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Small Intestinal Mucosal Biopsies for Case-Finding in Celiac Disease

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Abstract A number of studies have explored the role of different serological methods along with endoscopic biopsies for celiac disease population screening as well as case finding in clinical practice. Serological testing with quantitative assays is highly sensitive with a positive predictive value for strongly positive levels of tissue transglutaminase antibodies approaching 80% or more. In a recent comparative study, endoscopic biopsies were reported to have a positive predictive value up to 100% and appear to be especially valuable in selected groups with key symptoms, including diarrhea, weight loss and anemia. Overall, studies have suggested that celiac disease occurs in about 1% of the population in some nations of Europe and the United States. However, in some symptomatic patients referred for endoscopic evaluation, added duodenal biopsy is a critical investigative tool that, in many instances, has been underutilized as a case-finding tool. Some long-term studies have also suggested that detection of celiac disease has increased, possibly due to better awareness and recognition. Others believe that a recent increase in the disease *per se* may have occurred, possibly related to environmental factors, including newly developed pharmacologic or biologic agents.

Keywords: *intestinal biopsies, celiac disease*

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1. Introduction

Serological testing has been used in clinical research studies to assess the prevalence of celiac disease in different populations, but often, these have also been used as a case-finding method in routine clinical practice. Earlier versions of serological tests suffered from limited reliability and reproducibility. However, modern assays are either semi-quantitative (eg., antibodies to endomysium), and so, potentially subject to observer bias, or quantitative (eg., antibodies to tissue transglutaminase). These appear to be readily accessible to most clinicians, and quantitative assays are better standardized and available as commercially available "kits" for use in central hospital laboratories. Based on results in several studies, celiac disease is believed to affect approximately 1% of different populations in some European nations and the United States [1,2,3,4,5].

Often biopsies are done after serological testing, to confirm sero-positive results, while sero-negative patients are not biopsied. As a result, the precise accuracy of most serological assays are not known. Many, but not all [6] sero-positive patients appear to have typical pathological changes of untreated celiac disease detailed elsewhere [7,8] but some, even with strongly positive tissue transglutaminase antibodies, have only limited or no microscopic changes in subsequent small intestinal biopsies [6]. Treatment with a gluten-free diet in symptomatic patients with moderate to severe histopathological changes usually leads to improvement permitting the conclusion that celiac disease is critically important rather than another cause that could produce similar clinical and pathological features [8].

2. Use of Endoscopic Evaluation

During clinical assessment of most patients with symptoms referable to the upper gastrointestinal tract, direct endoscopic visualization of the mucosa has become an important method of evaluation. Often, however, and unfortunately, clinical usage is limited to macroscopic evaluation alone. Some have suggested that non-performance of duodenal biopsy during this upper endoscopic examination may be contributing to limitations in diagnosing celiac disease, particularly in the United States [9]. The same investigators noted that duodenal biopsy was not done in almost 60% of patients reviewed in their center despite endoscopic evaluation and noted that several patients eventually diagnosed with celiac disease had a prior endoscopic evaluation without biopsy [10]. Although a number of macroscopic features of celiac disease have been described, such as mucosal scalloping, these are not specific [11] and other methods to enhance mucosal imaging, including magnification techniques and chromoendoscopy may add substantially to costs and time for the procedure. Moreover, other methods, such as confocal endomicroscopy, require a substantial commitment to added training. Instead, routine duodenal biopsies have been popularly used during endoscopic evaluation to

confirm the macroscopic impression of normal mucosa or determine if microscopic features of small intestinal mucosal disease, including untreated celiac disease, are present, but only limited systematic data has emerged.

3. Use of Biopsies

Prediction of celiac disease, especially in a high risk setting (eg, diarrhea, weight loss, anemia), has been considered in several extended studies. From 1982 to 2011, over a period of over 30 years, consecutive adults referred for clinical evaluation for one or more symptoms (eg., abdominal pain, heartburn, nausea, vomiting, diarrhea and/or weight loss) had elective endoscopy and duodenal biopsies done [12]. During most of this period, reliable serological methods were not available. Patients with moderate to severe architectural changes in their biopsies consistent with celiac disease (i.e., Marsh 3) were evaluated by a dietitian and treated with a gluten-free diet. Patients with minimal changes (eg., epithelial lymphocytosis alone and no significant architectural change) were excluded from analysis. Compliance with the gluten-free diet was monitored by clinical evaluation, and most patients with initially abnormal biopsies were eventually re-biopsied within two years to provide confirmation of improved mucosal architecture.

There were a total of 4008 (41.5%) males and 5657 females (58.5%) that met the criteria for this evaluation. All patients were symptomatic, but were excluded from the study if celiac disease was previously defined, if there was a referral with a positive serological test (eg., tissue transglutaminase antibodies), or if the patient was a high risk because of a family history of celiac disease [13].

Overall, a total of 234 of 9665 patients, or 2.4%, were positive for newly detected biopsy features of adult celiac disease. These included 73 of 4009 males, or 1.8%, and 161 of 5657 females, or 2.8%. If these adults were compiled together on a decade basis, females with biopsy changes were more frequently detected than males for each decade of age range [12].

These results cannot be used to support screening entire populations for celiac disease, especially now with the availability of modern serological assay methods. A more reasonable approach might be that clinical evaluation, at least to determine a cause for some key symptoms, might include duodenal biopsies as part of any contemplated endoscopic evaluation.

Support for this approach has recently been emphasized by others using both serologically-based tools as well as endoscopic biopsies in referral clinical practice [14]. In these evaluations, endoscopy alone was shown to have a high miss rate for celiac disease. At the same time, the positive predictive value of the deamidated gliadin peptide (DGP) test was 34.2%, while that for a strongly positive tissue transglutaminase antibody assay was 80%. In the same report, a strategy focused on independent predictors (eg., anemia) noted that endoscopic biopsy had a sensitivity up to 100% with an acceptable “unnecessary” biopsy rate, i.e., about 25%. Even if sero-positive patients were excluded, up to 94% sensitivity with endoscopic biopsy was recorded with “added” biopsies in 52% [14].

In another report [15], biopsies for celiac disease were done in those with reflux symptoms, prospectively recruited over a 10-year period from 2004 to 2014. In their female-predominant adult group (58.7%), 344 of 3368 patients, or 10.2%, had biopsy changes of untreated celiac disease (Marsh 3). Although reflux patients did not appear to benefit from added duodenal biopsy, this tool appeared to be exceedingly powerful if “high-risk symptoms” (eg., anemia, diarrhea, weight loss) were present. In this group, a celiac disease prevalence rate of 15.9% was recorded. Stated differently, selected, but not all patients for endoscopic evaluation will benefit from duodenal biopsies for celiac disease.

4. Time Trends and Environmental Factors

Several serologically-based studies have suggested that detection rates of celiac disease, particularly in the United States, are increasing. In large part, this may simply reflect increased physician awareness of celiac disease and more common use of endoscopic biopsy evaluation, but some reports have also raised the possibility that the incidence of the disease *per se* is increasing, possibly related to some, as yet unidentified environmental factor. Over 30 years, 2 time trends in positive celiac biopsies were recorded (12): first, a progressive fall in detection rates from 3.9% to 1.7% during the initial 20 years, 1982 to 2001 ($p<0.0002$); followed by a second, a progressive rise during the last 10 years, 2002 to 2011 ($p<0.0391$). Several confounding variables need to be considered in extended serological or biopsy defined studies, including local clinical referral patterns and application of endoscopic methods for evaluation. However, other environmental factors, such as childhood infections, cigarette use and urban pollution, changes in dietary practices, including emerging genetically-altered forms of wheat, or even medications. A wide array of widely used pharmacological and biological agents have been recorded [16] to cause sprue-like mucosal changes, including commonly prescribed non-steroidal anti-inflammatory drugs and angiotensin II receptor antagonists, including olmesartan.

5. Conclusion

Although screening large populations for celiac disease might be accomplished with serological methods, endoscopic biopsy has proven to be a powerful investigative tool for celiac disease case-finding. To date, several studies have provided direct and indirect evidence for performance of endoscopic biopsies during clinical evaluation that requires endoscopic evaluation. Patients of any age with key symptoms, including diarrhea, weight loss and anemia should be considered. Further studies are needed to elucidate other potential factors that might play a role in precipitation of celiac disease or sprue-like intestinal diseases.

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