Small Intestinal Mucosal Biopsies for Case-Finding in Celiac Disease

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Received March 12, 2015; Revised April 01, 2015; Accepted April 23, 2015

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


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 when 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,
22 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.

References

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