Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus

J Dretzke, C Cummins,* J Sandercock, A Fry-Smith, T Barrett and A Burls

Department of Public Health and Epidemiology, University of Birmingham, UK

* Corresponding author

Executive summary

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Aim of the review

The aim of this review was to determine the role of autoantibody tests for autoimmune diseases in children with newly diagnosed type 1 diabetes mellitus.

Background

Type 1 diabetes mellitus is one of the most common severe chronic diseases to occur in childhood and adolescence. There is a genetic predisposition towards type 1 diabetes, which also predisposes patients to other autoimmune diseases such as coeliac disease, thyroid disease, Addison’s disease (adrenal insufficiency), vitiligo, alopecia and gastric autoimmunity. The association of autoantibodies with disease in the target tissues suggests that there may be a role for autoantibody testing in screening for autoimmune diseases, particularly in at-risk populations such as those with type 1 diabetes.

We used the UK National Screening Committee (NSC) criteria to identify the two most important conditions associated with type 1 diabetes in children, and found that both coeliac disease and thyroid disease met at least some of the criteria. There are detectable antibodies that are markers for both conditions, and both conditions can be present in the patient and do harm before they are detected clinically.

Thyroid disease is the most common autoimmune disease in children with diabetes and can lead to severe morbidity. If overt hypothyroidism is left untreated in type 1 diabetes, metabolic control of the diabetes itself may be complicated, while untreated hypothyroidism in a child may result in the child’s genetic growth potential not being realised. The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend testing for thyroid disease at the time of initial diagnosis as a baseline or to uncover asymptomatic thyroid disease, with repeat testing if a child becomes symptomatic or has high titres of antibodies.

Coeliac disease is an inflammatory disease of the upper small intestine that results in malabsorption and other consequent systemic problems. Serum antibody tests have been used as screening tests for coeliac disease both in the general population and in at-risk groups. Coeliac disease is treated by a lifelong gluten-free diet, and in most patients symptoms and gut pathology resolve. The ISPAD guidelines for juvenile diabetes state that the need for and frequency of screening tests is controversial.

Rationale for review

Sufficient evidence has been presented in the report to indicate that thyroid autoantibody tests are unlikely to be cost-effective for screening purposes relative to thyroid function tests. A systematic review of the test characteristics of autoantibody tests for coeliac disease has been carried out, as the use of autoantibody tests for screening purposes meets several of the NSC screening criteria.

Decision-analytic model

In order to inform the review further, we developed a decision-analytic model to estimate the costs and benefits of a single screening episode for coeliac disease at the time of diagnosis of type 1 diabetes in childhood. The model considered a number of screening strategies, including no screening, use of a single antibody test or a combination of antibody tests with or without confirmatory biopsy in those testing positive and a policy of biopsy testing of all children.

Survey of current practice

In order to inform the decision-analytic model in this report and prioritisation of future research concerning other autoantibody screening in children with diabetes, a national survey of current practice was also undertaken.

Methods of the systematic review

Search strategy

MEDLINE, EMBASE and the Cochrane Library were searched using appropriate search filters. Citation lists of included studies
were scanned and relevant professional and patient websites reviewed. Laboratories and manufacturers were contacted in order to identify ongoing or unpublished research.

Inclusion and exclusion
Cohorts of untreated patients with unknown disease status were included. All patients had to have undergone the reference test (biopsy) and antibody test or tests [immunoglobulin (Ig) A and/or IgG anti-gliadin (AGA), anti-endomysium (EMA), anti-reticulin (ARA) or anti-tissue transglutaminase (TTG)]. Sensitivity and specificity had to be reported or calculable from raw data. Titles and abstracts were reviewed independently by two reviewers, with retrieval of papers where there was disagreement. Retrieved papers were also reviewed independently by two reviewers.

Data extraction
The study design of all papers was reviewed and abstracted by at least two reviewers. All data were extracted by one reviewer on to piloted data abstraction forms. A subset of higher quality studies were double-data extracted, with involvement of a third reviewer to resolve any discrepancies.

Quality assessment
A suitable checklist for the quality evaluation of studies was used. It included assessment of the representative nature of the sample, whether there were explicit exclusion criteria, and took account of the potential sources of bias such as blinding, independence of tests and selection of patients.

Analysis
Summary statistics of diagnostic accuracy, that is sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios, were calculated for all studies. Sensitivities and false-positive rates of individual antibody tests were plotted in summary receiver operating characteristics plots, and the area under the curve calculated to give an indication of the overall diagnostic test performance of the individual antibody tests. Positive and negative likelihood ratios were calculated and pooled for individual antibody tests. Subgroup analyses were carried out according to study quality.

Results
Test accuracy of autoantibody tests
Seventy-six studies were included. Many studies were of poor quality on several indicators, particularly concerning the description of the study design and patient selection. Only 18 studies reported the method of patient selection. All but four studies were in symptomatic, not screening, populations.

All antibody tests showed reasonably good diagnostic test accuracy, with the area under the curve >0.9 for all tests. IgA EMA, IgA ARA and IgA TTG stood out as particularly good tests, followed by IgA AGA and then IgG AGA. IgA EMA tests have the highest pooled positive likelihood ratio and lowest negative likelihood ratio and IgA TTG tests have high positive likelihood ratio compared with AGA tests. Studies reported variable measures of test accuracy, which may be due to aspects of study quality, differences in the tests (including manufacturers and substrates) and their execution in the laboratories, different populations and reference standards.

Decision-analytic model
The use of antibody testing with confirmatory biopsy appeared cost-effective, with cost/QALY estimates ranging from £12,250 to £20,160, and a cost/case detected of £6190 to £9900, with the more accurate tests being the most cost-effective. Antibody testing strategies without confirmatory biopsy were more expensive and led to less overall benefit, due to the costs and disutility associated with the treatment of false positives. The use of more than one antibody test increases the sensitivity of the screening strategy, but also decreases the specificity. We estimated that the use of more than one test led to minimal additional benefit, or even a decrease in benefit, whilst being more expensive, owing to the cost of additional tests and the larger number of false positives requiring more biopsies or unnecessary treatment with gluten-free diet. A screening strategy of biopsying all patients was more expensive than any antibody screening strategy whilst leading to minimal increase in benefit or a loss in benefit compared with the more accurate testing strategies.

Uncertainty over parameter values used in the model was investigated using sensitivity analysis, varying each parameter in the model within a plausible range. Predictably, high test specificity or a low cost and disutility of gluten-free diet improves the relative cost-effectiveness of strategies that do not use confirmatory biopsy for those testing positive. Other than this, there were no variations in a single parameter value, which substantially changed the overall interpretation of results from the base case analysis. However, variations in the cost and disutility of gluten-free diet, the utilities
attached to treated and untreated coeliac disease and the decrease in life expectancy associated with treated and untreated coeliac disease did substantially affect the cost-effectiveness of the screening strategies considered; these parameter values are those for which we found the least evidence in the literature.

**Conclusion**

In terms of test accuracy in testing for coeliac disease, IgA EMA (using indirect immunofluorescence) is the most accurate test. If an ELISA test was required, which may be more suitable for screening purposes as it can be semi-automated, testing for IgA TTG is likely to be most accurate. The decision-analytic model shows that the most accurate tests combined with confirmatory biopsy are the most cost-effective, whilst combinations of tests add little or no further value. There is limited information regarding test accuracy in populations with diabetes, and there is some uncertainty over whether the test characteristics would remain the same, particularly as there may be a proportion of silent disease. Further research is required regarding the role of screening in silent coeliac disease and regarding long-term outcomes and complications of untreated coeliac disease.

**Publication**

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The research reported in this monograph was commissioned by the HTA Programme as project number 01/33/01. As funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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