Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests)

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CRD summary
This review concluded that human recombinant tissue transglutaminase antibody was the preferred test for excluding coeliac disease. These conclusions were not supported by the results presented, which showed very little difference in the accuracy of the two tests.

Authors' objectives
To compare the accuracy of the endomysial antibody (EMA) and tissue transglutaminase tests (tTG) for the diagnosis of coeliac disease.

Searching
MEDLINE was searched up to September 2005; the search terms were 'tTG' and 'EMA'. The reference lists of selected articles were screened for additional relevant studies. Only peer-reviewed studies published in the English language were included.

Study selection
Study designs of evaluations included in the review
No inclusion criteria relating to the study design were specified. It was unclear whether the studies used a diagnostic case-control or cohort design.

Specific interventions included in the review
Studies had to evaluate both the EMA and tTG antibody tests. The specific tTG assays investigated were the Eu-tTG, Celikey, Quanta-lite and in-house tests. Sources of antigens for the EMA tests included human recombinant tissue and guinea pigs.

Reference standard test against which the new test was compared
All patients with coeliac disease had to have this confirmed using biopsy, and the biopsy criteria for diagnosis had to be given. It also had to be clearly reported which controls were biopsy negative and which had not been biopsied. The histological criteria for diagnosing coeliac disease was partial or more severe villous atrophy in the majority of studies; other criteria included total villous atrophy or an abnormality ranging from an increase in intraepithelial lymphocytes alone to total villous atrophy.

Participants included in the review
Studies of patients with untreated coeliac disease and controls were eligible for inclusion. The studies were conducted in adults, children or mixed populations.

Outcomes assessed in the review
No inclusion criteria relating to the outcomes were specified. Sensitivity and specificity were the primary outcomes reported.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
The authors did not state how many reviewers performed the data extraction. The sensitivity and specificity of the EMA and tTG antibody tests were calculated for each study. For each study it was noted which of the tests gave the higher estimates of sensitivity and specificity. Fourteen authors were contacted to ascertain the use of serology to detect coeliac patients.

Methods of synthesis
How were the studies combined?
The number of studies in which each test gave the higher sensitivity and the higher specificity was added up. The pooled sensitivity and specificity, along with 95% confidence intervals (CIs), for EMA and tTG were calculated using simple fixed-effect pooling. Pooled positive and negative likelihood ratios were calculated from the pooled sensitivities and specificities.

How were differences between studies investigated?
Heterogeneity was not formally assessed. The pooled sensitivity and specificity were calculated separately for different types of tests, for studies of adults, and for those using commercial tests compared with in-house tests.

Results of the review
Thirty-four studies (13,134 patients) were included. Some studies assessed more than one type of EMA test.

Most studies did not provide sufficient details to determine whether ascertainment bias had been avoided (i.e. whether the EMA or tTG tests were used to identify coeliac patients for inclusion). The authors stated that most control groups consisted of patients in whom coeliac disease was suspected.

The sensitivities of both the tTG antibody and EMA tests ranged from 70 to 100%. The specificity of the tTG test ranged from 91 to 100%, and that of the EMA test ranged from 90 to 100%. The pooled sensitivity for the EMA test (34 studies) was 93% (95% CI: 92.1, 93.8) and the pooled specificity was 99.7% (95% CI: 99.5, 99.8). The estimates were similar when analysed separately for studies that used monkey oesophagus and human umbilical cord, and for adults alone. The pooled sensitivity for all tTG studies (42 studies) was 92.8% (95% CI: 91.9, 93.6) and the pooled specificity was 98.1% (95% CI: 97.8, 98.4). Recombinant tissue tTG (rhtTG) (19 studies) showed slightly higher pooled sensitivity and specificity than guinea pig tTG (gptTG) (23 studies): the pooled sensitivity was 93.8 (95% CI: 92.8, 94.7) for rhtTG and 90.4% (95% CI: 88.8, 91.9) for gptTG; the pooled specificity was 98.7% (95% CI: 98.5, 98.9) for rhtTG and 92.4% for gptTG (95% CI: 90.8, 93.8).

Head-to-head comparisons of EMA and tTG showed that EMA had higher sensitivity in 48% of studies and higher specificity in 62% of studies, while tTG had higher sensitivity in 28% of studies and higher specificity in 17%; in all other studies the estimates were equal. When only rhtTG was considered, EMA showed better sensitivity in 28% of studies and better specificity in 56%, while rhtTG showed better sensitivity in 44% of studies and higher specificity in 22%; in all other studies the estimates were equal.

Authors' conclusions
The EMA test had greater specificity than the tTG antibody test, whereas the tTG test had greater sensitivity. The rhtTG test antibody test was therefore the preferred test for screening for coeliac disease in asymptomatic people.

CRD commentary
This review suffered from a number of limitations. Whilst the review question was focused and supported by defined inclusion criteria, it was unclear whether any criteria relating to the outcomes were applied: only studies that reported sensitivity and specificity were included but it was unclear whether this was a selection criteria. The literature search was limited to one electronic database and only studies published in English were eligible for inclusion. It is therefore likely that relevant studies had been missed and that the review may be subject to publication and language bias. No details of the review process were reported, so it was unclear whether appropriate steps were taken to minimise bias. A
formal quality assessment was not undertaken and no methodological details of the primary studies were reported; it was therefore not possible to determine the reliability of the results reported.

A limited analysis, which did not include an appropriate investigation of heterogeneity, was undertaken. The authors’ conclusions were not supported by the results presented: there were only very small differences in pooled estimates between the two tests and these were not sufficient to recommend the use of one test above the other, especially given the heterogeneity between the studies. The authors’ conclusions also contained recommendations for the screening of asymptomatic individuals, but since none of the studies included in this review appear to have been conducted in such populations it is unclear whether the results can be applied to this setting. Overall, the findings of the review do not appear reliable.

Implications of the review for practice and research
Practice: The authors stated that the rhtTG antibody test is the preferred test for screening for coeliac disease in asymptomatic people and that the EMA test can be used to confirm coeliac disease in patients in whom biopsy is precluded. However, these statements are not supported by the data presented.

Research: The authors did not state any implications for further research.

Bibliographic details
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Other publications of related interest
This additional published commentary may also be of interest. Rangnekar AS, Chey WD. Review: tissue transglutaminase test is almost as accurate as endomysial antibody test for diagnosis of coeliac disease. Evid Based Med 2007;12:24.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.