Can serology alone reliably diagnose adult coeliac disease?

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The diagnosis of coeliac disease traditionally relies on a combination of serological testing and duodenal biopsy. But the prospect of replacing invasive biopsy with a simple blood test holds considerable appeal for both patients and clinicians. The question remains whether current serological assays offer sufficient diagnostic precision to stand alone, particularly given the complexities of villous atrophy aetiologies.

KEY TAKEAWAYS

- The Pivot: Serology offers high diagnostic accuracy for coeliac disease, but it does not eliminate the need for duodenal biopsy in all cases.
- The Data: Up to 5% of newly diagnosed coeliac patients present with negative serology, necessitating biopsy for diagnosis and differential exclusion.
- The Action: Clinicians should continue to use duodenal biopsy to confirm coeliac disease, especially when serology is negative or when other causes of villous atrophy are suspected.

Coeliac disease, an immune-mediated enteropathy triggered by gluten ingestion in genetically predisposed individuals, manifests with a spectrum of clinical presentations, from classic malabsorption to subtle symptoms. Definitive diagnosis has long hinged on demonstrating characteristic villous atrophy in duodenal biopsies, alongside positive serological markers. But the invasiveness of endoscopy and biopsy prompts ongoing debate about whether serology alone can suffice for diagnosis in adults, mirroring paediatric guidelines. The challenge lies in the diagnostic accuracy of serological tests and the existence of other conditions that mimic coeliac pathology.1,2

A prospective study published in European Journal of Gastroenterology & Hepatology examined the diagnostic accuracy of coeliac serological tests.2 The study enrolled patients presenting with symptoms suggestive of coeliac disease, evaluating their serological profiles alongside duodenal biopsies. The aim was to quantify the performance of various serological markers, including anti-tissue transglutaminase (tTG) antibodies, anti-endomysial antibodies (EMA), and anti-deamidated gliadin peptide (DGP) antibodies, against the gold standard of histological changes in the small bowel. The investigators sought to determine if a threshold of serological positivity could reliably predict villous atrophy, thereby potentially obviating the need for biopsy in certain patient subsets. The study population included both symptomatic and asymptomatic individuals at risk for coeliac disease, ensuring a broad representation of clinical scenarios. Patients underwent comprehensive clinical assessment, blood tests for serology, and upper endoscopy with multiple duodenal biopsies, typically four to six samples from the second part of the duodenum and at least one from the duodenal bulb. Histological assessment followed modified Marsh criteria, classifying villous architecture from normal to severe atrophy.2

The Limits of Serology

The diagnostic accuracy of coeliac serological tests, while generally high, does not reach 100%. Up to 5% of patients with newly diagnosed coeliac disease present with negative serology.1,2,3 This seronegative presentation complicates diagnosis significantly, as clinicians cannot rely solely on blood tests to identify these individuals. For these patients, duodenal biopsy becomes not just a confirmatory test, but the primary diagnostic tool. The absence of positive serology in the presence of villous atrophy necessitates a thorough investigation to rule out other potential causes, a critical step that serology cannot perform.1,2,3

The reasons for seronegativity in confirmed coeliac disease are varied. Some patients may have IgA deficiency, which can lead to false-negative results for IgA-based tTG and EMA tests. In such cases, IgG-based assays for tTG or DGP are often employed, but their sensitivity and specificity can differ. Other factors, such as early-stage disease with minimal mucosal damage, strict adherence to a gluten-free diet prior to testing, or rare genetic variations, can also contribute to seronegative presentations. The challenges in diagnosing primary immunodeficiency diseases also highlight the complexities of immune-mediated conditions.1,2

Beyond Coeliac: Other Causes of Villous Atrophy

Villous atrophy, the hallmark histological finding in coeliac disease, is not pathognomonic. Numerous other conditions can cause similar mucosal changes, making duodenal biopsy indispensable for differential diagnosis. These aetiologies typically fall into five broad categories: immune-mediated, infectious, iatrogenic, inflammatory, and infiltrative.1,3 Without a biopsy, distinguishing coeliac disease from these other conditions is impossible, potentially leading to misdiagnosis and inappropriate treatment. The refinement of diagnostic scores in conditions like cirrhosis shows the

importance of precise diagnostic tools.1,3

Immune-mediated causes of villous atrophy include autoimmune enteropathy, common variable immunodeficiency, and graft-versus-host disease. These conditions often present with symptoms similar to coeliac disease, but their management strategies differ significantly. Infectious causes, such as giardiasis, cryptosporidiosis, and tropical sprue, can also induce villous blunting. A case report highlighted the diagnostic challenges of tropical sprue, an old but often unrecognized disease that causes villous atrophy and malabsorption, particularly in individuals with a history of travel to endemic regions.3 This condition requires specific antibiotic treatment, not a gluten-free diet.3

Iatrogenic causes of villous atrophy are increasingly recognized. Certain medications, including olmesartan, mycophenolate mofetil, and non-steroidal anti-inflammatory drugs (NSAIDs), can induce enteropathy with villous changes. A rare but notable iatrogenic cause was reported in a 39-year-old male with end-stage renal failure and pancreatic insufficiency.1 This patient, treated with high-dose lanthanum carbonate for hyperphosphatemia, developed duodenal denudated mucosa with complete villous atrophy. Biopsy revealed accumulation of foreign material in mucosal histiocytes, identified as lanthanum deposits.1 This case illustrates a unique iatrogenic and infiltrative aetiology for villous atrophy, emphasizing the need for a multidisciplinary approach in managing dialysis patients and understanding the potential side effects of phosphate binders. The long-term consequences of lanthanum deposition in tissue remain unknown, adding another layer of complexity to diagnosis and management.1

Inflammatory conditions like Crohn's disease affecting the small bowel, and infiltrative diseases such as lymphoma or amyloidosis, can also cause villous atrophy. Each of these conditions requires distinct diagnostic workup and therapeutic interventions. For instance, diagnosing Crohn's disease involves endoscopic evaluation with biopsies, imaging studies, and sometimes capsule endoscopy. Lymphoma diagnosis requires specific immunohistochemical staining on biopsy samples. The comparison of bone biopsy to ulcer swab in diabetic foot osteomyelitis further illustrates the ongoing debate about optimal diagnostic methods in various clinical settings.1,3

The Role of Biopsy in Comprehensive Diagnosis

Given the potential for seronegative coeliac disease and the wide array of differential diagnoses for villous atrophy, duodenal biopsy remains a cornerstone of adult coeliac diagnosis. It provides direct histological evidence of mucosal damage, allows for assessment of severity, and, most importantly, enables the exclusion of other conditions that mimic coeliac disease. The biopsy also offers an opportunity to identify complications such as enteropathy-associated T-cell lymphoma (EATL), a rare but serious complication of long-standing coeliac disease.1,2,3

Still, the procedure is invasive, carries risks, and incurs costs. For this reason, guidelines for paediatric coeliac disease have evolved to allow diagnosis based on highly elevated tTG-IgA levels (typically >10 times the upper limit of normal) and positive EMA, without requiring biopsy, provided specific clinical criteria are met. This approach is not universally applied to adults, primarily due to the higher prevalence of other villous atrophy causes in adult populations and the greater likelihood of atypical presentations. The promise of non-invasive markers in MASH diagnosis represents a similar effort to reduce reliance on biopsy in other fields.2

The utility of serological tests in monitoring adherence to a gluten-free diet and assessing mucosal healing is also well-established. Declining antibody titres after initiating a gluten-free diet indicate therapeutic response, while persistently elevated levels may suggest poor adherence or refractory disease. But this monitoring role is distinct from initial diagnosis, where the stakes are higher for accurate differentiation from other conditions. The emerging role of

urinary exosomes in kidney disease diagnosis also points to the potential for less invasive monitoring in the future.2
The open-label design of many diagnostic accuracy studies is an obvious caveat. While blinding pathologists to serology results is standard practice, the clinical context can sometimes influence interpretation. The prevalence of coeliac disease and its mimics varies geographically, meaning diagnostic algorithms developed in one population may not be directly transferable to another. The challenge of diagnosing conditions like Lyme disease, where early diagnosis is often missed, highlights the need for robust diagnostic pathways tailored to specific contexts. The Oxford Handbook of Gastroenterology & Hepatology provides a concise guide to these complex diagnostic pathways.2,3
The current evidence base does not support replacing duodenal biopsy with serology alone for adult coeliac disease diagnosis. While serological tests are highly valuable as screening tools and for monitoring, the need to identify seronegative cases and differentiate coeliac disease from other causes of villous atrophy mandates the continued use of biopsy. Future research might explore advanced non-invasive imaging techniques or novel biomarkers that could provide histological-level detail without direct tissue sampling, but until then, the biopsy remains indispensable.1,2,3

CLINICAL IMPLICATIONS

For clinicians, the message is clear: do not abandon the duodenal biopsy for adult coeliac diagnosis. While serological tests are excellent screening tools, they are not infallible. The 5% of patients with seronegative coeliac disease, coupled with the myriad other causes of villous atrophy, mean that a biopsy is often the only way to secure an accurate diagnosis and prevent misdirection down an inappropriate treatment path.
The case of lanthanum deposition causing villous atrophy serves as a stark reminder of the diagnostic complexities. It shows that what appears to be coeliac disease on initial presentation could be an entirely different, iatrogenic condition requiring a change in medication, not a gluten-free diet. Relying solely on serology risks missing these important differential diagnoses, with potentially serious consequences for patient management.
Industry efforts should focus on developing more precise, non-invasive markers that can reliably distinguish coeliac disease from its mimics, even in seronegative cases. Until such advancements emerge, the current diagnostic algorithm, which integrates both serology and biopsy, remains the most robust approach. Patients deserve a definitive diagnosis, and that often means an endoscopy.

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