17]

The European Society of Paediatric Gastroenterology, Hepatology and Nutrition published revised guidelines for the diagnosis of celiac disease in 2012, which deemed intestinal biopsy no longer necessary when there is a very high level of tTG with additional supportive serologic markers.[18] However, the 2013 American Gastroenterological Association (AGA) notes these guidelines are lacking supportive data and recommends upper endoscopy with small bowel biopsy of the duodenal bulb in addition to at least four biopsies of the distal duodenum to confirm celiac disease.[1] Biopsies should reveal villous atrophy, hyperplastic crypts, and increased intraepithelial lymphocytes in persons with celiac disease.[17] It is also important to note that negative findings cannot be used to exclude celiac disease in patients already on a gluten-free diet.[1,17] Repeat endoscopy to assess for healing is recommended when symptoms persist or relapse despite gluten-free diet.[1,17]

Differential diagnoses. The vague symptomatology of celiac disease is a contributing factor to the delayed diagnosis. Differential diagnoses of celiac disease include: bacterial overgrowth syndrome, collagenous and lymphocytic colitis, eosinophilic gastroenteritis, parasitic infections, amyloidosis, and radiation enteritis.[17] While many of these have symptoms similar to celiac disease, there are those that also have similar endoscopic findings, such as: small intestinal bacterial overgrowth, tropical sprue, drug-associated enteropathy, collagenous sprue, Crohn disease, eosinophilic enteritis, and intestinal tuberculosis.[1]

Risks and complications. Multiple studies have shown that there is potential for complications and risk of additional comorbidities with celiac disease, particularly an increased incidence of other autoimmune disease.[19] (See *Potential complications of celiac disease*.) Celiac disease is associated with osteoporosis, nutritional deficiencies, anemia, obesity, anxiety/depression, chronic diseases, and malignancy. Many of these complications are reduced or eliminated with adherence to a gluten-free diet.

Potential complications of celiac disease

- Hypothyroidism
- Anxiety/depression
- Nutritional deficiencies/anemia
- Diabetes
- Obesity
- Malignancy
- Osteoporosis
- Dermatitis herpetiformis

Osteoporosis. Celiac disease is a risk factor for the development of reduced bone mineral density and osteoporosis.[20,21] However, once patients are established on a gluten-free diet, bone mineral density improves, therefore, decreasing risk of osteoporosis and fractures.[20,21] Individuals diagnosed with celiac disease should have a baseline bone mineral density scan (dual-energy X-ray absorptiometry) with continued evaluations based on results with treatment as necessary.

Nutritional deficiencies

Most patients with celiac disease also experience multiple nutritional deficiencies, including folate and vitamin B. Because of this deficiency, homocysteine levels are elevated, increasing the risk of cardiovascular disease.[22] Additionally, a large cohort study published by the American Heart Association found a 19% increase in risk of ischemic heart disease in patients with celiac disease.[4] This is thought to be related to the chronic inflammation in the gut. Ischemic heart disease is the leading cause of death in the United States, making cardiovascular risk assessments and potential interventions or treatments imperative for patients with celiac disease.[4] Additionally, vitamin D deficiency contributes to the decreased bone mineral density and should be assessed and treated as appropriate.[3,23]

Anemia. Anemia is one of the most common complications of celiac disease and is noted even in patients without gastrointestinal manifestations of the disorder. One of the underlying mechanisms for anemia in this population is related to malabsorption of folate, cobalamin, and iron.[24] Another mechanism is anemia of chronic disease, in which the proinflammatory cytokines influence the regulation of hepcidin, inhibiting iron release, and therefore, resulting in anemia.[24] Iron deficiency anemia in celiac disease has been reported as high as 46%.[24] It is important for NPs to be aware that iron deficiency anemia in celiac disease does not improve with oral iron supplementation.[24] However, once established on a gluten-free diet, the anemia should begin to improve.[24-27]

Obesity. Because of the increased caloric content of commercial gluten-free products, it is imperative for NPs

to monitor weight and body mass index to ensure proper nutritional habits. A study from 2010 found that after initiating a gluten-free diet, the percentage of overweight patients doubled.[28] This is concerning, especially considering another study of 371 patients with celiac disease found 39% to be overweight at diagnosis.[29] NPs should counsel patients regarding healthy eating habits to decrease risk of obesity associated comorbidities and refer to a dietitian, if needed.

Chronic illnesses

Two diseases in particular are frequently associated with celiac disease: hypothyroidism and insulin-dependent diabetes.[30] Of patients with celiac disease, as many as 15% are diagnosed with hypothyroidism.[30] Additionally, up to 5% of patients with autoimmune thyroiditis are positive for celiac disease.[30] Persons with untreated celiac disease often require higher doses of levothyroxine as treatment for hypothyroidism.[30] This need often decreases once a gluten-free diet is implemented and the thyroid-stimulating hormone should be monitored more closely during these changes to minimize risk of resultant hyperthyroidism.[30]

Not only has there been an association of celiac disease and type 1 diabetes mellitus (T1DM), studies have found an increased subsequent development of T1DM after the diagnosis of celiac disease and have found there may be some protective factor in adherence to a gluten-free diet in adults.[19,31] Patients should be screened for diabetes at the diagnosis of celiac disease and routinely based on results and other risk factors to minimize microvascular complications, especially in those nonadherent to the gluten-free diet. Although there have been reports of decreased hypoglycemic events despite increased insulin requirements for patients who have T1DM and celiac disease, the AGA reports this as inconclusive.[32,33]

Anxiety and depression are frequently found in celiac disease.[6,8-10] There is opposing research to whether the gluten-free diet improves quality of life. A study of the pediatric population found increases in depressive and anxiety symptoms, while a different study found that adults with celiac disease had significant improvements in quality of life scores after dietary modification.[8,9] It is important to assess patients with celiac disease for signs of depression or anxiety and provide referral to a support group or counseling and implement treatment if needed. It has been reported that depression is a contributing factor to nonadherence with medical treatment.[6] However, in this population, adherence is necessary for the well-being of the patient and for decreasing risk of complications.

Gluten-free diet guide[38]

Safe
- Fruits and vegetables
- Fresh beef, poultry, pork, seafood
- Eggs
- Beans, seeds, and nuts
- Wine and distilled liquor

Potential risks
- Caramel color: some say it is safe, however, the FDA permits caramel color to be derived from barley malt, which does contain gluten.
- Dressings and condiments: may contain caramel color or malt vinegar.
- Soft drinks
- Processed meats
- Medications may contain gluten, including over-the-counter vitamins.
- Restaurants: Even if a gluten-free menu is available for foods such as pasta or pizza, assess for the risk of cross-contamination.

Never
- Any product containing wheat, barley, rye, spelt, triticale, semolina.
- Cakes, pastries, cookies, and crackers
- Breads, pasta, rolls, pizza.
- Beer

Malignancy

A condition known as refractory celiac disease (RCD) can develop in a very small population of patients with celiac disease. In this condition, villous atrophy with crypt hyperplasia persists despite strict adherence to a gluten-free diet.[5] There are two types of RCD recognized: RCD I is noted by a normal expression of T-cell surface markers, and the prognosis is markedly greater than RCD II. In the RCD II population, there is aberrant intraepithelial T lymphocytes present and an associated greater risk of the development of enteropathy-associated T-cell lymphoma (EATL).[5]

A retrospective analysis of patients with complicated celiac disease found that of patients diagnosed with RCD II, EATL developed in 52% of patients.[5] EATL has an estimated 5-year survival rate of 11% to 20%.[5] It is imperative that NPs monitor patients with celiac disease for persistent symptoms of celiac disease and potential signs of RCD. Additionally, there is an increased risk of lymphoproliferative malignancies.[34] However, celiac disease has been found to have some protective effect from the development of breast, endometrial, and ovarian cancers.[35]

Treatment and adherence to treatment

Adherence to the gluten-free diet is one of the greatest challenges to the treatment of celiac disease. (See *Gluten-free diet guide*.) Adherence rates are often below 50% despite

this being the only treatment.[36] Additionally, these patients are not being followed closely enough by providers and dietitians. One study found that at 1 year of diagnosis, only 41% of patients had seen a provider for a follow-up visit, and only 3.3% had seen a registered dietitian despite recommendations by the AGA for routine follow-up visits.[33,36] The AGA states, "Improved knowledge of celiac disease, the GFD, gluten-containing food products, and outcomes of untreated celiac disease would likely improve compliance."[33]

All primary care providers, including NPs, need to emphasize the importance of these follow ups as well as managing patients' needs that are not being met by gastroenterologists. In the study conducted by Herman and colleagues, of those patients who did attend a follow-up visit, 56% were with a primary care provider compared with 39% seen by a gastroenterologist.[36] Primary care providers are essential to the diagnosis and management of celiac disease.

There are other barriers to adherence to a gluten-free diet in addition to poor attendance at follow-up visits by patients. One of these barriers is the cost of a gluten-free diet, which has been found to be significantly more expensive and difficult to follow. A study found that more than half of the parents of a child with celiac disease thought of a gluten-free diet as a financial burden.[26] A study from Practical Gastroenterology showed that the cost of wheat flour per pound was estimated at $0.34, whereas a gluten-free substitute, brown rice flour, was estimated to cost $1.89 per lb. Chocolate chip cookies estimated at $2.69 per lb with gluten-free substitute at $12.83 per lb.[13]

This barrier is best overcome by choosing foods that are naturally gluten free from regular grocery stores, such as fruits, vegetables, nuts, and fresh meats.[13] Additionally, access to gluten-free foods may be limited and even in schools or restaurants with gluten-free options, contamination is a concern.[3,7] There is also some evidence that implementation of a gluten-free diet can be linked with an increase in depression and anxiety in pediatric patients, likely related to the perceived negative influence in social life. This is a contributing factor in decreased diet adherence rates.[8,37] However, there is also opposing evidence that shows increased quality of life scores in adults once on a gluten-free diet.[9] This may be related to the age at diagnosis and reinforces need for appropriate referrals to dietitians and/or social support groups.

Implications for nursing practice

It is essential for providers to be aware of the disease process in order to minimize serious and even potentially life-threatening complications. Issues with nonadherence have been discussed and NPs have the opportunity to be the cornerstone in providing a strong foundation for resources, as increased adherence to a gluten-free diet improves outcomes. While research exists on the potential complications of celiac disease, additional research is needed to find more causes for nonadherence with the gluten-free diet and more effective interventions and resources. Considering many patients have symptoms for years before being accurately diagnosed, it will also be important for NPs to become educated regarding the atypical presentations of celiac disease, as this field is on the forefront of detecting the symptoms and making appropriate referrals.

REFERENCES

1. Rubio-Tapia A, Hill I, Kelly C, et al. ACG Clinical guidelines: Diagnosis and management of celiac disease. *The American Journal of Gastroenterology.* May 2013; 108: 656-76.
2. Pope R, Sheiner E. celiac disease during pregnancy: to screen or not to screen? *Arch Gynecol Obstet.* 2009;279(1):1-3.
3. Ludvigsson JF, Green PH. Clinical Management of coeliac disease. *J Intern Med.* 2011;269(6):560-571.
4. Ludvigsson JF, James S, Askling J, Stenestrand U, Ingelsson E. Nationwide cohort study of risk of ischemic heart disease in patients with celiac disease. *Circulation.* 2011;123(5):483-490.
5. Al-Toma A, Verbeek WH, Hadithi M, von Blomberg BM, Mulder CJ. Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. *Gut.* 2007;56(10):1373-1378.
6. Addolorato G, Mirijello A, D'Angelo C, et al. State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to internal medicine outpatient setting. *International Journal of Clinical Practice.* 2008;62(7):1063-1069.
7. Caproni M, Antiga E, Melani L, Fabbri P; Italian Group for Cutaneous Immunopathology. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. *J Eur Acad Dermatol Venereol.* 2009;23(6):633-638.
8. Mazzone L, Reale L, Spina M, et al. Compliant gluten-free children with celiac disease: an evaluation of psychological distress. *BMC Pediatr.* 2011;11:46.
9. Kurppa K, Collin P, Sievänen H, Huhtala H, Mäki M, Kaukinen K. Gastrointestinal symptoms, quality of life and bone mineral density in mild enteropathic coeliac disease: a prospective clinical trial. *Scand J Gastroenterol.* 2010;45(3):305-314.
10. Smith DF, Gerdes LU. Meta-analysis on anxiety and depression in adult celiac disease. *Acta Psychiatr Scand.* 2012;125(3):189-193.
11. Picarelli A, Di Tola M, Borghini R, et al. The high medical cost of celiac disease missed diagnosis: Is it cheaper to suspect it in time? *Internal Medicine: Open Access.* 2014;4(3):1-4.
12. Pietzak M. celiac disease, wheat allergy, and gluten sensitivity: when gluten free is not a fad. *JPEN J Parenter Enteral Nutr.* 2012;36(1 suppl):68S-75S.
13. Cureton P. The gluten-free diet: Can your patient afford it? *Practical Gastroenterology.* 2007:75-84.
14. Losowsky MS. A history of coeliac disease. *Dig Dis.* 2008;26(2):112-120.
15. Swinson CM, Levi AJ. Is coeliac disease underdiagnosed? *Br Med J.* 1980;281(6250):1258-1260.
16. Hardwick C. Prognosis in coeliac disease: a review of seventy-three cases. *Arch Dis Child.* 1939;14(80):279-294.
17. Greenberger N, Blumberg R, Burakoff R. *Current Diagnosis and Treatment: Gastroenterology, Hepatology, & Endoscopy.* United States: McGraw-Hill; 2012.
18. Gosink J. Laboratory diagnostics for celiac disease: the new ESPHAN guidelines can be incorporated into diagnostic criteria. *MLO.* 2012. www.mlo-online.com.
19. Cosnes J, Cellier C, Viola S, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. *Clin Gastroenterol Hepatol.* 2008;6(7):753-758.
20. Passananti V, Santonicola A, Bucci C, et al. Bone mass in women with celiac disease: role of exercise and gluten-free diet. *Dig Liver Dis.* 2012;44(5):379-383.

21. Mora S, Barera G, Beccio S, et al. A prospective, longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. *J Pediatr.* 2001;139(4):516-521.
22. Dickey W, Ward M, Whittle CR, et al. Homocysteine and related B-vitamin status in coeliac disease: effects of gluten exclusion and histological recovery. *Scand J Gastroenterol.* 2008;43(6):682-688.
23. Lerner A, Shapira Y, Agmon-Levin N, et al. The clinical significance of 25OH-Vitamin D status in celiac disease. *Clin Rev Allergy Immunol.* 2012; 42(3):322-330.
24. Hershko C, Patz J. Ironing out the mechanism of anemia in celiac disease. *Haematologica.* 2008;93(12):1761-1765.
25. Annibale B, Severi C, Chistolini A, et al. Efficacy of gluten-free diet alone on recovery from iron deficiency anemia in adult celiac patients. *Am J Gastroenterol.* 2001;96(1):132-137.
26. Jadresin O, Misak Z, Sanja K, Sonicki Z, Zizi_ V. Compliance with gluten-free diet in children with coeliac disease. *J Pediatr Gastroenterol Nutr.* 2008;47(3):344-348.
27. Bergamaschi G, Markopoulos K, Albertini R, et al. Anemia of chronic disease and defective erythropoietin production in patients with celiac disease. *Haematologica.* 2008;93(12):1785-1791.
28. Valletta E, Fornaro M, Cipolli M, Conte S, Bissolo F, Danchielli C. celiac disease and obesity: need for nutritional follow-up after diagnosis. *Eur J Clin Nutr.* 2010;64(11):1371-1372.
29. Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. *Am J Gastroenterol.* 2006;101(10):2356-2359.
30. Collins D, Wilcox R, Nathan M, Zubarik R. celiac disease and hypothyroidism. *Am J Med.* 2012;125(3):278-282.
31. Ludvigsson JF, Ludvigsson J, Ekbom A, Montgomery SM. celiac disease and risk of subsequent type 1 diabetes: a general population cohort study of children and adolescents. *Diabetes Care.* 2006;29(11):2483-2488.
32. Abid N, McGlone O, Cardwell C, McCallion W, Carson D. Clinical and metabolic effects of gluten free diet in children with type 1 diabetes and coeliac disease. *Pediatr Diabetes.* 2011;12(4 Pt 1):322-325.
33. AGA Institute. AGA Institute medical position statement on the diagnosis and management of celiac disease. *Gastroenterology.* 2006;131(6):1977-1980.
34. Elfström P, Granath F, Ekström Smedby K, et al. Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. *J Natl Cancer Inst.* 2011;103(5):436-444.
35. Ludvigsson JF, West J, Ekbom A, Stephansson O. Reduced risk of breast, endometrial and ovarian cancer in women with celiac disease. *Int J Cancer.* 2012;131(3):E244-E250.
36. Herman L, Rubio-Tapia A, Lahr BD, Larson JJ, Van Dyke CT, Murray JA. Patients with celiac disease are not followed up adequately. *Clin Gastroenterol Hepatol.* 2012;10(8):893-899.
37. Häuser W, Stallmach A, Caspary WF, Stein J. Predictors of reduced health-related quality of life in adults with coeliac disease. *Aliment Pharmacol Ther.* 2007;25(5):569-578.
38. Ingredients. Gluten Free Living website. 2013. www.glutenfreeliving.com/ingredient.php.

Brittani Ledford Robinson is a family nurse practitioner at Gastroenterology Associates, Greenville, S.C.

Stephanie C. Davis is a graduate coordinator and associate professor at Clemson University School of Nursing, Clemson, S.C.

Joy Vess is an instructor at Medical University of South Carolina College of Nursing, Charleston, S.C.

Joseph Lebel is a physician at Physician, Gastroenterology Associates, Greenville, S.C.

The authors and planners have disclosed that they have no financial relationships related to this article.

DOI-10.1097/01.NPR.0000459728.54533.ac