Follow-up of Patients With Celiac Disease: Achieving Compliance With Treatment

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Celiac disease is the only autoimmune condition for which we know the environmental trigger: gluten. Complete removal of gluten from the diet in a patient with celiac disease should result in symptomatic, serologic, and histologic remission. However, compliance with the gluten-free diet, especially in the United States, is extremely challenging. Compliance can be measured both noninvasively, by dietary history and measurement of serum antibodies, and invasively, by using endoscopic and histologic criteria. The advantages and disadvantages of these various modalities are discussed. The highest rates of compliance are reported in patients who are diagnosed as young children, whereas adolescents and those diagnosed via mass serologic screening have the most transgressions. Barriers to compliance include the poor palatability of gluten-free foods, confusing food-labeling practices, and common comorbid psychologic burdens such as anxiety and depression. Because celiac disease is a multisystemic disorder, physicians need to be aware of the potential autoimmune, nutritional, and malignant complications. An algorithm for the follow-up and management of the newly diagnosed celiac disease patient is presented, which includes regular follow-up; measurement of serum antibodies; eliciting a detailed dietary history; and examination for signs and symptoms of nutritional deficiencies, malignancy, and other autoimmune diseases. Ideally, a team approach to the follow-up of the newly diagnosed patient should include regular supervision by an interested physician, medical nutritional counseling by a registered dietician, and access to local and national support groups knowledgeable about this condition.

Once an individual has been diagnosed with celiac disease (CD), and received appropriate counseling about the gluten-free diet (GFD), how can the physician measure compliance? Prior to the advent of serology, the diagnosis of CD was based on criteria published in 1970 by the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition.[1] These criteria recommended the confirmation of CD with 3 small bowel biopsies: villous atrophy at the time of initial presentation, intestinal healing after being on a GFD, and recurrence of damage after a gluten challenge. Revised criteria were published in 1990, which stated that the diagnosis was definitive in those over the age of 2 years who had initial characteristic histologic findings, suggestive serology, and clinical resolution of symptoms following the institution of a GFD. Repeat biopsy was deemed not necessary.[2] Despite these recommendations in pediatric patients, recent studies have shown the utility of endoscopy with repeat biopsies in adults to measure compliance. Intestinal damage has been significantly associated with poor dietary compliance, presence of serum antiendomysial IgA antibodies (EMA), and low plasma albumin.[3] Despite a good clinical response to a GFD, abnormal endoscopic and histopathologic appearances persisted in 77% of adult CD patients in New York, even in those reporting compliance. Abnormalities included reduced and scalloped folds, mucosal nodularity and fissures, and partial or total villous atrophy.[4] The American Gastroenterological Association medical position statement recommended a repeat biopsy as early as 4 to 6 months after starting the GFD to assess improvement.[5]

Capsule endoscopy has the potential to become a valuable tool for both monitoring compliance to the GFD by documenting small bowel mucosal healing as well as screening for the intestinal complications of CD. Nodularity and ulcerations of the mucosa and notching or scalloping of the folds of the small intestine may be seen at the initial presentation of CD or with GFD noncompliance or refractory sprue. Capsule endoscopy has the added advantage over traditional upper endoscopy in that it can visualize the entire length of the duodenum, jejunum, and ileum. Thus, capsule endoscopy may prove useful in monitoring for complications of

Abbreviations used in this paper: AAA, antiactin IgA antibodies; AGA, antigliadin IgA and IgG antibodies; CD, celiac disease; EMA, antiendomysial IgA antibody; GFD, gluten-free diet; PCP, primary care physician; tTG, tissue transglutaminase IgA antibody.

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CD, such as ulcerative jejuno-ileitis or enteropathy-associated T-cell lymphoma.[6] However, at present, the capsule is not recommended to make the initial diagnosis of CD because it is not capable of taking small bowel biopsy specimens for histologic confirmation of the disease (The 11th International Symposium on Coeliac Disease, Belfast, Ireland, April, 2004).

Antigliadin antibodies (AGA), the first serum measurements used to screen for CD in the 1980s, were also the first antibodies evaluated to noninvasively monitor for GFD compliance. Studies from Australia, Brazil, Finland, Italy, and the United Kingdom all correlated AGA titers to dietary adherence.[7–12] In Italy, it was reported that patients with poor to moderate compliance with the GFD had high levels of both AGA IgA and IgG 75% and 40% of the time, respectively.[11] However, AGA were elevated in 24% of those reporting good compliance, indicating perhaps a fictitious patient account, inadvertent gluten contamination of the diet, or a poor positive predictive value of AGA for villous damage. It has also been suggested that the persistent finding of AGA IgG positivity in patients with CD could be secondary to immunologic memory, rather than an index of poor compliance with the GFD.[13] Italian children with good compliance had normalization within the second month of the GFD for AGA IgA and within the sixth month of the GFD for AGA IgG.[9] Gluten challenge caused a rapid increase in AGA IgA but a slow increase in AGA IgG.[9] Adults from the United Kingdom with CD were shown to have no significant difference in AGA IgA from normal controls after 2 years of a strict GFD.[8]

The EMA titer was originally proposed to be indirectly related to mucosal recovery.[14] However, there is not agreement in the literature that EMA is a reliable marker in either monitoring compliance or histologic response to treatment. EMA positivity in CD patients on a GFD has been reported to vary from 0% to 68%.[15] Of 53 initially EMA positive patients in Belfast, EMA was undetectable in 58% after 3 months, in 75% after 6 months, and in 87% after 12 months on the GFD.[16] However, only 40% of all seronegative patients had complete villous recovery by 12 months, and only 33% with subtotal or total villous atrophy remained EMA positive. Several researchers believe that EMA negativity reflects the absence of gluten in the diet in those who were initially EMA positive, but is not a predictor of mucosal damage, and that biopsy remains the best tool to measure villous injury.[17–19]

The reliability of tissue transglutaminase IgA antibodies (tTG) as a predictor of compliance in CD has also been examined. tTG levels correlated with the duration of the GFD, and tTG normalized for most patients after 1 year of the GFD in Switzerland and Sweden.[20] Furthermore, elevated tTG and EMA could be detected within 3 to 12 months after a gluten challenge.[20] In one Italian study, tTG better correlated with reported compliance than with intestinal biopsy morphology.[21] These authors suggested that an accurate dietary interview with tTG measurement be performed before considering a repeat biopsy of a patient.[21] Because of the false positivity of tTG and EMA with other autoimmune diseases, such as type 1 diabetes and autoimmune hepatitis, these antibodies may remain elevated in a certain subset of patients despite strict adherence to a GFD.[22–26]

The presence of an immune reaction toward the intestinal epithelial cell cytoskeletal actin network has been established in CD.[27] The presence of antiactin IgA antibodies (AAA) in children and adults was strongly correlated with more severe degrees of intestinal villous atrophy (Marsh grade IIIa or higher: $P < .0001$; relative risk, 86.17). In all of these patients, AAA became undetectable within 5 months of initiating a GFD. This was in contrast to AGA IgA, which took 12 months to normalize, and tTG and EMA, for which 20% and >80% of these patients, respectively, tested positive 1 year after a GFD.[28] The use of AAA as a serologic marker for CD and as a measure of adherence to the GFD, although still investigational, holds great potential.

The highest rates of compliance are reported for patients diagnosed with CD at a very young age. In Sweden, whereas 80% of adults who had been diagnosed with CD prior to 4 years of age were compliant, only 36% of those who were older than 4 years of age at diagnosis were compliant.[29] In France and Belgium, less than half of the adult CD patients who were studied strictly adhered to a GFD for more than 1 year after diagnosis.[30] Reasons for transgressions included poor palatability of GF foods, the absence of symptoms after "cheating," high cost of the GFD, and the nonspecified presence of gluten or erroneous affirmation of gluten absence in foods and medications.[30] Only 56% to 83% of teenagers with CD were considered to be on a strict GFD,[31–33] whereas the reported adult compliance has varied between 17% and 45%.[34,35] Adolescents diagnosed with CD via serologic mass screening in Italy showed more EMA positivity and lower compliance in comparison with age-matched patients diagnosed with "classic" symptoms during childhood.[36] Less than one fourth of patients diagnosed via screening followed a strict GFD, and 23% had returned to a completely normal diet 5 years after the original diagnosis.[36]

There are also many psychologic barriers to compliance with the GFD. Women with CD perceive a greater

burden of illness and express less satisfaction with the outcome of treatment. Women are also more concerned about needing more knowledge regarding CD, interference of the GFD with socializing, and the possibility that their children could get CD. Both genders express bitterness over not being diagnosed earlier, believing that this could have led to better outcomes.[37] For many CD patients, the major complaints are general poor health, fatigue, and a feeling of decreased well-being.[38] These symptoms may improve once the patient starts a GFD.[39] Corrao et al published that the overall mortality in adult CD patients was double that of the general population and that a delay in diagnosis, poor adherence to treatment, and severity of symptoms at presentation unfavorably affected patients' outlook.[40] The GFD has been shown to improve the quality of life even in patients with "silent" CD (ie, without gastrointestinal symptoms).[41] There are little data to support the idea that poor adaptation to CD is due to impaired intellect or a deviate personality pattern.[42,43] However, depression appears to be the most common neuropsychiatric complication among treated adults,[44] which may ultimately affect compliance. It is important for the diagnosing physician to have a reassuring and positive attitude with the clinical management of CD from the beginning. Patients at the time of CD diagnosis express fear, anger, anxiety, and sadness. Anger can worsen the patient-clinician relationship and has been inversely correlated with dietary compliance.[45]

Additional barriers to compliance with the diet in the United States are ambiguous labels on prepared foods, which do not indicate whether the product contains wheat or could have been processed with wheat. The American Celiac Task Force (http://capwiz.com/celiac/home/) made its debut in March 2003 to advocate for changing the food-labeling laws. On August 2, 2004, President George W. Bush signed the "Food Allergen Labeling and Consumer Protection Act." This law requires food manufacturers, within the next 2 years, to state clearly on the label if a product contains any of the top 8 food allergens (milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, soybeans, and wheat). In addition, it calls for the FDA to issue rules defining and permitting the term "gluten-free" on food labeling. Once these laws are enacted, compliance with the GFD will be greatly facilitated for CD patients in the United States.

Ideally, the education of the newly diagnosed CD patient should consist of a team approach between the patient (or parents) and the gastroenterologist, primary care physician (PCP), dietician, and local branches of national support groups. The medical management of CD primarily consists of monitoring for compliance with the GFD and screening for the well-known complications of this autoimmune condition. The patient should follow up with the gastroenterologist who performed the biopsy once the results confirm CD and be referred to a knowledgeable dietician for medical nutrition therapy (Figure 1). Patients should be encouraged to join local chapters of national support organizations, which can aid in finding local resources, such as supermarkets, food manufacturers, literature, and restaurants that are familiar with the GFD.

Patients should be screened for nutritional deficiencies that can accompany this malabsorptive disorder, such as iron deficiency anemia and fat-soluble vitamin deficiencies. Patients should also be monitored for common complications, including osteoporosis and neurologic complaints and the development of other autoimmune diseases, especially of the thyroid and liver.[46,47] Individuals with biopsy-proven CD who do not have a clinical response to the GFD should be evaluated for the presence of refractory sprue, ulcerative enteritis, T-cell lymphoma, and other gastrointestinal cancers. Bone density should be measured in the newly diagnosed CD patient. Numerous studies have documented low bone density in both children and adults at the time of initial diagnosis of CD, which can improve with the GFD.[48–51] Deficient intake and absorption of vitamin D and calcium, and the development of secondary hyperparathyroidism, should be evaluated in osteopenic patients.[52] Children should be examined for protein-calorie malnutrition, linear growth failure, and delayed puberty. First- and second-degree relatives should be offered screening for CD with serum antibodies.

Once the patient has undergone initial counseling for the GFD, the PCP (or gastroenterologist) and dietician should follow up with the patient in 3 to 6 months to discuss compliance with the diet and reinforce its importance. If the patient has been able to adjust to the gluten-free lifestyle, and has had no complications of the disorder, he or she can be seen annually by either the PCP or gastroenterologist. At the annual visit, a detailed nutritional history should be elicited, and serum antibodies should be measured to gauge adherence to the GFD. Again, the physician should perform a detailed history and physical aimed at screening for nutritional deficiencies and looking for signs and symptoms of other autoimmune disorders, gastrointestinal cancers, and refractory sprue. If the patient is doing well without clinical symptoms of CD and normal antibody titers, he or she should continue to be followed annually. If the patient is doing poorly, indicated by either clinical symptoms, nutritional deficiencies, or elevated antibodies, more extensive counseling regarding the GFD should

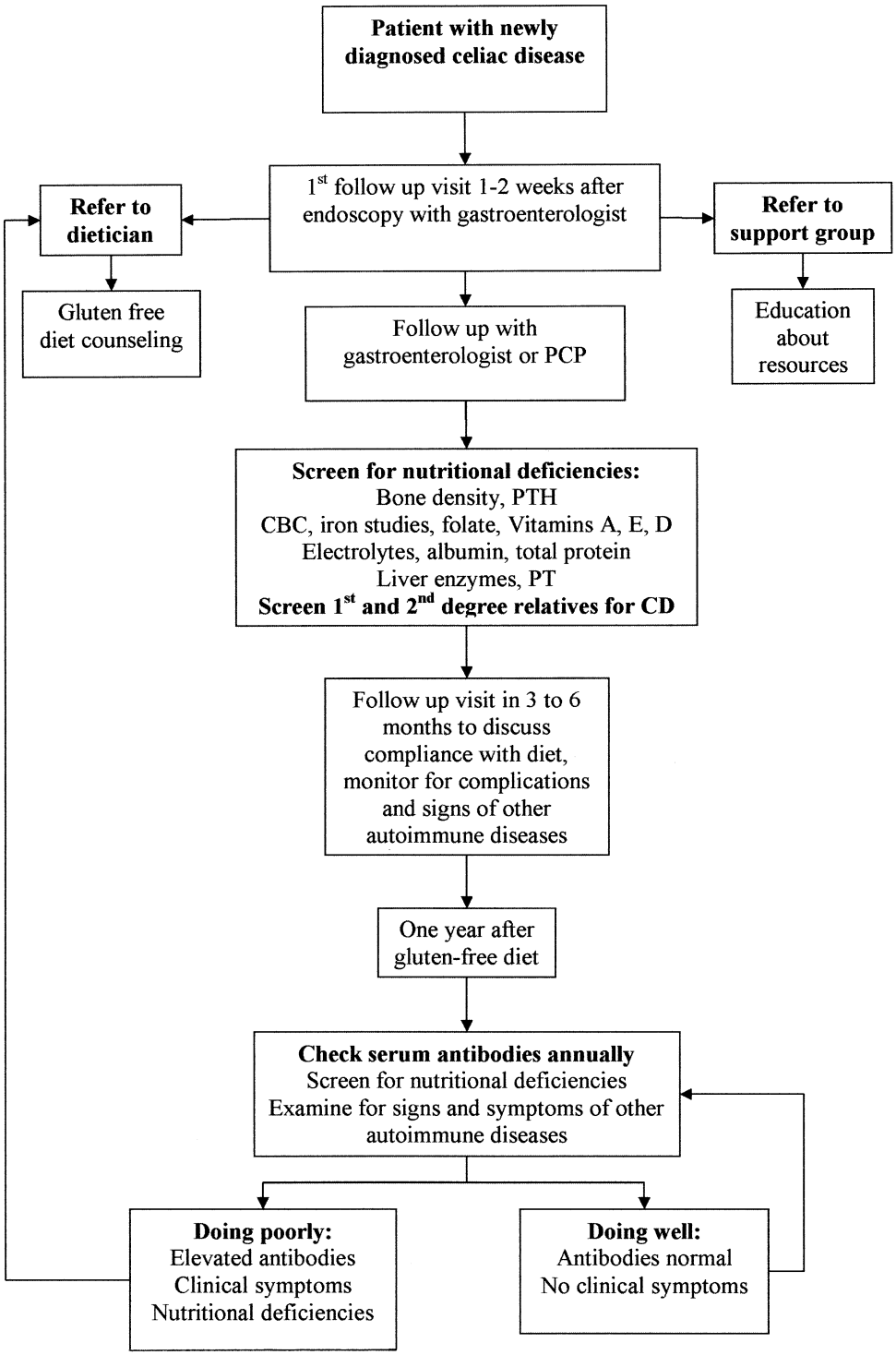

Figure 1. An approach to the management of a patient with newly diagnosed celiac disease.

be given by a dietician. This patient will also require closer monitoring for the development of the above-mentioned nutritional and autoimmune complications (Figure 1).

Special considerations need to be given to patients who have both CD and type 1 diabetes. Many of the well-known complications of type 1 diabetes can be exacerbated by nutritional deficiencies. Nocturnal hypoglycemia with seizures and recurrent, unexplained hypoglycemia with a reduction in insulin requirements should prompt the physician to investigate for CD.[53–55] In the young child, growth failure and delayed sexual

maturation may be seen. Vitamin deficiencies may aggravate retinopathy (vitamin A), systemic and peripheral neuropathy (vitamins B-12 and E), complications of pregnancy (iron deficiency anemia and folic acid deficiency), dental disease, limited joint mobility, osteopenia, and osteoporosis (vitamin D). There is also an increased incidence of other autoimmune diseases in type 1 diabetics who have "silent" CD and their first-degree relatives who are EMA positive.[56,57] The GFD presents an additional challenge to the patient with diabetes. The diabetic patient with CD may see acute hyperglycemia with the initiation of a GFD and a steady rise in hemoglobin A1c. This can be due to intestinal healing and better absorption, as well as gluten-free substitutes, which may be corn, rice, or potato based, and have a higher glycemic index.

Patient education, close supervision by an interested physician, and regular nutritional counseling by a registered dietician with expertise in CD are the most important factors in achieving dietary compliance in CD.[58] Compliance is improved, even in adolescents, who are seen by a physician on regular basis.[59,60] Dietary compliance assessed by a trained interviewer (either a physician or dietician) may be the best marker of CD control because of the low cost and noninvasivity and a strong correlation to intestinal damage.[60] It will also at the same time reinforce the need for strict adherence to a GFD and educate the subjects in the avoidance of gluten-containing foods.

Future research must be directed at finding alternatives to the GFD, which will, in turn, increase compliance with treatment. These future potential treatments include the development of genetically detoxified grains, oral and intranasal "celiac vaccines" to induce tolerance, inhibitors of the effects of zonulin on intestinal permeability,[61] inhibitors of tTG, and detoxification of immunogenic gliadin peptides via oral peptidase supplement therapy.[62]

In summary, compliance with a GFD diet can be measured by dietary history, serum antibody titers, and endoscopic and histologic pathology. Given that the criteria for the diagnosis of CD relies on pathology, repeat endoscopy documenting endoscopic and histologic remission after 6 months to a year on the GFD could be considered the "gold standard" for the evaluation of compliance. In the future, capsule endoscopy will likely become valuable in documenting small bowel mucosal damage and screening for ulcerative jejuno-ileitis and enteropathy-associated T-cell lymphoma. A more practical, cost-effective and noninvasive way to monitor compliance would include a detailed dietary history with analysis by a registered dietician, in combination with measurement of serum antibodies. The "dietary antibodies" AGA IgG and IgA normalize within 2 to 6 months of the GFD, and similarly increase after gluten challenge, making them useful tools to noninvasively measure adherence and transgression from the GFD within a relatively short period of time. The IgA "auto-antibodies" EMA and tTG take longer to normalize on a GFD and respond to a gluten challenge, although they have been suggested to better correlate with the degree of villous atrophy. In patients with other autoimmune conditions, such as type 1 diabetes, these antibodies may remain elevated despite strict adherence to the diet and thus may not be useful to measure compliance in this subset of patients. The patient groups at increased risk for noncompliance include those diagnosed as adolescents and adults and those identified through mass serologic screenings who are asymptomatic. The newly diagnosed patient with CD requires intensive support with frequent reinforcement from a physician knowledgeable about the disease's complications, a dietician familiar with the nuances of the GFD, and an informed national support group with local access. Future research should focus on alternatives to the GFD, which will block the interactions between gluten and the immune system and ultimately improve patient compliance.

References

1. Meeuwisse GW. Diagnostic criteria in coeliac disease. Acta Paediatr Scand 1970;59:461–463.
2. European Society of Paediatric Gastroenterology and Nutrition. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 1990;65:909–911.
3. Ciacci C, Cirillo M, Cavallaro R, Mazzacca G. Long-term follow-up of celiac adults on gluten-free diet: prevalence and correlates of intestinal damage. Digestion 2002;66:178–185.
4. Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. Gastrointest Endosc 2003;57:187–191.
5. American Gastroenterological Association medical position statement: celiac sprue. Gastroenterology 2001;120:1522–1525.
6. Petroniene R, Dubcenco E, Baker JP, Warren RE, Streutker CJ, Gardiner GW, Jeejeebhoy KN. Given capsule endoscopy in celiac disease. Gastrointest Endosc Clin N Am 2004;14:115–127.
7. Gonczi J, Skerritt JH, Mitchell JD. A reliable screening test for coeliac disease: enzyme-linked immunosorbent assay to detect anti-gliadin antibodies in serum. Aust N Z J Med 1991;21:723–731.
8. Hill PG, Thompson SP, Holmes GK. IgA anti-gliadin antibodies in adult celiac disease. Clin Chem 1991;37:647–650.
9. Rotolo N, Bottaro G, Spina M, Azzaro F, Pasqualetto A, Castiglione N, Randazzo C, Patane R. Importance of antigliadin antibodies determination during the follow-up of childhood coeliac disease. Minerva Pediatr 1993;45:357–361.
10. Medeiros EH, Patricio FR, de Morais MB, Leser PG, Wehba J. Serum antigliadin antibodies in the diagnosis and follow-up of celiac disease. Arquivos de Gastroenterologia. 1994;31:154–158.

11. Valletta EA, Mastella G. Adherence to gluten-free diet and serum antigliadin antibodies in celiac disease. Digestion 1990;47:20–23.
12. Rautonen J, Rautonen N, Savilahti E. Antibodies to gliadin in children with coeliac disease. Acta Paediatr Scand 1991;80: 1200–1206.
13. Troncone R, Ferguson A. Antigliadin antibodies. J Pediatr Gastroenterol Nutr 1991;12:150–158.
14. Sategna-Guidetti C, Pulitano R, Grosso S. Serum IgA antiendomysium antibody titres as a marker of intestinal involvement and diet compliance in adult celiac sprue. J Clin Gastroenterol 1993; 17:123–127.
15. Ferreira M, Lloyd Davies S, Butler M. Endomysial antibody: is it the best screening test for coeliac disease? Gut 1992;33:1633–1637.
16. Dickey W, Hughes DF, McMillan SA. Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery. Am J Gastroenterol 2000;95:712–714.
17. Sategna-Guidetti C, Grosso S, Bruno M. Reliability of immunological markers of coeliac sprue in the assessment of mucosal recovery after gluten withdrawal. J Clin Gastroenterol 1996;23: 101–104.
18. Troncone R, Mater M, Ispagnuolo F. Endomysial antibodies an unreliable marker for slight dietary transgression in adolescents with coeliac disease. J Pediatr Gastroenterol Nutr 1995;21:69–72.
19. James MW, Scott BB. Endomysial antibody in the diagnosis and management of coeliac disease. Postgrad Med J 2000;76:466–468.
20. Bürgin-Wolff A, Dahlbom I, Hadziselimovic F, Petersson CJ. Antibodies against human tissue transglutaminase and endomysium in diagnosing and monitoring coeliac disease. Scand J Gastroenterol 2002;37:685–691.
21. Ciacci C, Cavallardo R, della Valle N, d'Argenio G. The use of serum tTG-ab assay in patients on gluten-free diet as a measure of dietetic compliance. Gastroenterology 2002;122:588.
22. Clemente MG, Musu MP, Frau F, Lucia C, De Virgiliis S. Antitissue transglutaminase antibodies outside celiac disease. J Pediatr Gastroenterol Nutr 2002;34:31–34.
23. Kordonouri O, Dieterich W, Schuppan D, Webert G, Muller C, Sarioglu N, Becker M, Danne T. Autoantibodies to tissue transglutaminase are sensitive serological parameters for detecting silent coeliac disease in patients with type 1 diabetes mellitus. Diabet Med 2000;17:441–444.
24. Chan AW, Butzner JD, McKenna R, Fritzler MJ. Tissue transglutaminase as a screening test for celiac disease in pediatric patients. Available at WWW.PEDIATRICS.ORG/CGI/CONTENT/FULL/107/1/E8. Pediatrics 2001;107:E8.
25. Abdo A, Meddings J, Swain M. Liver abnormalities in celiac disease. Clin Gastroenterol Hepatol 2004 2:107–112.
26. Volta U, Defranceschi L, Molinaro N, Cassani F, Muratori L, Lenzi M, Bianchi FB, Czaja AJ. Frequency and significance of antigliadin and antiendomysial antibodies in autoimmune hepatitis. Dig Dis Sci 1998;43:2190–2195.
27. Clemente MG, Musu MP, Frau F, Brusco G, Sole G, Corazza GR, De Virgiliis S. Immune reaction against the cytoskeleton in coeliac disease. Gut 2000;47:520–526.
28. Clemente MG, Musu MP, Troncone R, Volta U, Congia M, Ciacci C, Neri E, Not T, Maggiore G, Strisciuglio P, Corazza GR, Gasbarrini G, Cicotto L, Sole G, Fasano A, De Virgiliis S. Enterocyte actin autoantibody detection: a new diagnostic tool in celiac disease diagnosis: results of a multicenter study. Am J Gastroenterol 2004;99:1551–1556.
29. Högberg L, Grodzinsky E, Stenhammar L. Better dietary compliance in patients with coeliac disease diagnosed in early childhood. Scand J Gastroenterol 2003:38:751–754.
30. Vahedi K, Mascart F, Mary J-Y, Laberenne J-E, Bouhnik Y, Morin M-C, Ocmant A, Velly C, Colombel J-F, Matuchansky C. Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease. Am J Gastroenterol 2003;98:1079–1087.
31. Kumar PJ, Walker-Smith J, Milla P, Harris G, Colyer J, Halliday R. The teenage coeliac: follow-up study of 102 patients. Arch Dis Child 1988;63:916–920.
32. Baker PG, Barry RE, Read AE. Detection of continuing gluten ingestion in treated celiac patients. Br Med J 1975;1:486–488.
33. Mayer M, Greco L, Troncone R. Compliance of adolescents with celiac disease with a gluten-free diet. Gut 1991;32:881–885.
34. Kluge F, Koch HK, Grosse-Wilde H, Lesch R, Gerok W. Follow-up of treated adult celiac disease: clinical and morphological studies. Hepatogastroenterology 1982;29:17–23.
35. Bardella MT, Molteni N, Prampolini L, Giunta AM, Baldassarri AR, Morganti D. Need for follow-up in coeliac disease. Arch Dis Child 1994;70:211–213.
36. Fabiani E, Taccari LM, Rätsch I-M, Di Giuseppe S, Coppa GV, Catassi C. Compliance with gluten-free diet in adolescents with screening-detected celiac disease: a 5-year follow-up study. J Pediatr 2000;136:841–843.
37. Hallert C, Grännö C, Hultén S, Midhagen G, Ström M, Svensson H, Valdimarsson T. Living with coeliac disease: controlled study of the burden of illness. Scand J Gastroenterol 2002;37:39–42.
38. Hallert C, Derefeldt T. Psychic disturbances in adult coeliac disease. I. Clinical observations. Scand J Gastroenterol 1982;17: 17–19.
39. Fabiani E, Catassi C, Villari A, Gismondi P, Pierdomenico R, Rätsch IM. Dietary compliance in screening-detected coeliac disease adolescents. Acta Paediatr Suppl 1996;412:65–67.
40. Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Guidetti CS, Usai P, Cesari P, Pelli MA, Loperfido S, Volta U, Calabró A, Certo M, for the Club del Tenue Study. Group mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001;358:356–361.
41. Mustalahti K, Lohiniemi S, Laippala P, Collin P, Mäki M. Improvement of the quality of life of silent celiac disease patients during the gluten-free diet warrants screening. Gastroenterology 2000; 118:A369.
42. Hallert C, Åström J. Intellectual ability of adults after lifelong intestinal malabsorption due to coeliac disease. JNNP 1983;46: 87–89.
43. Hallert C, Åström J. Psychic disturbances in adult coeliac disease II. Psychological findings. Scand J Gastroenterol 1982;17:21–24.
44. Holmes GKT. Neurological and psychiatric complications in coeliac disease. In: Gobbi G, Andermann F, Naccarato S, Banchini G, eds. Epilepsy and other neurological disorders in coeliac disease. London: John Libbey, 1997:251–264.
45. Ciacci C, Iavarone A, Siniscalchi M, Romano R, De Rosa A. Psychological dimensions of celiac disease: toward an integrated approach. Dig Dis Sci 2002;47:2082–2087.
46. Sategna-Guidetti C, Volta U, Ciacci C, Usai P, Carlino A, De Franceschi L, Camera A, Pelli A, Brossa C. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. Am J Gastroenterol 2001;96:751–757.
47. Kaukinen K, Halme L, Collin P, Farkkila M, Mäki M, Vehmanen P, Partanen J, Hockerstedt K. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. Gastroenterology 2002;122:881–888.
48. Sategna-Guidetti C, Grosso SB, Grosso S, Mengozzi G, Aimo G, Zaccaria T, Di Stefano M, Isaia GC. The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutritional status in newly-diagnosed adult coeliac disease patients Aliment Pharmacol Ther 2000;14:35–43.

49. Mora S, Barera G, Beccio S, Menni L, Proverbio MC, Bianchi C, Chiumello G. A prospective, longitudinal study of the long-term effect of treatment on bone density in children with celiac disease. J Pediatr 2001;139:516–521.
50. Kemppainen T, Kröger H, Janatuinen E, Arnala I, Lamberg-Allardt C, Kärkkäinen M, Kosma V-M, Julkunen R, Jurvelin J, Alhava E, Uusitupa M. Bone recovery after a gluten-free diet: a 5-year follow-up study. Bone 1999;25:355–360.
51. Kemppainen T, Kröger H, Jatatuinen E. Osteoporosis in adult patients with celiac disease. Bone 1999;24:249–255.
52. Valdimarsson T, Toss G, Löfman O, Ström M. Three years' follow-up of bone density in adult coeliac disease: significance of secondary hyperparathyroidism. Scand J Gastroenterol 2000;35: 274–280.
53. Iafusco D, Rea F, Prisco F. Hypoglycemia and reduction of the insulin requirement as a sign of celiac disease in children with IDDM. Diabetes Care 1998;21:1379–1380.
54. Smith CM, Clarke CF, Porteous LE, Elsori H, Cameron DJS. Prevalence of celiac disease and longitudinal follow-up of antigliadin antibody status in children and adolescents with type I diabetes mellitus. Pediatr Diabetes 2000;1:199–203.
55. Mohn A, Cerruto M, Iafusco D, Prisco F, Tumini S, Stoppoloni O, Chiarelli F. Celiac disease in children and adolescents with type I diabetes: importance of hypoglycemia. J Pediatr Gastroenterol Nutr 2001;32:37–40.
56. Not T, Tommasini A, Tonini G, Buratti E, Pocecco M, Tortul C, Valussi M, Crichiutti G, Berti I, Trevisiol C, Azzoni E, Neri E, Torre E, Martelossi S, Soban M, Lenhardt A, Cattin L, Ventura A. Undiagnosed coeliac disease and risk of autoimmune disorders in subjects with type I diabetes mellitus. Diabetologia 2001;44: 151–155.
57. Jaeger C, Hatziagelaki E, Petzoldt R, Bretzel R. Comparative analysis of organ-specific autoantibodies and celiac disease-associated antibodies in type 1 diabetic patients, their first-degree relatives, and healthy control subjects. Diabetes Care 2001;24:27–32.
58. Högberg L, Grodzinsky E, Stenhammar L. Better dietary compliance in patients with coeliac disease diagnosed in early childhood. Scand J Gastroenterol 2003:38:751–754.
59. Ljungman G, Myrdal U. Compliance in teenagers with coeliac disease—a Swedish follow-up study. Acta Paediatr 1993;82: 235–238.
60. Mäki M, Lähdehaho M-L, Hällström O, Viander M, Visakorpi JK. Postpubertal gluten challenge in coeliac disease. Arch Dis Child 1989;64:1604–1607.
61. Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Goldblum SE. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. Lancet 2000; 355:1518–1519.
62. Shan L, Molberg Ø, Parrot I, Hausch F, Filiz F, Gray GM, Sollid LM, Khosla C. Structural basis for gluten intolerance in celiac sprue. Science 2002;297:2275–2279.

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