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Serological and Histological Concordance in the Diagnosis of Adult Coeliac Disease: A Review of Multicentre Evidence

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Abstract

Coeliac disease in adults is diagnosed by agreement between a blood test and a duodenal biopsy, and the question of whether the biopsy can be omitted when the antibody titre is high enough has been settled in children and remains contested in adults. Both halves of the comparison turn out to be less firm than the phrase gold standard suggests.

Objectives: *To review the multicentre evidence on concordance between coeliac serology and duodenal histology in adults: how well a high antibody titre predicts villous atrophy, how that prediction depends on the population tested, how reproducibly the histology is graded, and what follows for the no-biopsy approach.*

Material and Methods: *Narrative review of multicentre cohorts, systematic reviews and meta-analyses, interobserver agreement studies and society guidelines indexed in PubMed and the major gastroenterology journals. Studies were eligible if they reported the performance of serology against duodenal histology in a defined adult population, the reproducibility of histological grading, or guideline positions on diagnosis. No new patient data were generated; every accuracy estimate quoted is one published by the original investigators.*

Results: *Pooling 18 studies covering 12,103 participants from 15 countries, IgA anti-tissue transglutaminase at or above ten times the upper limit of normal had a sensitivity of 51 per cent (95% CI 42-60) and a specificity of 100 per cent (95% CI 98-100), with a summary area under the curve of 0.83. Positive predictive value varied with the population tested, from 65 per cent where prevalence was 1 per cent to 99 per cent where it was 40 per cent. A three-cohort study reported sensitivity of 54.0 per cent, specificity of 90.0 per cent and positive predictive value of 98.7 per cent in a specialist clinic population. On the histological side, mean kappa between pathologist pairs was 0.35 for the Marsh-Oberhuber classification and 0.55 for a simplified three-tier system.*

Conclusion: *Discordance between serology and histology arises from both directions. A high titre is close to specific but misses around half of cases, so it can confirm but not exclude. Histology, the nominal reference standard, is graded with only fair agreement between pathologists at the mild end of the spectrum. The no-biopsy approach is defensible where pretest probability is high and indefensible as a population screening tool, and the difference is entirely a function of who is tested.*

Abbreviations: *CD – Coeliac Disease, tTG – Tissue Transglutaminase, IgA-tTG – Immunoglobulin A Anti-Tissue Transglutaminase, EMA – Endomysial Antibody, DGP – Deamidated Gliadin Peptide, ULN – Upper Limit of Normal, IEL – Intraepithelial Lymphocyte, Vi:Cr – Villus Height to Crypt Depth Ratio, PPV – Positive Predictive Value, NPV – Negative Predictive Value, AUC – Area Under the Curve, HLA – Human Leukocyte Antigen.*

Keywords: *Coeliac Disease; Tissue Transglutaminase; Duodenal Biopsy; No-Biopsy Approach; Diagnostic Concordance*

Introduction

The diagnosis of coeliac disease in adults rests on two measurements made in different laboratories by different specialists: a serum antibody titre, most commonly IgA against tissue transglutaminase, and the histological appearance of duodenal biopsies taken at endoscopy [1,2]. Current guidelines for adults require both, with histology treated as the reference standard [1,3].

In children that requirement has been relaxed. Paediatric guidance now permits diagnosis without biopsy where the antibody titre is at least ten times the upper limit of normal and endomysial antibodies are positive on a separate sample [2], a position supported by a prospective multicentre study reporting a positive predictive value above 99 per cent [4].

Whether the same applies to adults has been the central question of the past decade, and it is a question about concordance rather than about either test in isolation. If serology and histology agreed closely, the biopsy would be redundant. They do not agree closely, and the interesting part is why [5,6].

Two sources of discordance run in opposite directions. Serology at a high threshold is highly specific but insensitive, so a substantial share of patients with villous atrophy fall below the cutoff [5,6]. Meanwhile the histological reference standard is itself imperfectly reproducible, particularly for the mild changes that generate most diagnostic uncertainty [1,7]. The aim of this review is to set out the multicentre evidence on both, and what follows for practice.

Material and Methods

Search strategy: PubMed and the archives of the major gastroenterology and pathology journals were searched for studies of diagnostic concordance in adult coeliac disease. Search terms combined coeliac disease and celiac disease with tissue transglutaminase, endomysial antibody, duodenal biopsy, villous atrophy, Marsh classification, no-biopsy, interobserver agreement and diagnostic accuracy. Reference lists of retrieved guidelines and meta-analyses were screened by hand for further primary sources.

Eligibility: Studies were included if they reported the performance of serological testing against duodenal histology in a defined adult population; the reproducibility of histological grading between observers; or society guidance defining current diagnostic requirements. Multicentre cohorts and pooled analyses were included preferentially. Paediatric studies are cited where they established the approach now under consideration in adults and are identified as such.

Data extraction and handling: Design, sample size, assay, threshold applied, reference standard and reported accuracy estimates with confidence intervals were extracted as published. Accuracy figures are reported alongside the population in which they were obtained, because predictive values in this field depend more on pretest probability than on the assay. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What a high titre predicts: The most comprehensive synthesis pooled 18 studies covering 12,103 participants from 15 countries. IgA-tTG at or above ten times the upper limit of normal had an overall sensitivity of 51 per cent (95% CI 42-60) and an overall specificity of 100 per cent (95% CI 98-100) for coeliac disease, with a summary area under the receiver operating characteristic curve of 0.83 (95% CI 0.77-0.89) and moderate between-study heterogeneity at $I^2 = 30.3$ per cent (Figure 2) [6].

A specificity of 100 per cent with a sensitivity of 51 per cent describes a test that confirms but cannot exclude. Roughly half of adults with biopsy-proven disease do not reach the threshold, so a titre below it carries essentially no reassurance and the biopsy remains necessary in that group [5,6].

The same test performs differently in different clinics: The critical finding for practice is that positive predictive value tracked the prevalence of disease in the population tested rather than any property of the assay. It was 65 per cent where prevalence was 1 per cent, 88 per cent at 4 per cent, 95 per cent at 10 per cent and 99 per cent at 40 per cent (Figure 1) [6]. A threshold that is safe in a specialist coeliac clinic is therefore unsafe in unselected primary care, using the identical assay and cutoff.

A three-cohort study made the same point by design, comparing a specialist clinic population of 740 patients, 532 patients referred for endoscopy with low suspicion of coeliac disease, and 145 patients with raised titres from multiple international sites, against Marsh 3 histology as reference. In the specialist cohort, sensitivity was 54.0 per cent, specificity 90.0 per cent, positive predictive value 98.7 per cent and negative predictive value 12.5 per cent (Figure 3) [5]. The negative predictive value is the figure to dwell on: in a population enriched for disease, a titre below the threshold tells the clinician almost nothing.

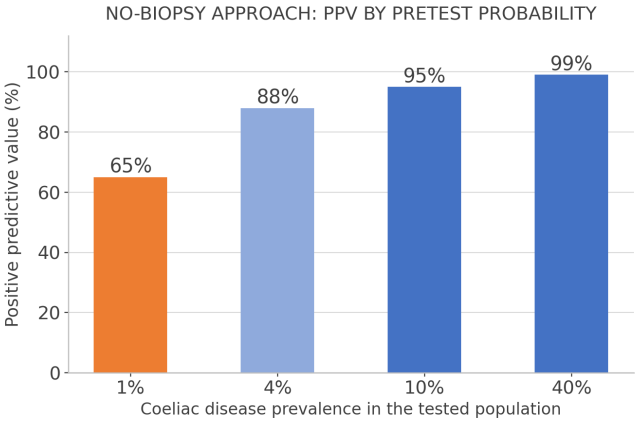

Figure 1: Positive predictive value of the no-biopsy threshold by coeliac disease prevalence in the population tested [6]

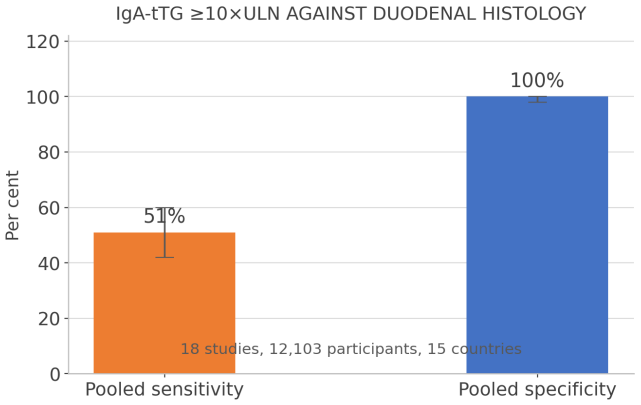

Figure 2: Pooled sensitivity and specificity of IgA-tTG at ten times the upper limit of normal against duodenal histology [6]

Study	n	Design	Principal reported finding
Corazza et al. 2007 [7]	60	Observer	Kappa 0.35 Marsh-Oberhuber vs 0.55 simplified
Werkstetter et al. 2017 [4]	—	Multicentre	No-biopsy PPV above 99% in children
Husby et al. 2020 [2]	—	Guideline	Biopsy may be omitted in selected children
Penny et al. 2021 [5]	1,417	Three cohorts	PPV 98.7% but NPV only 12.5% in specialist clinic
Shiha et al. 2024 [6]	12,103	Meta-analysis	Sensitivity 51%, specificity 100%; PPV varies with prevalence
Al-Toma et al. 2025 [1]	—	Guideline	Substantial interobserver variability acknowledged

Table 1: Principal studies reviewed, with design and the finding as reported by the original investigators

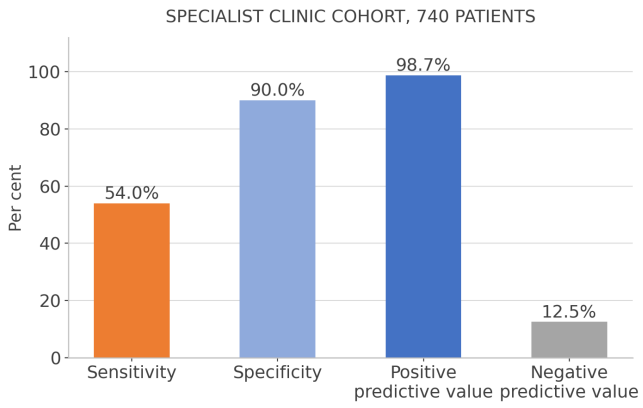

Figure 3: Performance of the ten-fold threshold against Marsh 3 histology in a specialist clinic cohort of 740 patients [5]

The reference standard is not fixed either: Concordance studies treat histology as truth, which understates the problem. In a study in which 60 biopsy sets were circulated to six blinded pathologists on two separate occasions, mean kappa between pathologist pairs was 0.35, conventionally described as fair agreement, for the Marsh-Oberhuber classification, and 0.55, moderate agreement, for a simplified three-tier system (Figure 4) [7]. Neither reaches the threshold usually taken to indicate substantial agreement, and comparable variability has been documented in paediatric series [8].

Current adult guidance states the problem directly, noting substantial interobserver variability in histological interpretation, particularly for mild or borderline changes at Marsh I to II, and recommending that histological assessment be performed together with clinical and serological information rather than in isolation [1]. Paediatric guidance makes the same observation and recommends re-cutting biopsies or seeking a second opinion where serology and histology disagree [2].

Two technical factors compound this. Only about half of biopsies in one agreement study were considered optimally oriented, and Marsh-Oberhuber grading can only be assigned reliably with correct orientation [2]. Guidance therefore specifies that pathology reports record the number of biopsies received, the quality of orientation, the villus height to crypt depth ratio, the intraepithelial lymphocyte count and the Marsh stage, rather than a grade alone [1]. Sampling adds a further layer: biopsies from the duodenal bulb increase diagnostic yield over distal duodenal sampling alone, and multicentre paediatric series established this before it was adopted in adults [13,14].

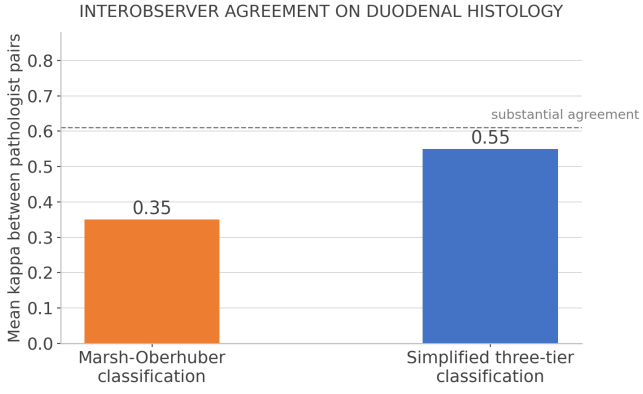

Figure 4: Mean interobserver agreement between six pathologists using two grading systems on the same 60 cases [7]

Source of discordance	Direction	What the evidence shows
Titre below threshold, atrophy present	Serology negative	Around half of confirmed cases; sensitivity 51% [6]
Titre above threshold, no atrophy	Serology positive	Rare in enriched populations; PPV 98.7% [5]
Same slides, different grade	Histology unstable	Kappa 0.35 for Marsh-Oberhuber between pairs [7]
Same assay, different clinic	PPV shifts	65% at 1% prevalence against 99% at 40% [6]

Table 2: The four ways serology and histology come apart, and what the published evidence reports for each

Discussion

The evidence supports a position that is neither the traditional one nor the enthusiastic one. Serology at ten times the upper limit of normal is close to perfectly specific, so a patient who exceeds it and has compatible symptoms almost certainly has the disease, and in a specialist setting the biopsy adds little [5,6]. But the same test misses about half of cases, so it cannot function as a rule-out, and the biopsy remains necessary for everyone below the threshold [6].

The more consequential point is that positive predictive value is a property of the population, not of the assay. Moving the same test from a clinic where 40 per cent of those tested have the disease to a setting where 1 per cent do takes the predictive value from 99 to 65 per cent [6]. A protocol written for one setting and applied in the other will misdiagnose a substantial number of people, and nothing about the laboratory report will signal that.

What discordance should trigger

Where the two disagree, the reflex should not be to trust one over the other by default. Guidance recommends re-cutting the biopsy or obtaining a second histological opinion when serology is strongly positive but histology is not diagnostic, precisely because grading of mild change is unreliable [1,2,7]. Conversely, villous atrophy with negative serology raises the possibility of causes other than coeliac disease and warrants a different investigation rather than a presumptive diagnosis [1,9]. A prospective series of 200 adults with seronegative villous atrophy assembled over fifteen years found a broad differential, and non-coeliac enteropathies account for a meaningful share of atrophy seen in contemporary practice [9,10,11]. Lymphocytic enteritis without atrophy in first-degree relatives occupies a further grey zone [12].

The reporting standard matters here more than it usually does. A report that gives only a Marsh grade conveys less than one that records biopsy number, orientation quality, villus to crypt ratio and lymphocyte count, because it is precisely those components that determine whether the grade is reliable [1].

Study limitations

The limitations belong to the underlying literature. In the pooled analysis only one of 18 included studies had a low risk of bias across all domains, and between-study heterogeneity was moderate [6]. Most cohorts were assembled in secondary or tertiary care, so the prevalence estimates that drive predictive value are not those of primary care [5,6]. Serological assays differ between laboratories, and normalising results as multiples of an assay-specific upper limit is a pragmatic device rather than a true standardisation [5]. Interobserver studies circulate selected slides to interested

pathologists, which may overstate the agreement achievable in routine reporting [7]. Much of the supporting evidence for the no-biopsy approach originates in paediatric populations, in whom pretest probability and the spectrum of alternative diagnoses both differ [2,4].

Two gaps deserve naming. No randomised comparison has tested a no-biopsy pathway against biopsy confirmation in adults with clinical outcomes as the endpoint, so the safety of omitting endoscopy is inferred from accuracy rather than demonstrated [6]. And no study reviewed here reports what happens to the patients who are diagnosed serologically and later prove not to have the disease, which is the population the approach puts at risk of a lifelong dietary restriction they do not need [1,6].

Conclusion

Serology and duodenal histology in adult coeliac disease agree well at the top of the antibody range and poorly elsewhere. An IgA-tTG titre at ten times the upper limit of normal is essentially specific, with pooled specificity of 100 per cent, but detects only about half of cases, so it confirms and cannot exclude. Its positive predictive value is governed by who is being tested, ranging from 65 to 99 per cent across plausible prevalences, which means a no-biopsy protocol is not transferable between settings. The histological reference standard is itself graded with only fair agreement between pathologists at the mild end. The practical conclusion is to reserve the no-biopsy route for high pretest probability, to biopsy everyone below the threshold, and to treat discordance as an indication for review of the slides rather than for a default preference between the two tests.

Acknowledgements

We record our debt to the multicentre study groups and to the pathology panels whose published work is drawn together in the pages that follow.

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Conflict of Interest

The authors have nothing to disclose in this regard.

Ethics Statement

What follows is a synthesis of material already in print. No fresh patient records were consulted and nobody was recruited, so the work fell outside the remit of an ethics committee.

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