

ADVANCES IN ENDOSCOPY

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The Role of Endoscopy in the Diagnosis of Celiac Disease



Peter H. R. Green, MD
Phyllis and Ivan Seidenberg Professor of Medicine
Director, Celiac Disease Center
Columbia University College of Physicians and Surgeons
New York, New York

G&H How prevalent is celiac disease, and what are the causes of this condition?

PG Celiac disease is common worldwide, occurring in approximately 1% of the population. However, in the United States, only 17% of that 1% are currently diagnosed, making for a very high rate of underdiagnosis, especially compared with some European countries and Australia.

Celiac disease occurs due to an immune reaction to gluten, the term for the protein in wheat, rye, and barley. Approximately 30% to 40% of the general population is genetically predisposed to celiac disease, as these persons have the *HLA-DQ2* or *-DQ8* genes. Since the vast majority of people eat wheat but only 1% develop celiac disease, there must be environmental factors at play in addition to the genetic factors. According to various studies, it appears that celiac disease may be associated with antibiotic use; history of gastroenteritis, rotavirus, or *Campylobacter* infection; proton pump inhibitor use; and birth by elective Cesarean section, among other risk factors. Nevertheless, we still do not completely understand why celiac disease develops in 1% of the population and is actually increasing in incidence. In fact, in the past 50 years, celiac disease has increased approximately 4- to 5-fold in the United States as assessed by studies of frozen serum. We do not know why the incidence of this condition is very high in some countries (such as Sweden) and low in other countries (such as Germany).

G&H How is celiac disease usually diagnosed?

PG In a patient with suspected celiac disease, the path to diagnosis usually starts with the ordering of blood tests for tissue transglutaminase antibodies, which have been

shown to be fairly sensitive and specific for celiac disease. If these test results are positive, the patient is referred for endoscopy, as duodenal biopsy is currently the gold standard for diagnosing celiac disease.

One of the difficulties of this diagnostic process, however, is that, in the United States, physicians often do not consider celiac disease in their differential diagnoses, which is likely one of the reasons why the condition is underdiagnosed in this country. Using various scenarios of ages and sexes, my colleagues and I recently surveyed hematologists about their evaluation process for patients with iron-deficiency anemia (which can be indicative of celiac disease) and found that they would test for celiac disease in only less than 20% of cases.

G&H Are there any pitfalls or difficulties to using biopsy in this setting?

PG Although biopsy is the gold standard for diagnosis, this procedure does not come without expense or risks (though the risks are minimal). In addition, even though there are guidelines as to the number of biopsies that are recommended, endoscopists often do not take enough pieces; the most frequent number of pieces taken at endoscopy is 2, whereas guidelines recommend taking 4 to 6 pieces. My colleagues and I demonstrated in a study that significantly more patients are diagnosed when 4 to 6 biopsy pieces are taken. This is likely because the disease is patchy, and the biopsy pieces may not be well oriented.

Likewise, the location of the biopsy should also be kept in mind when performing an endoscopy. Typically, endoscopists biopsy the descending duodenum, but they should also biopsy the duodenal bulb because sometimes changes appear only in the bulb. Thus, endoscopists

should take 4 to 6 pieces from the descending duodenum and then 2 more pieces from the duodenal bulb.

Another potential pitfall associated with biopsy is pathologic interpretation. Endoscopists should always keep in mind that the pathology report is subject to the interpretation bias of the pathologist and that different pathologists have different abilities to diagnose celiac disease.

G&H Which patient groups should undergo endoscopic screening for celiac disease?

PG In addition to people with positive celiac antibody test results, people who should undergo a biopsy include those who have been evaluated for symptoms or signs that could represent celiac disease, such as iron-deficiency anemia, diarrhea, or weight loss. In fact, it could be argued that there should be routine duodenal biopsy for the presence of celiac disease whenever a patient undergoes endoscopy because the physician might not be aware that the patient is actually in a high-risk group (eg, a family member of a person with celiac disease, a person with type 1 diabetes, or a man or a young person with osteoporosis). As already mentioned, celiac disease is underdiagnosed even though it is common, so this condition needs to be more prominently on the radar of physicians, particularly endoscopists.

G&H Is there a role for the use of video capsule endoscopy for diagnosing celiac disease?

PG Video capsule endoscopy has been shown to be sensitive and specific for the diagnosis of celiac disease. If a patient has positive antibody test results and a negative biopsy, the celiac disease may be beyond the reach of a routine endoscopy; in this scenario, video capsule endoscopy could be used to search for visual changes indicating the presence of villous atrophy. As with standard endoscopy, if a patient is undergoing video capsule endoscopy for an indication such as iron-deficiency anemia, the endoscopist reading the capsule should also look for signs of celiac disease (ie, scalloping, a mosaic pattern, or a reduced appearance of villi) in addition to the reason for blood loss. Video capsule endoscopy also has an important role in the evaluation of patients with celiac disease who are poorly responsive to dietary therapy or have alarm symptoms, such as blood in the stool.

G&H Now that serologic tests are available to help diagnose celiac disease, how important is histologic confirmation?

PG Guidelines from the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition suggest that symptomatic children with very high antibody levels to tissue transglutaminase (>10 times normal) who also have

a positive endomysial antibody test result from a different blood sample can be diagnosed with celiac disease without pathologic confirmation. However, this guideline has not been accepted in the United States as of yet, as there are several downsides to avoiding endoscopy. It is possible to get a false-positive tissue transglutaminase test result; for example, temporary gluten autoimmunity can cause patients to have a positive tissue transglutaminase level yet no celiac disease. Performing an endoscopy also allows for biopsy of other areas and the opportunity to make other diagnoses, such as eosinophilic esophagitis, which appears to run along with celiac disease in both children and adults, or perhaps even peptic ulcers or other conditions that can be missed in children. In the United States, guidelines advocate that a positive tissue transglutaminase antibody test result should prompt a biopsy. A biopsy can confirm whether a patient actually has celiac disease as well as provide a baseline for comparison in case follow-up biopsies are required (eg, as in a patient who does not respond to a gluten-free diet).

G&H What were the principal findings of your recent study on patients undergoing endoscopy and serologic testing for suspected celiac disease?

PG My colleagues and I conducted a study of 999 consecutive consenting patients in Beirut, Lebanon, who were undergoing endoscopy for a variety of reasons. During endoscopy, markers for celiac disease were noted, and duodenal biopsies were taken. The patients also completed a questionnaire and underwent serologic testing. The diagnosis of celiac disease required abnormal duodenal histology and positive serology, and patients were classified as having high or low risk for celiac disease based on risk factors. We found that the presence of classic celiac disease symptoms such as diarrhea and weight loss did not predict the presence of celiac disease. In contrast, celiac disease was most commonly associated with ethnicity (Shiite; odds ratio [OR], 5.4; 95% CI, 1.1-26.6), history of eczema (OR, 4.6; 95% CI, 0.8-28.8), endoscopic features of villous atrophy (OR, 64.8; 95% CI, 10.7-391.3), anemia (OR, 6.7; 95% CI, 1.2-38.4), and a positive tissue transglutaminase antibody test (OR, 131.7; 95% CI, 29.0-598.6), which was the strongest predictor. Using independent predictors to determine if a patient should undergo duodenal biopsy was associated with a sensitivity of 93% to 100% for diagnosing celiac disease as well as an acceptable (22%-26%) rate of unnecessary biopsy. In comparison, excluding serologic testing before endoscopy yielded a sensitivity of 93% to 94% and an unnecessary biopsy rate of 52% for the diagnosis of celiac disease. Therefore, we concluded that using only standard clinical suspicion and endoscopic find-

ings was associated with a significant miss rate for celiac disease, whereas using risk factors to determine which patients required biopsy maximized the diagnosis of celiac disease and minimized unnecessary biopsies.

Interestingly, patients in a similar study in England showed different predictive factors for having celiac disease. This means that, to be cost-effective, endoscopists need to determine what patients are like in their area. One of the reasons we conducted this study was to see whether there could be a cost-effective approach to avoiding biopsy. Not all patients require biopsy, but, at the same time, we do not want to miss the disease in any patients. By studying the surrounding patient population, it may be possible to develop an algorithm for biopsying selected people so that those at high risk for celiac disease are identified while those at low risk forego biopsy. Unfortunately, such a study has not yet been conducted in the United States.

G&H Are there any new developments in the use of endoscopy for diagnosing celiac disease?

PG Several groups have looked at ways of targeting biopsies to increase the yield, such as using chromoendoscopy or water immersion magnification endoscopy. In the hands of the investigators, these techniques appear to be effective at improving the yield; however, they are not yet widely available or used, and endoscopists have not yet been trained in them, so these techniques are not for routine use at this stage.

G&H What further research is needed?

PG We need a good cost-effectiveness study of the role of endoscopy and biopsy in the diagnosis of celiac disease

in the United States. My colleagues and I recently conducted a study looking at refractory reflux disease, since some people with reflux have celiac disease that improves when they go on a gluten-free diet. This is traditionally not a group that is associated with celiac disease, but there needs to be more research on all aspects of celiac disease to highlight how common the condition is and why so many different physicians, including endoscopists, come into contact with it on a regular basis, yet still are not able to diagnose all of these patients.

Dr Green is on the scientific advisory board of Alvine Pharmaceuticals and ImmusanT.

Suggested Reading

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