

## Celiac disease: how many biopsies for diagnosis? CME

Celiac disease is now considered to be common, occurring in rates approaching 1% of the population worldwide.<sup>1,2</sup> However, the rate of diagnosis, while increasing in the United States,<sup>3</sup> does not approach this figure. In contrast, in Finland an active program involving the education of physicians in how and when to consider the diagnosis of celiac disease has resulted in an increase in the rate of diagnosis.<sup>4</sup> The nationwide prevalence of celiac disease in Finland is now 0.45%—0.7% in the highest to 0.3% in the lowest prevalence areas of the country. In Ireland the increased rate of diagnosis has been attributed to testing and referral by primary care physicians.<sup>5</sup>

In 2004, the National Institutes of Health convened a Consensus Development Conference because of the low rate of celiac disease diagnosis in the United States.<sup>6</sup> This low rate has been attributed to failure of physicians to recognize the diverse manifestations of the disease.<sup>7</sup> This failure of awareness has led to failure to test the patient when indicated. This applies to both the use of serologic testing in the primary care setting,<sup>8</sup> as well as the failure to perform duodenal biopsies by endoscopists, even when it would appear indicated. This failure to perform a biopsy when indicated was addressed by Harewood et al,<sup>9</sup> who used the large Clinical Outcomes Research Initiative (CORI) national endoscopic database to analyze the rate of small-bowel biopsy performed in patients undergoing EGD for the evaluation of anemia, iron deficiency without anemia, weight loss, and diarrhea. They found that only 10% of those with anemia, 7% with iron deficiency, 6% with weight loss, and 19% with diarrhea underwent a duodenal biopsy. In all of these conditions it would be appropriate to consider the diagnosis of celiac disease and perform duodenal biopsies, irrespective of the results of serologic tests or the endoscopic appearance of the duodenum.

Biopsy is currently the criterion standard in the diagnosis of celiac disease. Serologic testing is used to screen those at risk for the disease in order to triage for endoscopy and biopsy. These serologic tests, including those for endomysial and tissue transglutaminase antibodies, have a high sensitivity and specificity,<sup>10</sup> although not 100%. The sensitivity of the serologic tests correlates with the degree of villous atrophy; thus, a negative serologic test does not exclude the diagnosis of celiac disease.<sup>11,12</sup>

Who should undergo a biopsy? Certainly anyone in whom there is a consideration of celiac disease, irrespective of the results of the serologic tests. This applies to those undergoing EGD for weight loss, anemia, and diarrhea, as well those with an increased risk of the disease. This includes relatives of those with celiac disease,<sup>2</sup> patients with irritable bowel syndrome,<sup>13</sup> inflammatory bowel disease,<sup>14</sup> chronic liver disease,<sup>15</sup> Down syndrome,<sup>16</sup> and various autoimmune diseases, especially type I diabetes mellitus.<sup>17</sup>

Celiac disease is common, and the list of those who could possibly have celiac disease can be extensive. Thus, endoscopists should consider routine biopsy of the duodenum at EGD.<sup>18</sup> This is especially so in the era of open-access endoscopy when many of the possible disease associations

**We recommend that 4 to 6 biopsy specimens be taken from the descending duodenum, because villous atrophy in celiac disease is patchy and orientation of the specimens is variable.**

are not included in the referral indication or endoscopy unit intake history sheet. Who asks patients if they carry the diagnosis of irritable bowel syndrome prior to an EGD? Pediatric gastroenterologists typically do routine biopsies of all portions of the upper GI tract, but adult endoscopists rarely do.

In this issue of *Gastrointestinal Endoscopy*, Pais et al<sup>19</sup> address the number of biopsy specimens needed for diagnosis of celiac disease, an area that has not been addressed recently. What is known about duodenal biopsies in the diagnosis of celiac disease? First, although considered the criterion standard, they are not a perfect standard. In a large multicenter study, 10.7% of biopsy procedures were inadequate for diagnosis.<sup>20</sup> This is mainly due to inadequate orientation of the small specimens. There is no doubt that duodenal biopsy specimens are not as hardy as those from esophageal or gastric biopsy. The pieces of tissue are more readily subject to preparation artifact as well as poor orientation. Orientation of the small pieces in the endoscopy room is, to my mind, impossible. It is time consuming, requires expertise among endoscopy assistants, and is rarely worthwhile. It is a throwback to past eras when large-piece, single-capsule or suction-tube biopsy specimens were oriented by

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gastroenterologists and viewed under a dissecting microscope.<sup>21,22</sup>

Another important variable in diagnosis of celiac disease is the fact that not all endoscopic biopsy specimens are viewed and interpreted by GI pathologists. It is important to consider just who is rendering the opinion on the biopsy specimen. Not all general pathologists are aware of the spectrum of pathologic changes seen in celiac disease as originally classified by Marsh<sup>23</sup> and later by Oberhuber et al.<sup>24</sup>

There is information on the location, or site, of biopsies. Endoscopic biopsy specimens of the descending duodenum were originally shown to be as good as jejunal specimens taken by capsule or suction tube.<sup>25,26</sup> Usually, biopsy specimens are taken of the descending duodenum. However, contrary to common teaching and practice, duodenal bulb biopsy specimens appear adequate, and possibly should be taken as well. In 3 different studies they were adequate for diagnosis and may be the only site demonstrating villous atrophy.<sup>27-29</sup>

What about biopsy forceps size or type? The type of the biopsy forceps (pediatric, regular, or jumbo) has been shown to be irrelevant.<sup>26,30</sup> Jumbo forceps are not needed.

What about the number of biopsy specimens? One frequently sees patients who undergo EGD either for diagnosis or follow-up of celiac disease, and when the slides are obtained for review, only one or two biopsy specimens are on the slide. Upon review they are either not well oriented or have some kind of preparation artifact. It seems a waste of effort to subject a patient to an EGD and take only one biopsy specimen.

In a recent review we have recommended that 4 to 6 biopsy specimens be taken from the descending duodenum.<sup>1</sup> This is based on the fact that the villous atrophy in celiac disease is patchy, and orientation of the biopsy specimens is variable.<sup>27,28</sup> Patchiness of villous atrophy in celiac disease has been clearly demonstrated by magnification endoscopy,<sup>31,32</sup> especially when combined with chromoendoscopy.<sup>33</sup> Pais et al,<sup>19</sup> in their current retrospective study, have addressed this issue of the number of biopsy specimens necessary for diagnosis of celiac disease.<sup>19</sup> They demonstrated that 4 biopsy specimens established the diagnosis in 100% of their cases. This conclusion was also reached by Mee et al.<sup>26</sup> In addition, Pais et al confirmed that the disease is patchy, with variable degrees of atrophy within some patients, and that orientation of the biopsy specimens was not necessary, at least in their hands.

In conclusion, celiac disease is common and diagnosed by duodenal biopsy. Think of it and take at least 4 biopsy specimens of the descending duodenum! Maybe we should add a biopsy of the bulb?

## DISCLOSURE

*The author reports the following conflicts: P. H. R. Green is on the Speakers' Bureau of Prometheus Labs; a*

*consultant for Alvine Pharmaceuticals; and has received a clinical trial grant from Alba Therapeutics.*

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*Abbreviation: CORI, Clinical Outcomes Research Initiative.*

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