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Q/Is an intestinal biopsy necessary when the blood work suggests celiac disease?

EVIDENCE-BASED ANSWER

A/ IT DEPENDS ON THE ANTIBODY LEVELS in the blood work. Symptomatic patients with serologic levels of immunoglobulin A anti-tissue transglutaminase (IgA anti-tTG) or immunoglobulin G anti-deamidated gliadin peptide antibody (IgG anti-DGP) greater than 10 times the upper limits of normal—especially if they also are positive for endomysial antibodies (EMA) and human leukocyte antigen DQ2 (HLA-DQ2 or HLA-DQ8)—may not need an intestinal biopsy to confirm the diagnosis of celiac disease (strength of recommendation [SOR]: **B**, inconsistent or limited-quality cohort studies).

Patients with antibody levels lower than 10 times the upper limits of normal or who are asymptomatic most likely need an intestinal biopsy to confirm the diagnosis (SOR: **B**, inconsistent or limited-quality cohort studies).

Evidence summary

A 2013 Belgian prospective study of 104 non-IgA–deficient adults and children diagnosed with celiac disease and 537 adults and children without celiac disease evaluated the accuracy of 4 manufacturers' serologic tests for IgA anti-tTG.[1] All patients underwent serologic testing followed by a diagnostic biopsy. A Marsh type 3 or greater lesion on duodenal biopsy was considered diagnostic for celiac disease.

Anti-tTG levels greater than 10 times the manufacturer-recommended level for a positive test (cut-off) were associated with a likelihood ratio of 111 to 294 (depending on the manufacturer) of positive biopsy. Post-test probabilities were calculated based on various pretest probabilities using an anti-tTG level of greater than 10 times the cut-off (**TABLE**[1]).

Investigators also obtained IgG anti-DGP levels from 2 of the manufacturers.[1] Likelihood ratios increased along with antibody levels. Ratios of 80 and 400, depending on the manufacturer, were found at IgG anti-DGP levels 10-fold greater than the cut-off. Pre- and post-test probabilities weren't calculated.

Positive predictive value rises with antibody levels

A 2013 retrospective study evaluated the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition's recommendation to forego intestinal biopsy in non-IgA–deficient, symptomatic children and adolescents with positive IgA anti-tTG levels greater than 10 times the cut-off value, positive EMA, and positive HLA-DQ2 or HLA-DQ8.[2]

Overall, 153 symptomatic patients referred to the gastroenterology unit met these criteria. The age range was 9 months to 14.6 years (mean 4 years). All but 3 of the patients had Marsh 2 or greater lesions with biopsy-confirmed diagnoses of celiac disease. The remaining 3 developed biopsy-positive celiac disease on follow-up. The positive predictive value of combined serologic testing in this small selected patient population was 100%.

A 2013 retrospective study of 2477 symp-

TABLE

Post-test probability of celiac disease in patients with an elevated anti-tissue transglutaminase antibody level[1]

	Post-test probability by manufacturer (for antibody level >10 times recommended cut-off for a positive test)			
Pretest probability	Nova	Bio-Rad	Thermo Fisher	Genesis
1%*	53%	56%	75%	64%
7%	89%	90%	96%	93%
14%	95%	95%	98%	97%
20%	97%	97%	99%	98%

*Asymptomatic patients.

tomatic adults (older than 18 years) who received diagnostic testing for celiac disease at 2 academic institutions in Cleveland, Ohio, evaluated the predictive value of IgA anti-tTG and EMA. Of the patients, 610 (25%) had abnormal serologic tests, and 240 (39%) underwent endoscopy with biopsy.

A total of 50 patients (21%) had biopsy results consistent with celiac disease, defined as a Marsh 3 lesion or greater.[3] An IgA anti-tTG level of 118 U/mL (5.9-fold the upper limit of normal on the test) had a positive predictive value of 86.4% with a false-positive value of 2%. An EMA titer greater than 1:160 when IgA anti-tTG was between 21 and 118 U/mL had a positive predictive value of 83%.

Antibody levels 10 times normal show 100% positive predictive value

A 2008 retrospective study of one manufacturer's IgA anti-tTG serologic test sought to establish the serologic antibody level at which the positive predictive value was 100%.[4] Overall, 148 people, 15 years and older, with a positive IgA anti-tTG before biopsy or within 21 days of biopsy were included.

Of the patients biopsied, 139 (93%) had positive biopsies of Marsh 2 or greater and were diagnosed with celiac disease. Using a cut-off of 3.3 and 6.7 times the upper limit of normal, investigators calculated a positive predictive value of 95% and 98%, respectively.

A cut-off of 10 times the upper limit of normal or greater had a positive predictive value of 100%. The highest level of IgA anti-tTG in a patient who didn't have celiac disease on biopsy was 7.3 times the upper limit of normal. JFP

Symptomatic patients with serologic levels of certain antibodies greater than 10 times the upper limits of normal may not need an intestinal biopsy to confirm the diagnosis of celiac disease.

References

1. Vermeersch P, Geboes K, Mariën G, et al. Defining thresholds of antibody levels improves diagnosis of celiac disease. *Clin Gastroenterol Hepatol*. 2013;11:398-403;quiz e32.
2. Klapp G, Masip E, Bolonio M, et al. Celiac disease: The new proposed ESPGHAN diagnostic criteria do work well in a selected population. *J Pediatr Gastroenterol Nutr*. 2013;56:251-256.
3. Wakim-Fleming J, Pagadala MR, Lemyre MS, et al. Diagnosis of celiac disease in adults based on serology test results, without small-bowel biopsy. *Clin Gastroenterol Hepatol*. 2013;11:511-516.
4. Hill PG, Holmes GK. Coeliac disease: a biopsy is not always necessary for diagnosis. *Aliment Pharmacol Ther*. 2008;27:572-577.