

Update on the evaluation and diagnosis of celiac disease

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Purpose of review

Our understanding of the pathophysiology of celiac disease has advanced with associated improvement in diagnostic modalities. Recent studies have placed the prevalence of celiac disease in Western populations at between 1:250 and 1:67. Celiac disease is common throughout the world and most cases go undiagnosed. Understanding the risk factors, clinical presentations and diagnostic modalities is necessary to identify and treat patients with this commonly misdiagnosed disorder.

Recent findings

Increased prevalence of celiac disease in individuals with autoimmune diseases, reduced bone mineral density and undiagnosed liver disease have been confirmed. However, celiac disease may not be associated with Down's syndrome or epilepsy. Evidence supports high sensitivity and specificity of endomysial- and tissue transglutaminase-based tests in most settings. In children, high or low tissue transglutaminase levels may preclude the need for duodenal biopsy. Cost-effectiveness studies suggest using tissue transglutaminase or endomysial initially, while distal duodenal or jejunal biopsy may confirm celiac disease in the absence of proximal changes.

Summary

There is insufficient evidence to support mass screening for celiac disease. However, case finding in individuals with risk factors for celiac disease is recommended. Further study is necessary to define diagnostic algorithms and target populations likely to benefit from testing.

Keywords

biopsy, celiac disease, diagnosis, screening, serology

Introduction

This review covers recent advances in the diagnosis of celiac disease. Efforts have focused on three of key issues. The first issue is the characterization of populations enriched for celiac disease. Due to the cost and unclear benefit in minimally symptomatic individuals, mass screening cannot be recommended at this time. It is therefore necessary to determine which individuals are at highest risk for celiac disease and should be tested. Second is the issue of the impact of diagnosis and treatment of celiac disease. As the spectrum of clinical presentations of celiac disease widens, more individuals are being diagnosed without the classical complications seen in previous decades. In individuals mildly affected by celiac disease, the benefit of gluten withdrawal is less obvious and requires further study. Finally, there is the issue of the role of different serologic tests in diagnosis and monitoring of disease activity. The new generations of serologic tests have superior sensitivity and specificity yet are subject to important limitations. Diagnostic algorithms for celiac disease have continued to evolve. Understanding of each of these areas is necessary for the cost-effective diagnosis of celiac disease in individuals likely to benefit from treatment.

Utility of screening

The utility of mass screening has long been debated in the medical community. Although celiac disease is prevalent and accurate screening tests exist, there are currently few data on the benefits of diagnosis in individuals without clinically obvious manifestations. There has been no definitive study, in the form of either a randomized trial of diagnosis and treatment in screen-detected individuals or the long-term follow up of a large cohort of screen-detected untreated individuals. At present there is equipoise between the potential benefits of treatment such as improved well-being, avoidance of nutritional deficiencies and protection against intestinal neoplasia and the concern for the negative effects of diagnosis of celiac disease in symptomless individuals including disease labeling, dietary restriction and possibly increasing body mass index and cardiovascular disease through increased nutrient absorption and greater reliance on low-fiber, high-calorie, gluten-free foods.

Addressing the latter issue, a study by West *et al.* [1] identified 3790 adults with diagnosed celiac disease and 17 925 age- and sex-matched controls from the UK General Practice Research Database. Adults with celiac disease were less likely to have had a diagnosis of

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Abbreviations

BMD	bone mineral density
CI	confidence interval
OR	odds ratio
tTG	tissue transglutaminase

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hypertension [odds ratio (OR), 0.68; 95% confidence interval (CI), 0.60–0.76] or hyperlipidemia (OR, 0.58; 95% CI, 0.47–0.72). However, the hazard ratios for myocardial infarction, stroke and atrial fibrillation were similar between groups.

Few studies have prospectively followed individuals with celiac disease detected by screening. One study evaluated quality of life, gastrointestinal symptoms and bone mineral density (BMD) in 53 consecutive screen-detected celiac patients diagnosed an average of 14 years previously, compared to 44 symptom-detected celiac patients and 110 healthy controls [2[•]]. Quality of life and gastrointestinal symptoms were similar in all groups and BMD was decreased in participants with symptomatic celiac disease only. Johnston *et al.* [3] evaluated quality of life in screen-detected celiac disease by comparing the change in SF-36 score over the first year after diagnosis of celiac disease in 14 screen-detected individuals, 17 symptomatic celiac patients and 24 healthy controls. They found that symptomatic celiac patients had worse initial quality of life and improved with gluten withdrawal; however, there was no difference between screen-detected individuals and controls initially or at 1 year.

Haapalahti *et al.* [4[•]] described the nutritional status of 26 subjects with screen-detected celiac disease and 29 healthy controls. Compared with controls, celiac disease patients had lower median values of folic acid, ferritin and pre-albumin, and higher transferrin receptor levels. Body mass index was not different between groups, yet females with celiac disease were shorter than the controls. Thus data on screening for celiac disease are inconclusive, suggesting both possible risks and benefits. Guidelines for screening cannot be made until data from well-designed prospective studies documenting the natural history and response to treatment of silent celiac disease are available.

Aggressive case finding

In contrast to screening, the current standard of care is aggressive case finding. This strategy, reaffirmed by the 2004 National Institutes of Health consensus development conference on celiac disease [5^{••}], places responsibility for detection of celiac disease in the hands of individual clinicians and encourages increased awareness of the risk factors and presentations of celiac disease. Furthermore, Lanzini *et al.* [6^{••}] have shown that targeted physician education can increase regional celiac disease diagnosis rates by as much as 50%.

High-risk populations

The 'classic' presentation of celiac disease in adults and children remains diarrhea with malabsorption, nutritional deficiencies and weight loss or failure to thrive. However,

there are a number of other symptoms and diagnoses which should trigger consideration of testing for celiac disease in the absence of the classic signs.

Osteopenia/osteoporosis

Reduced BMD is a common complication of celiac disease affecting up to 70% of individuals with celiac disease [7]. One study [8] of 148 unselected celiac patients and 296 matched controls found an increased number of fractures in the peripheral skeleton in those with symptomatic celiac disease (OR, 5.2; 95% CI, 2.8–9.8) but not in screen-detected cases (OR, 1.7; 95% CI, 0.7–4.4).

Studies investigating the prevalence of celiac disease in individuals with reduced BMD have yielded contradictory results. An American study of 840 individuals, 266 with and 574 without osteoporosis, found 3.4% of patients with osteoporosis and 0.2% of patients without osteoporosis to have celiac disease [9^{••}]. A similar study of 978 patients in the UK undergoing dual energy X-ray absorptiometry found celiac disease in 0.7% of those with normal BMD, 1.2% with osteopenia and 2.1% with osteoporosis. However, all patients with unrecognized celiac disease had either gastrointestinal symptoms or anemia, suggesting that this combination of findings should prompt testing [10^{••}]. A third study [11[•]] of 89 premenopausal women with osteoporosis found a prevalence of celiac disease of 10%. These results differ from two earlier studies from Ireland that found no increased prevalence of celiac disease in unselected cohorts of females with reduced BMD [12,13].

Nutritional abnormalities

Celiac disease is more common in unselected individuals with iron-deficiency anemia. Kalayci *et al.* [14^{••}] described 135 children with iron-deficiency anemia of whom six (4.4%) had undiagnosed celiac disease compared with none of the 223 control children without iron-deficiency anemia. Two studies of 150 [15^{••}] and 103 [16] consecutive adults referred for evaluation of unexplained or refractory iron-deficiency anemia also found similar rates of celiac disease (5 and 9% respectively). Of note, in the former study, all patients determined to have celiac disease had been refractory to oral iron supplementation. Similarly, a study of 97 consecutive individuals with secondary hyperparathyroidism detected by screening found four (4.1%) of these to be due to celiac disease [17[•]].

Fertility

Studies in the past year have helped to clarify the interaction between celiac disease and fertility. A study from the Swedish national register [18^{••}] identified 2078 offspring of women diagnosed with celiac disease between 1964 and 2001. A total of 1149 women had been diagnosed prior to giving birth and 929 women were

diagnosed after infant birth. Celiac disease diagnosed after, but not prior to, giving birth was associated with an increased risk of intrauterine growth retardation (OR, 1.62; 95% CI, 1.22–2.15), low birth weight (OR, 2.13; 95% CI, 1.66–2.75), very low birth weight (OR, 2.45; 95% CI, 1.35–4.43), preterm birth (OR, 1.71; 95% CI, 1.35–2.17) and Cesarean section (OR, 1.82; 95% CI, 1.27–2.60). A British study [19^{••}] used primary care data for 1521 women with celiac disease, over 90% of which were recorded as having a prescription for gluten-free diet, and 7732 matched controls to estimate population-based rates of fertility and adverse pregnancy outcomes. This study found identical crude fertility rates, although childbirth among celiac patients was skewed toward a later age. Risks of Cesarean section (OR, 1.33; 95% CI, 1.03–1.70) and miscarriage (rate ratio, 1.31; 95% CI, 1.06–1.61) were moderately higher in women with celiac disease, but all other outcomes, including pre-eclampsia, stillbirth and termination, were similar. A third study [20[•]] tested 200 Italian women undergoing assisted reproduction and 200 women without reproductive problems for celiac disease. Five women (2.5%) from the study group and two (1.0%) from the control group were found to have celiac disease, which was not statistically significant.

Down's syndrome

While Down's syndrome has been found in past studies to be a strong risk factor for celiac disease with a prevalence of 6–8% [21,22], one recent study has called this association into question, reporting a 1% prevalence of celiac disease in an unselected cohort of 100 Turkish children with Down's syndrome [23[•]].

Gastrointestinal symptoms

The role of abdominal pain in detection of celiac disease was recently evaluated [24[•]] in 300 individuals admitted to a surgery service for non-specific abdominal pain compared with 300 matched healthy controls. In the group with abdominal pain there were nine cases of biopsy-confirmed celiac disease compared with two in the control group (OR, 4.6; 95% CI, 1.11–19.05).

Autoimmune disorders

Recent evidence both supporting and contradicting the association of celiac disease with autoimmune thyroid disease have been published. In one study [25^{••}], 111 patients with Graves' hyperthyroidism attending a thyroid clinic over a 9-month period were offered screening for celiac disease. Comparison was made with matched healthy controls. Six cases of celiac disease were identified, five (4.5%) from the Graves' group and one (0.9%) from the controls. In contrast, a study by Fanciulli *et al.* [26[•]] found no cases of celiac disease in a sample of 231 patients with newly diagnosed autoimmune thyroid disease.

Type 1 diabetes mellitus has been associated with celiac disease and some existing data support diagnosis and treatment in this population. Buysschaert *et al.* [27^{••}] screened 400 type 1 diabetic patients, of whom 10 (2.5%) were found to have celiac disease. Although eight of the 10 patients were symptom-free, all had laboratory findings suggesting significant malabsorption. A second study [28^{••}] evaluated the prevalence of celiac disease in 281 children with type 1 diabetes and monitored the effect of gluten withdrawal in newly diagnosed cases. Eighteen participants (6.4%) had positive serology, and 12 agreed to small-intestinal biopsy, of whom nine (3.2%) had celiac disease. In those adhering to a gluten-free diet, the majority with gastrointestinal symptoms or iron-deficiency anemia improved and there was a significant increase in height and improvement in HbA1c (8.0 compared with 7.3%, $P = 0.05$). Rami *et al.* [29^{••}] identified 98 diabetic patients diagnosed with celiac disease by screening and 195 matched controls negative for endomysial. Over 1 year, mean HbA1c, episodes of hypoglycemia or ketoacidosis and applied insulin dosage were similar between cases and controls. Although body mass index and height at celiac disease diagnosis did not differ between cases and controls, children with celiac disease had less subsequent weight gain than matched controls. Kaspers *et al.* [30] report similar data from 127 diabetic adolescents with screen-detected celiac disease. They found that the celiac cohort were significantly younger at diabetes onset, and had significantly lower height, body mass index and HbA1c. Additionally, they found thyroid disease to be significantly increased in the group with diabetes and celiac disease compared to diabetes alone (6.3 compared with 2.3%). Taken together, these data support an increased prevalence of celiac disease in individuals with type 1 diabetes and are suggestive of clinically relevant improvements in nutritional status with gluten withdrawal.

Psoriasis and juvenile idiopathic arthritis have also been evaluated for association with celiac disease. Woo *et al.* [31] found no significant increase of celiac disease in unselected cases of psoriasis (three out of 130 or 2.3%) but reported a significantly higher incidence of celiac disease in patients requiring systemic immunosuppressants or psoralen/ultraviolet light A ($P = 0.04$ and 0.03 respectively). Stagi *et al.* [32[•]] found celiac disease (10 cases or 6.6%, $P < 0.005$) and autoimmune thyroid disease to be significantly increased in 151 children with juvenile idiopathic arthritis compared with 158 matched controls.

Inflammatory bowel disease

A study from New York [33[•]] of 455 patients with celiac disease identified 10 cases with inflammatory bowel disease (2.2%; five ulcerative colitis and five Crohn's disease). This represented adjusted prevalence rate ratios

for ulcerative colitis of 3.56 (95% CI, 1.48–8.56) and for Crohn's disease of 8.49 (95% CI, 3.53–20.42). A second study [34•] of 27 patients with newly diagnosed Crohn's disease found five patients (18.5%) with biopsy-verified celiac disease.

Liver disease

Villalta *et al.* [35••] evaluated 47 consecutive patients with autoimmune hepatitis for celiac disease, compared to both healthy and chronic hepatitis C controls. Three of the 47 autoimmune hepatitis patients (6.4%) were found to have celiac disease compared with none in either control group, which was significantly higher than the estimated population prevalence of celiac disease (0.5–1%). Another study [36••] of 168 cases of cryptogenic liver disease drawn from 2512 consecutive patients with abnormal liver tests confirmed celiac disease in six cases (3.6%), suggesting that celiac disease be considered in cases where preliminary tests for etiology of liver disease are negative.

Epilepsy

Epilepsy with cerebral calcification is an accepted association of celiac disease [37•], but the prevalence of celiac disease in unselected individuals with seizure disorders does not appear to be increased. Ranua *et al.* [38•] found no increased risk of celiac disease as determined by serology alone in a cohort of 968 patients with epilepsy and a population-based reference group of 584 subjects.

Means of diagnosis

In this section, we will examine different means of diagnosis.

Serology

The advent of highly sensitive and specific blood tests for celiac disease has, in large part, driven the increases in awareness and diagnosis of this disorder. Studies characterizing the performance of these tests in various populations are ongoing and accuracy appears to vary between different groups. In one study of 168 individuals with unexplained elevations in liver function tests [36••], only six of nine patients positive for IgA tissue transglutaminase (tTG) were found to have celiac disease at biopsy. Conversely Collin *et al.* [39••] evaluated 126 celiac patients and 106 controls, verified by duodenal biopsy. In this study, the sensitivity of anti-human IgA-tTG was 94% and IgA-endomysial 89%, the specificities were 99 and 98%, respectively. A meta-analysis [40••] confirmed the equivalence of endomysial- and tTG-based tests and their superiority to anti-gliadin antibody. The pooled specificity of endomysial was close to 100%, and 95–99% for tTG. The sensitivity of endomysial monkey esophagus was 96–97% while endomysial human umbilical cord demonstrated a sensitivity of 97% in children

but 90% in adults. The pooled sensitivities of tTG guinea pig and tTG recombinant human were 90–93% and 96–98%, respectively. This study highlights two points. First, many earlier studies were done with anti-guinea pig tTG which has lower sensitivity than recombinant anti-human tTG. Second, sensitivity of these tests is lower when milder histologic grades are used to define celiac disease.

Cost-effectiveness

Three studies have assessed the cost-effectiveness of different screening and diagnosis strategies. Yagil *et al.* [41•] evaluated 643 individuals referred for evaluation of possible celiac disease based on clinical suspicion. They assessed the use of tTG, endomysial and anti-gliadin antibody, and the number of subsequent tests performed per diagnosis of celiac disease to estimate cost. This found endomysial, followed by biopsy if positive, to be the most cost-effective strategy; however, anti-guinea pig tTG was used rather than a more accurate anti-human tTG assay. Barker *et al.* [42•] studied the effect of different tTG cut-off levels in determining need for further workup in a sample of 103 children undergoing evaluation for celiac disease. In IgA-sufficient individuals, IgA-tTG values of less than 20 and greater than 100 had negative and positive predictive values of nearly 100% for the exclusion and diagnosis of celiac disease, respectively. They suggest that, in the pediatric population, only individuals with IgA deficiency or with tTG levels between 20 and 100 need undergo duodenal biopsy. There is currently little evidence to guide the use of routine testing for IgA deficiency or the use of non-IgA-based celiac disease serologic tests, although these may be considered in cases of very low tTG titer or high suspicion for celiac disease with negative IgA-tTG. An earlier study [43] evaluated the cost-effectiveness of celiac disease screening using tTG, in diarrhea-predominant irritable bowel syndrome. They found a cost of US\$11 000 per symptomatic improvement attributable to diagnosis of celiac disease. This was cost-effective with a celiac disease prevalence of greater than 1%, and cost-saving with a prevalence of greater than 8%, a cost for treatment of irritable bowel syndrome of more than \$130 per month, or a screening-test specificity exceeding 98%.

Human leukocyte antigen typing

The role of human leukocyte antigens DQ2 and DQ8 as necessary but not sufficient for the development of celiac disease [44] has been known for over a decade. A recent review of the role of genetic testing in celiac disease [45•], as well as the National Institutes of Health consensus statement on celiac disease [5••], confirm the more limited use of human leukocyte antigen typing for the exclusion, but not diagnosis, of celiac disease in indeterminate cases.

Endoscopy/histology

Endoscopy with duodenal biopsy remains the gold standard for diagnosis and monitoring of celiac disease and is recommended currently prior to dietary treatment for all patients with positive serology [5**]. Recent reports highlight the patchy nature of mucosal changes in celiac disease and suggest an increased number and area of biopsies. In a study of 110 individuals, Ravelli *et al.* [46*] found an increasing degree of mucosal damage in the distal duodenum suggesting better diagnostic accuracy of biopsy from this location. Another study of 146 patients [47] found that, of 71 patients with biopsies positive for celiac disease, three had changes in the jejunum alone. Similar findings were reported by Horoldt *et al.* [48] who repeated endoscopy with jejunal biopsy on 31 individuals with positive serology, for whom initial duodenal biopsy had been negative. Five patients were found to have celiac disease and three of these had changes in the jejunum alone. These studies suggest the use of jejunal biopsy in cases of high suspicion where initial duodenal biopsy is negative.

Conclusion

The evaluation of celiac disease has progressed substantially and the use of sensitive and specific serologic tests has greatly facilitated case finding in symptomatic individuals. Anti-human IgA-tTG currently appears to be the initial test of choice for individuals suspected of having celiac disease. Endoscopy with biopsy remains necessary for confirmation of diagnosis, but whether this is necessary in all settings needs to be clarified, as does the optimal distribution of biopsies. Evaluation for the many signs and symptoms of celiac disease, with emphasis on high-risk groups, remains the standard of care for diagnosis. Future studies are needed to assess the utility of screening for celiac disease in specific groups or the general population to attempt to reduce the burden of this common disease.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 244–245).

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